IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	)	C.A. No. 06-438-GMS **REDACTED –** **PUBLIC VERSION**

DECLARATION OF DIANA KRUZE IN SUPPORT OF ABRAXIS'S RESPONSE TO ELAN'S MOTION IN LIMINE NO. 3

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Dated: April 4, 2008

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	)	Case No. 06-438-GMS

DECLARATION OF DIANA KRUZE IN SUPPORT OF ABRAXIS'S RESPONSE TO ELAN'S MOTION IN LIMINE NO. 3

I, Diana Kruze, declare as follows:

1. I am an attorney admitted to practice law in the State of California, and I am admitted *pro hac vice* in the above-captioned action. I am a associate in the law firm of Morrison & Foerster LLP, attorneys for Abraxis BioScience, Inc. ("Abraxis") in the above-captioned action. I submit this Declaration in Support of Abraxis's Response to Elan's Motion in Limine No. 3 to Exclude Abraxis's Experts, Drs. Jerry L. Atwood and Mansoor Amiji From Testifying on Subjects As To Which They Are Not Qualified. I have personal knowledge of the matters set forth herein, and if called upon to do so, I could and would competently testify thereto.

2. Attached hereto as Exhibit 1 is a true and correct copy of the Expert Report of Jerry L. Atwood, Ph.D. dated September 28, 2007.

3. Attached hereto as Exhibit 2 is a true and correct copy of the Rebuttal Expert Report of Jerry L. Atwood dated October 29, 2007.

4. Attached hereto as Exhibit 3 is a true and correct copy of the Supplemental Expert Report of Jerry L. Atwood dated February 29, 2008.

5. Attached hereto as Exhibit 4 are true and correct copies of relevant pages from the deposition transcript of Jerry L. Atwood dated December 5, 2007.

6. Attached hereto as Exhibit 5 is a true and correct copy of the Opening Expert Report of Dr. Mansoor M. Amiji dated September 27, 2007.

7. Attached hereto as Exhibit 6 is a true and correct copy of the Rebuttal Expert Report of Dr. Mansoor M. Amiji dated October 29, 2007.

8. Attached hereto as Exhibit 7 are true and correct copies of relevant pages from the deposition transcript of Mansoor M. Amiji dated December 12, 2007.

9. Attached hereto as Exhibit 8 are true and correct copies of relevant pages from the deposition transcript of Samuel Danishefsky dated December 11, 2007.

10. Attached hereto as Exhibit 9 are true and correct copies of relevant pages from the deposition transcript of Eric J. Munson dated November 29, 2007.

11. Attached hereto as Exhibit 10 is a true and correct copy of a scientific literature search for literature authored by Jerry Atwood concerning Nuclear Magnetic Resonance ("NMR"). This search revealed 84 unique publications, 3 of which were not authored by the Dr. Jerry Atwood who is an expert in this case. The articles that were not authored by our Dr. Jerry

Atwood are designated with strike-through text. According to this search, Dr. Atwood is an author of 81 publications referring to NMR.

12. Attached hereto as Exhibit 11 is a true and correct copy of certain articles referencing NMR authored by Dr. Jerry Atwood.

13. Attached hereto as Exhibit 12 is a true and correct copy of treatises with chapters discussing ssNMR edited by Dr. Jerry Atwood.

14. Attached hereto as Exhibit 13 is a true and correct copy of Dr. Jerry Atwood's declaration, without exhibits, submitted in support of Abraxis's MIL No. 2.

15. Attached hereto as Exhibit 14 is a true and correct copy Emily Evans's declaration, without exhibits, submitted in support of Abraxis's MIL No. 2.

16. Attached hereto as Exhibit 15 is a true and correct copy of "ISI's 50 Most Cited Chemists, 1981-June 1997, ranked by total citations," by David A. Pendlebury, available at http://pcb4122.univ-lemans.fr/citation.html.

I declare under penalty of perjury of the laws of the United States of America that the foregoing is true and correct.

Executed this 3rd day of April, 2008 at Palo Alto, California.

Diana Kruze

CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire, hereby certify that on April 15, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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I further certify that on April 15, 2008**,** I caused a true and correct copy of the foregoing document to be served by e-mail on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

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EXHIBITS 1-9

REDACTED IN THEIR ENTIRETY

EXHIBIT 10

1) STRUCTURE OF JUNCUNONE A BIOGENETICALLY INTRIGUING MOLECULE FROM THE MARSH PLANT JUNCUS-ROEMERIANUS
Author: MILES D H (Reprint); RANDLE S; SHAKIR R; ATWOOD J L
Journal: Journal of Organic Chemistry 46 (13): -2815 1981

2) OF SARRACENIN AN UNUSUAL ENOL DI ACETAL MONO TERPENE FROM THE INSECTIVOROUS PLANT SARRACENIA-FLAVA
Author: MILES D H; KOKPOL U; BHATTACHARYYA J; ATWOOD J L; STONE K E; BRYSON T A; WILSON C
Journal: Journal of the American Chemical Society 98 (6): p 1569-1573 1976

3) Anion binding within the cavity of pi-metalated calixarenes
Staffilani M.; Hancock K.S.B.; Steed J.W.; Holman K.T.; Atwood J.L et al
Journal of the American Chemical Society (J. AM. CHEM. SOC.) (United States) September 16, 1997 , 119/27 (6324-6335)

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Nakano A.; et al,
Tetrahedron Letters (TETRAHEDRON LETT.) (United Kingdom) November 7, 1989 , 30/38 (5099-5102)

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Atwood, Jerry L; Szumna, Agnieszka
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SCORDILIS-KELLEY C, et al,
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~~12)~~ MEDINA J C, et al, Journal: Journal of the American Chemical Society, 1992, 114 (26) 10583-10595

13) Naked' SF SUB 5 SUP - anion: the crystal and molecular structure of (CsSUP + .(18-crown-6) SUB 2)(SF SUB 5 SUP -)
CLARK M, et al European journal of solid state and inorganic chemistry, 1992, 29(4-5) 809-833

14) Synthese und Stuktur eines Diphosphadigalletans : ein neuartiges, basenstabilisiertes Ga SUB 2 P SUB 2 -Ringsystem
VON COWLEY A H, et al, Journal: Angewandte Chemie; Angewandte Chemie, 1990, 102 (10)1169-1171 Language: German

15) Aluminium-fused bis-p-tert-butylcalix(4)arene : a double cone with two pi -arene...H interactions for included methylene chloride
ATWOOD J L, et al, Journal: Journal of the Chemical Society. Chemical communications, 1992 (18)1349-1351

16) Metallocene catalysts for olefin polymerization. XXIV: Stereoblock propylene polymerization catalyzed by rac-(anti-ethylidene(1- eta SUP 5-tetramethylcyclopentadienyl)(1-eta SUP 5 -indenyl)dimethyltitatnium : a two-state propagation
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19) Synthesis and X-ray crystal structure of a five-coordinate d SUP 8 complex : (Pt(Me SUB 2 NN)(PMe SUB 2)(PPh SUB 2)) SUB 2 Cl)(Cl)
HARLAN C J, et al, Journal: Journal of crystallographic and spectroscopic research, 1992, 22(1) 71-75

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23) Variable coordination numbers in crystalline bis(pentamethylcyclopentadienyl) samarium oxide, iodide and alkoxide complexes
EVANS W J, et Journal: Polyhedron, 1988, 7 (18) 1693-1703

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SINGH Y P, et al Journal: Inorganic chemistry, 1986, 25 (17) 3076-3081

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HOLMES-SMITH R D, et al Journal: Dalton Transactions, 1982 (12) 2461-2468

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41) SYNTHESIS AND CRYSTAL STRUCTURE OF HYDRIDO (TETRAHYDROBORATO) TETRAKIS-(TRIMETHYLPHOSPHINE) MOLYBDENUM(II)
ATWOOD J L, et al Journal: J. CHEM. SOC., DALTON TRANS.,1980 (3) 467-470

42) STUDIES ON ORGANODISULPHIDES AS METAL LIGANDS. II. THE CRYSTAL AND MOLECULAR STRUCTURE OF RE SUB 2 BR SUB 2 (CO) SUB 6 S SUB 2 ME SUB 2 , A COMPOUND CONTAINING A DIMETHYLDISULPHIDE BRIDGE ACROSS THE TWO METALS. COMPARISON BETWEEN SOLID STATE AND SOLUTION DATA FOR RE SUB 2 BR SUB 2 (CO) SUB 6 S SUB 2 R SUB 2 (R=ME,PH).
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43) TETRAZOLO (1,5-B)-1,2,4-TRIAZINES. SYNTHESES AND STRUCTURE DETERMINATION.
GOODMAN M M, et al Journal: J. ORG. CHEM., 1976, 41 (17) 2860-2864

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MAHAFFEY R L, et al Journal: J. ORG. CHEM., 1976, 41 (18) 2963-2965

45) MU -DIALKYL INNER TRANSITION METAL(III) TETRA-ALKYLALUMINATES; THE CRYSTAL AND MOLECULAR STRUCTURE OF DI-MU -METHYL-(DIMETHYLALUMINIUM)BISCYCLOPENTADIENYL-YTTRIUM AND-YTTERBIUM.
HOLTON J, et al Journal: J. CHEM. SOC., CHEM. COMMUNIC.1976 (12) 425-426

46) FERROCENYLALANES. THE PREPARATION AND PROPERTIES OF (ETA -C SUB 5 H SUB 5)FE(ETA -C SUB 5 H SUB 4 AL SUB 2 ME SUB 4 CL)
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47) Title: Series of bis(eta-cyclopentadienyl)uranium(III) dichloro-bridged-alkali-metal and dihalogenobis(eta-cyclopentadienyl)uranate(III) complexes: single-crystal X-ray structure determination of (UCp"/sub 2/(.-Cl)/sub 2/Li(pmdeta)) and (PPh/sub 4/)(UCp"/sub 2/Cl/sub 2/) (Cp" =eta-C/sub 5/H/sub 3/(SiMe/sub 3/)/sub 2/-1,3, pmdeta =(Me/sub 2/NCH/sub 2/CH/sub 2/)/sub 2/NMe)
Author(s): Blake, P.C, et al Source: J. Chem. Soc. (London), Chem. Commun. (United Kingdom) v 21 Publication Date: 1 Nov 1988 p 1436-1438

48) Title: Complete series of uranocene(III) halides :braceUCp"/sub 2/Xbracesub(n): :X=F, Cl, Br, or I; Cp" = eta-C/sub 5/H/sub 3/(SiMe/sub 3/)/sub 2/); Single-crystal x-ray structure determinations of the chloride and bromide (n=2 for X/sup -/=..mu..-Cl/sup -/ or ..mu..-Br/sup -/)
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49) SYNTHETIC, STRUCTURAL, AND REACTIVITY STUDIES OF THE REDUCTION AND CO DERIVATIZATION OF AZOBENZENE MEDIATED BY DIVALENT LANTHANIDE COMPLEXES
Author: EVANS WJ, et al Journal: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 1988 , V 110 , N15 , P 4983-4994

50) SYNTHESIS AND X-RAY CRYSTAL-STRUCTURE OF AN UNUSUAL OLIGOMERIC BIS(PENTAMETHYLCYCLOPENTADIENYL) HALIDE COMPLEX OF CERIUM - [(C5ME5)2CECL2K(THF)]N
Author: EVANS WJ, et alJournal: ORGANOMETALLICS , 1988 , V 7 , N3 , P 629-633

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Author: MILES DH, et al Journal: ACS SYMPOSIUM SERIES , 1987 , V 330 , P 491-501

52) Investigations into chain length control over solid-state pyrogallol[4]arene nanocapsule packing
Author: Cave GWV, et al Journal: SUPRAMOLECULAR CHEMISTRY , 2008 , V 20 , N1-2 , P 157-159
ISSN: 1061-0278

53) Gas-induced transformation and expansion of a non-porous organic solid
Author: Thallapally PK (REPRINT) et al
Journal: NATURE MATERIALS , 2008 , V 7 , N2 (FEB) , P 146-150
ISSN: 1476-1122

54) Cocrystallization and encapsulation of a fluorophore with hexameric pyrogallol[4]arene nanocapsules: Structural and fluorescence studies
Author: Dalgarno SJ, et al Journal: ANGEWANDTE CHEMIE-INTERNATIONAL EDITION , 2006 , V 45 , N42 , P 7019-7022 ISSN: 1433-7851

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Author: Dalgarno SJ, et al Journal: CHEMICAL COMMUNICATIONS , 2006 , N36 , P 3803-3805

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Author: Cave GW, et al Journal: CHEMICAL COMMUNICATIONS , 2005 , N22 , P 2787-2789

57) Supramolecular blueprint approach to metal-coordinated capsules
Author: McKinlay RM, et al Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA , 2005 , V 102 , N17 (APR 26) , P 5944-5948

58) Polymorphism of pure p-tert-butylcalix[4]arene: conclusive identification of the phase obtained by desolvation
Author: Atwood JL (REPRINT) ; Barbour LJ; Jerga A
Journal: CHEMICAL COMMUNICATIONS , 2002 , N24 , P 2952-2953

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Author: Holman KT; Orr GW; Steed JW; Atwood JL (REPRINT)
Journal: CHEMICAL COMMUNICATIONS , 1998 , N19 (OCT 7) , P 2109-2110
ISSN: 1359-7345

60) Bowl vs saddle conformations in cyclononatriene-based anion binding hosts
Author: Staffilani M; Bonvicini G; Steed JW (REPRINT) ; Holman KT; Atwood JL; Elsegood MRJ
Journal: ORGANOMETALLICS, 1998, V 17 , N9 (APR 27),P 1732-1740

61) Organometallic chemistry of the actinides Part 4 - The chemistry of some tris(cyclopentadienyl) actinide complexes
Author: Blake PC, et alJournal: JOURNAL OF ORGANOMETALLIC CHEMISTRY , 1998 , V 551 , N1-2 (JAN 30) , P 261-270 ISSN: 0022-328X

62) SYNTHESIS AND CHARACTERIZATION OF THE CATALYTIC ISOTACTIC-SPECIFIC METALLOCENE COMPLEX (ETA(5)-C5H3C4H9-CME(2)-ETA(5)-C13H8)ZRCL2 - MECHANISTIC ASPECTS OF THE FORMATION OF ISOTACTIC POLYPROPYLENE, THE STEREOREGULATIVE EFFECT OF THE DISTAL SUBSTITUENT AND THE RELEVANCE OF C-2 SYMMETRY
Author: RAZAVI A; ATWOOD JL
Journal: JOURNAL OF ORGANOMETALLIC CHEMISTRY , 1996 , V 520 , N1-2 (AUG 9) , P 115-120

63) SYNTHESIS, SPECTROSCOPIC PROPERTIES AND CRYSTAL-STRUCTURES OF [ML(2)CL(2)] [M=TH OR U L=ETA-C5H3(SIME(3))(2)-1.3] AND [UL(2)X(2)] (X=BR, I OR BH4)
Author: BLAKE PC, et al Journal: JOURNAL OF THE CHEMICAL SOCIETY-DALTON TRANSACTIONS , 1995 , N20 (OCT 21) , P 3335-3341 ISSN: 0300-9246

64) STRUCTURE OF THE P-SULFONATOCALIX[4]ARENE COMPLEX WITH TETRAMETHYLAMMONIUM IONS, [NME(4)](5)[P-SULFONATOCALIX[4]ARENE]CENTER-DOT-4H(2)O
Author: ATWOOD JL; BARBOUR LJ; JUNK PC; ORR GW
Journal: SUPRAMOLECULAR CHEMISTRY , 1995 , V 5 , N2 , P 105-108 ISSN: 1061-0278

65) **Duplicate** ~~PREPARATION AND CRYSTAL-STRUCTURES OF THE COMPLEXES (ETA(5)-C(5)H(3)ME-CME(2)-ETA(5)-C13H8)MCL(2) (M=ZR OR HF) - MECHANISTIC ASPECTS OF THE CATALYTIC FORMATION OF A SYNDIOTACTIC-ISOTACTIC STEREOBLOCK-TYPE POLYPROPYLENE~~
~~Author: RAZAVI A; ATWOOD JL Journal: JOURNAL OF ORGANOMETALLIC CHEMISTRY , 1995 , V 497 , N1-2 (JUL 26) , P 105-111 ISSN: 0022-328X~~

66) PREPARATION AND CRYSTAL-STRUCTURES OF THE COMPLEXES (ETA(5)-C5H4CPH2-ETA(5)-C13H8)MCL2 (M = ZR, HF) AND THE CATALYTIC FORMATION OF HIGH-MOLECULAR-WEIGHT HIGH TACTICITY SYNDIOTACTIC POLYPROPYLENE
Author: RAZAVI A; ATWOOD JL Journal: JOURNAL OF ORGANOMETALLIC CHEMISTRY , 1993 , V 459 , N1-2 (OCT 19) , P 117-123 ISSN: 0022-328X

67) SUPRAMOLECULAR COMPLEXES OF FLEXIBLE, EXTENDED-CAVITY CALIX[4]ARENES - STRUCTURAL CHARACTERIZATION OF A MOLECULAR VENUS FLYTRAP
Author: ATWOOD JL; ORR GW; BOTT SG; ROBINSON KD
Journal: ANGEWANDTE CHEMIE-INTERNATIONAL EDITION IN ENGLISH , 1993 , V 32, N7 (JUL) , P 1093-1094 ISSN: 0570-0833

68) STRUCTURE OF MAP-MNA, THE 1/1 ADDUCT BETWEEN (R)-METHYL 2-(2,4-DINITROANILINO)PROPANOATE (MAP) AND 2-METHYL-4-NITROANILINE (MNA), A NEW NONLINEAR-OPTICAL CRYSTAL
Author: METZGER R, et al Journal: ACTA CRYSTALLOGRAPHICA SECTION C-CRYSTAL STRUCTURE COMMUNICATIONS , 1993 , V 49 , APR (APR 15) , P 738-741 ISSN: 0108-2701

69) CYCLIC TRIMERIC HYDROXY, AMIDO, PHOSPHIDO, AND ARSENIDO DERIVATIVES OF ALUMINUM AND GALLIUM - X-RAY STRUCTURES OF [T-BU2GA(MU-OH)]3 AND [T-BU2GA(MU-NH2)]3
Author: ATWOOD DA, et al Journal: ORGANOMETALLICS , 1993 , V 12 , N1 (JAN) , P 24-29

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INDENYL)FE(CO)2))CR(CO)3, AND (ETA-6-1,4-C6H4ME((ETA-5-C5H5)FE(CO)2))CR(CO)3
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Author: Edwards, Bruce H Citation: J.Amer.Chem.Soc. (1983) Series: 105-3, 416-426

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Author: Haberkorn, R. A., et al Citation: J.Amer.Chem.Soc. (1981) Series: 103-10, 2534-2539~~

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Author: Carmona, Ernesto, et al Citation: J.Chem.Soc.Dalton Trans. (1980) 2108-2116

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Author: Daniels, Paul H., et al. Citation: J.Org.Chem. (1980) Series: 45-3, 435-440

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Author: Rausch, Marvin D. Citation: J.Organomet.Chem. (1990) Series: 383, 227-252

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Author: Gray, Gary M., et al Citation: J.Organomet.Chem. (1990) Series: 381-1, 53-67 CODEN: JORCAI Language: English
Abstract Language: English

EXHIBIT 11

Solvent-free, direct synthesis of supramolecular nano-capsules

Jochen Antesberger,[a] Gareth W. V. Cave,[a] Matthew C. Ferrarelli,[a] Michael W. Heaven,[a] Colin L. Raston[b] and Jerry L. Atwood*[a]

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The single step direct synthesis of pyrogallol[4]arene *via* a solvent free protocol yields the pure product as a self-assembled nano-capsule, comprised of six macrocyclic building blocks.

Traditional methods employed in the preparation of supramolecular nano-capsules involve the dissolution of previously prepared pure building blocks into an appropriate solvent system.[1,2] This approach uses at least two solvent-based processes and potentially more if a purification step is required after the synthesis. As a result, guest inclusion chemistry in such supramolecular systems is dominated by entrapment of solvent molecules within the nano-architectures.[2] Implementation and application down stream of technologies based on these nano-capsules can therefore be problematic, in particular for those processes that require the use of volatile organic solvents.[3] Environmental awareness globally has led to a rise in the implementation of benign chemical processes whenever possible. The rapidly emerging field of green chemistry seeks to deal with issues of sustainability, pollution and economics.[3] By adopting the principles of green chemistry we are making advances in the benign synthesis of supramolecular compounds.

Solvent-free reactions are becoming established in a wide range of reactions,[4] and have been successfully employed in the synthesis of calixarenes and related macrocycles.[4–6] Pyrogallol[4]arenes in the cone conformation are typically synthesised in an alcohol solution by an acid catalysed condensation reaction between pyrogallol and an appropriate aldehyde.[7] The reported solvent-free preparation of the *C*-resorcinol[4]arenes by Roberts *et al.*[5] results in the formation of the both the *cis–cis–cis* (*rccc*) and the *cis–trans–trans* (*rctt*) isomers. Attempts at synthesising the cone (*rccc*) conformation exclusively were unsuccessful.[5] Although the reported method is a significant improvement over traditional methodologies, the separation of the different structural isomers by chromatography is counter productive when addressing the minimisation of chemical waste. Herein, we report the near quantitative formation of *C*-isobutylcalix[4]pyrogallolarene, **1**, in the cone conformation and its subsequent spontaneous formation into nano-capsules in the absence of solvent.

Isovaleraldehyde (0.89 ml, 7.9 mmol) was added dropwise to a fine dispersion of pyrogallol (1.00 g, 7.9 mmol) and a catalytic amount of solid *p*-toluenesulfonic acid (50 mg, 0.3 mmol) with constant milling using a mortar and pestle (Fig. 1).[8] The condensation reaction yielded a brittle white solid within two minutes of grinding. This solid was easily milled to a fine, yellow powder upon further aggregation. The reaction was followed by TLC and NMR techniques and was found to have reached completion within five minutes of constant grinding. This method is significantly faster than the solvent-based methods traditionally employed in the synthesis of calix[4]pyrogallolarene.[7] The reduced reaction time, elimination of energy needed for heating and/or cooling, minimal quantities of catalyst, elimination of solvent and subsequent waste-related issues are all important factors in complying with the underling principles of green chemistry.[3]

The aggregation behaviour of pyrogallol[4]arenes in alcohols and in chloroform has attracted much recent interest.[9] The macrocycles are observed to exist as monomers in alcohol, and crystallise out of solution as bilayer-type structures.[9] Remarkably, treatment of the pyrogallol[4]arenes with chloroform affords the spontaneous self-assembly of six monomers into a nano-capsule held together by an extensive hydrogen bonded network, as previously reported in the solid state.[9,10] It is therefore clear that

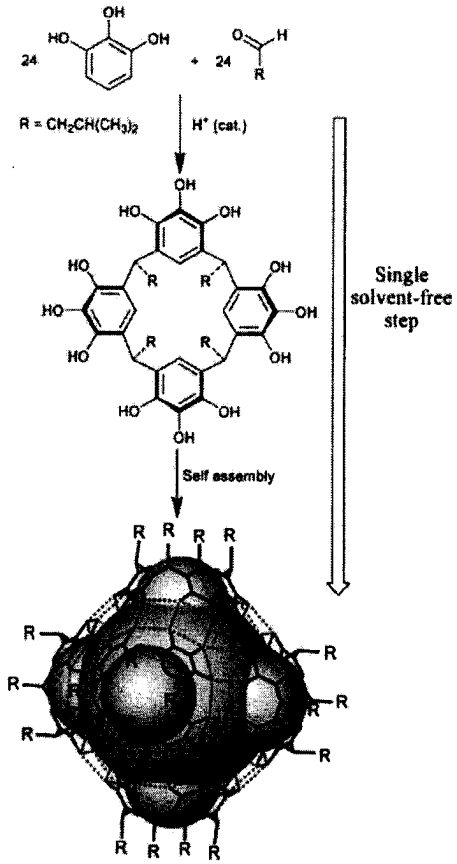


Fig. 1 One pot solvent-free synthetic route to nano-capsule formation.

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any dissolution of the material resulting from the solvent-free synthesis would preclude structural analysis of the product as prepared.

Solid state ^{13}C-NMR analysis† of the solvent-free product was compared to the known bilayer and nano-capsule forms of the pyrogallol[4]arene **1** prepared using conventional protocols,[8-10] and crystallised from methanol and chloroform, respectively. The solid state ^{13}C-NMR spectra of the pyrogallol[4]arene **1** crystallised from methanol (bilayer structure) and chloroform (nano-capsules) are markedly different, as is shown in Fig. 2. The bilayer structure affords more signals than that from the nano-capsule sample. These results are interpreted as resulting from a decrease in molecular symmetry of the macrocycle in the bilayer structure compared to that of the nano-capsules. This is also observed in the solution studies, and is attributed to the additional hydrogen bonds between the methanol and the macrocycle in the bilayer structure.[9] By comparison, the nano-capsule provides a high degree of symmetry between the six pyrogallol[4]arene building blocks. Comparison of the ^{13}C-NMR spectrum of the product from the solvent-free reaction with those of the two standards (Fig. 2) demonstrates that the material from the solvent free synthesis exists as hexameric spheres. In fact, the spectra of the nano-capsule materials from the two different reaction pathways vary only slightly, with the product from the solvent-free reaction having a shoulder on the signal at 114 ppm and a low intensity peak at 50 ppm. These signals occur at the same chemical shifts as the pure *p*-toluenesulfonic acid catalyst, and therefore arise as a result of the obtaining the spectra without removal of the catalyst.

The nano-capsule formed by the self-assembly of six pyrogallol[4]arene macrocycles is known to enclose an internal molecular volume of over 1300 Å^3.[10] Studies of this molecular capsule show it to contain solvent guest molecules.[9,10] In an attempt to ascertain the guest species within the nano-capsule from the solvent-free reaction we studied the nano-capsule in solution. The resulting ^{1}H and ^{13}C NMR spectra were analogous to those of the nano-capsule made using traditional synthetic techniques, with the additional signals corresponding to water and the catalyst. There are also traces of unreacted starting materials. We were unable to observe a distinct separation of chemical shifts attributed to guest molecules *exo* and *endo* with respect to the nano-capsule. DOSY NMR studies of the product from the solvent-free reaction confirm the existence of nanometre scale aggregates but did not conclusively indicate the existence of water within the cavity. Diffusion studies of the chemical shifts arising from the unreacted starting materials indicate that they are entombed within the nano-capsules. A diffusion coefficient of 3.8775×10^{-10} m^2 s^{-1} (at 298 K in acetone-D_6, 3 mM) was calculated for the solvent-free pyrogallol[4]arene corresponding to an estimated solvated molecular diameter of approximately 3.7 nm. A similar experiment was performed on the pyrogallol[4]arene **1** crystallised from methanol, resulting in a diffusion coefficient of 7.221×10^{-10} m^2 s^{-1} (at 298 K in acetone-D_6, 3 mM) relating to a solvated diameter of 1.8 nm. These results are in excellent agreement with our previously reported molecular structure of the nano-capsule and the solid-state structures of the pyrogallol[4]arene, **1**, in the bilayer conformation.[9,10] Electrospray ionisation mass spectrometry of the product from the solvent-free reaction in ethyl acetate substantiates the existence of the nano-capsule formation, exhibiting a $[M - 3H]^{3-}$ molecular ion of the nano-capsule (calcd.: 1551.75; found: 1552.16).

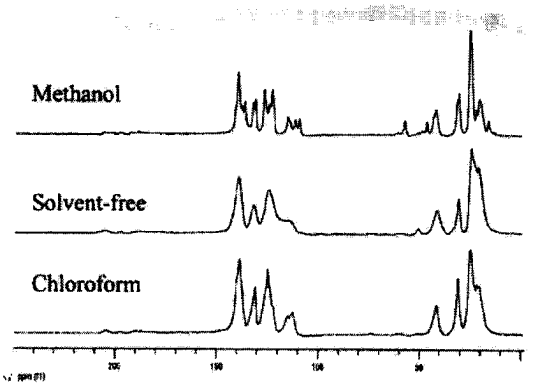


Fig. 2 Solid-state ^{13}C-NMR analysis of *C*-isobutylcalix[4]pyrogallolarene, **1**, crystallised into bilayer (from methanol) and nano-capsule (chloroform and solvent-free methods) morphologies.

We speculate that the nano-capsule entraps the water molecules liberated by the condensation reaction during the formation of the macrocycle, arising from atmospheric moisture and the deliquescent nature of the catalyst. Trace amounts of the starting materials also help to fill the internal volume of the nano-capsule during formation. These polar guest molecules interfere with the hydrogen bonding network that holds the nano-capsule together, allowing them to exchange and diffuse into the surrounding solvent system. A similar solvent–guest exchange mechanism has been reported by Rebek and co-workers for the nano-capsules formed by the self-assembly of six calix[4]resorcinarene and eight water molecules.[11]

We have demonstrated that the facile formation of pyrogallol[4]arene macrocycles in the cone conformation using green chemistry methodologies is attainable. The spontaneous self-assembly of these supramolecular building blocks even in the absence of solvent into nano-sized molecular capsules provides an insight into polar guest inclusion logistics. We are continuing our studies of these molecular containers, investigating their potential as drug delivery systems and as affordable biological cell models.[10] Acid functionalised potential guests are also being investigated as an alternative catalyst in the formation of the nano-capsule and subsequent inclusion, with resulting increased atom efficiency.

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Notes and references

† Solid state ^{13}C-NMR analysis was carried out on a Bruker ARX 300 with a MAS probe. Samples were packed in 7 mm ZrO_2 rotors spinning at 5000 Hz. DOSY NMR studies were performed on a Bruker DRX 500 spectrometer equipped with a Acustar II gradient system using a 5 mm TXI probe and a simulated echo and LED sequence,[12] with the following parameters: relaxation delay 7.5 s, diffusion time 50 ms, pulse gradient duration 2 ms. The diffusion gradients were increased incrementally from 2 to 96 G mm^{-1} in 64 equal steps.

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Engineering void space in organic van der Waals crystals: calixarenes lead the way

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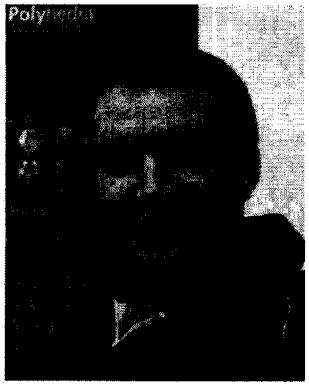
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Seemingly non-porous organic solids have the ability for guest transport and have also been shown to absorb gases, including hydrogen, methane and acetylene, to varied extents. These materials also show potential for gas separation technology, display remarkable water transport through hydrophobic crystals, and clearly show that molecules within crystals are capable of cooperating with guests as they move through non-porous environments. This work is presented within a broader topic which also encompasses crystal engineering and (microporous) metal-organic frameworks (MOF's).

The impending energy crisis and related global pollution issues have inspired the investment of much effort towards the discovery of new materials for gas storage and sequestration. In this regard, many researchers are focusing their efforts on the design and construction of novel porous materials with large void spaces that can accommodate volatile molecular species (*e.g.* energy carriers such as hydrogen gas). A significant target is the 6.0 weight percentage (wt%) storage of H_2, set out by the U.S. Department of Energy (DOE) for the development of H_2 fuelled transportation by 2010, although these targets are set somewhat higher for the future.[1] Thus the development of a material that would store this amount of hydrogen at room temperature would no doubt generate enormous commercial and industrial interest.

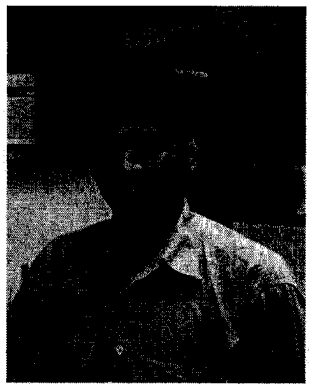
The primary purpose of this tutorial review is to describe our own recent work in the area of guest transport and storage using porous organic solids. The remarkable phenomenon of crystal porosity is attracting increasing attention, and we aim to describe this work in the context of other materials that are used for guest storage. We begin by describing some of the tremendous recent advances in the area of crystal engineering, with particular reference to the development of microporous coordination networks (or metal-organic frameworks, commonly referred to as MOF's). These topics are too expansive to cover comprehensively in this tutorial review and we have therefore selected a limited number of key references that outline recent progress in the field. Typically these are themselves reviews that cover vast contributions by individual research groups involved in these areas of research (and that cite all the relevant literature from other research groups). We then describe our own work with calixarenes in the context of

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Scott J. Dalgarno

Scott J. Dalgarno was born in Aberdeen, Scotland in 1978. He obtained his MChem and PhD at The University of Leeds, working with Colin Raston and Michaele Hardie, on molecular capsules and coordination networks based on the self-assembly of the p-sulfonatocalix[4,5,6,8]arenes. He graduated in 2004 and till present has been a postdoctoral research fellow in the Atwood research group at the University of Missouri-Columbia, working on the self-assembly of pyrogallol[4]arenes and the inclusion and characterisation of other molecules within these very large capsular assemblies.



Praveen K. Thallapally

Praveen K. Thallapally was born in Khajipally, Medak, India in 1973. He obtained his PhD in 2003 from the University of Hyderabad working with Gautam R. Desiraju on crystal engineering and polymorphism of C_3 symmetrical molecules. After graduation he moved to the Atwood research group at the University of Missouri-Columbia (UMC) as a postdoctoral research associate where he investigated gas storage and separation using porous and nonporous calixarene derivatives, self assembled pyrogallol[4]arenes using hydrogen and metal coordination bonds. In 2006 he moved to Pacific Northwest National Laboratory (PNNL) as a Sr. Research Scientist. His research interests include gas storage and separation, gas hydrates, and solid-state chemistry.

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crystal engineering of porosity and highlight the recent literature and developments.

Crystal engineering

Crystal engineering has come to the fore in recent years with several journals now being devoted to the subject. The concept has been known for some time, and the use of the theory in important areas such as novel pharmaceutical discovery/development is attracting increasing attention.[2] For a recent, concise, and general review of crystal engineering, the reader is directed to a Focus article by Braga.[3] In this report, the author addresses the question, "Crystal engineering, Where from? Where to?" In terms of the "where from?", some work dating back to the 1990's is cited, but the concept is also proposed to have existed from around 1955—rather than the more commonly referenced year of 1971—and the author also describes other important works through the 70's and 80's. By far the most important aspect of this article, in the context of the current review, is the focus it places on the significance of the supramolecular perception as a paradigm shift for crystal engineering. What about the 'where to?' While crystal engineering has its roots primarily in organic chemistry (see below for an example) the article by Braga shows how this field has developed into periodical coordination chemistry and the discovery of whole new classes of materials.

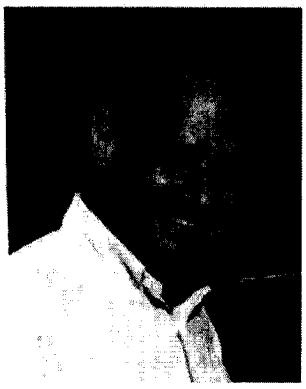
One of the most promising areas of research in this field has been the formation and structual identification of MOF's. These materials are rigid, offer structural and thermal stability, and are ideal for solvent removal to generate void space that is suitable for guest storage. The importance of this field is demonstrated by the fact that the reader can typically find a new MOF report on a near daily basis in journals commonly subscribed to by the majority of academic institutions. The predicted construction or synthesis of MOF's lies well within the realms of crystal engineering, and single crystal X-ray diffraction is invaluable in elucidating the salient structural features of the materials and characterising void spaces.

Microporous coordination networks: MOF's through crystal engineering

As is the case for crystal engineering with organic molecules (only), searches for articles in the areas of microporous coordination networks and MOF's will return equally as many diverse reports from the literature if not more. Therefore, we will focus again on select articles, but will examine these areas further as they have gained much interest at the highest levels in recent times.

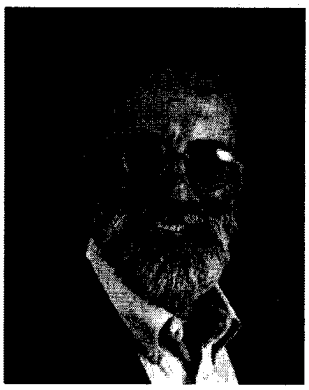
As suggested in the previous paragraph, the formation of coordination polymers (or networks) is an expansive topic that encompasses the formation of porous materials, highly connected materials and interpenetrated nets, or networks with unusual topologies. To demonstrate the versatility associated with this area of chemistry, we have selected an Account of high connectivity materials by Schröder, Hubberstey, Champness and co-workers,[4] and a review of functional porous coordination polymers by Kitagawa and co-workers.[5] Both articles discuss how the majority of coordination polymers reported to date are formed by building-block methodology through designed motifs. This typically involves the combination of metal centres with bridging organic ligands that results in the formation of networks that can have anions (and or solvent molecules) residing in interstitial space, although anions can also be coordinating. Metal centre geometry therefore plays a large part in determining the topology of the resultant networks, although bridging ligand shape is also very important.

In the Account, the authors cover many other important works, and their own extends into high connectivity materials by combining lanthanide(III) metal centres (that have high coordination numbers) with 4,4′-bipyridine-*N*,*N*′-dioxide.[4] This ligand forms different types of coordination with lanthanide(III) centres (Fig. 1), and these materials are placed amongst a number of other coordination polymers in order to describe these collective examples in terms of 4^4- and 6^3-subnet tectons (topological classifications based on the angles present at each node in a specific network). The authors' extensive



Leonard J. Barbour

Len Barbour was born in Pretoria, South Africa in 1965. In 1994 he obtained his PhD under the supervision of Luigi Nassimbeni at the University of Cape Town where he investigated thermodynamic and structural aspects of solvate formation and decomposition. He then undertook a postdoctoral fellowship with Jerry Atwood at the University of Missouri-Columbia (UMC) where he continued to pursue his interest in supramolecular chemistry. In 1997 he was appointed as Research Assistant Professor at UMC but in 2003 he moved back to South Africa as an Associate Professor at the University of Stellenbosch. He was promoted to Professor of Chemistry in 2005 and his research interests include the study of solid-state phenomena with particular emphasis on the design and characterisation of porous materials for gas sorption.



Jerry L. Atwood

Jerry L. Atwood was born in Missouri, where he received a BS in 1964. After receiving his PhD from the University of Illinois, in 1968, while working in the lab of Galen D. Stucky, he accepted a position as Assistant Professor at the University of Alabama, where he rose to the position of University Research Professor in 1987. He then moved to the University of Missouri-Columbia in 1994, where he is currently a Curators' Professor and Chair of Chemistry. His research interests include molecular capsules and aspects of porosity in the solid state.

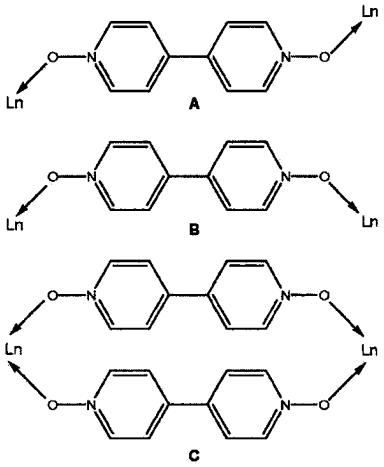


Fig. 1 Different coordination modes formed by 4,4′-bipyridine-*N*,*N*′-dioxide. The ligand can form anti (A), syn (B), and double bridged (C) arrangements that result in the formation of highly connected coordination networks. (Reproduced with permission from ref. 4. Copyright 2005 the American Chemical Society.)

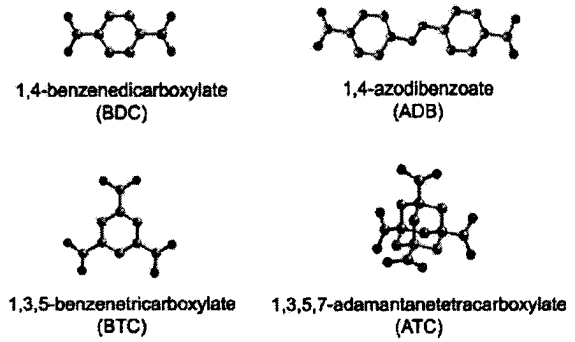


Fig. 2 Examples of polytopic ligands that can be used to taylor MOF construction. (Reproduced with permission from ref. 9. Copyright 2001 the American Chemical Society.)

works with this system serve as a good example of how particular reaction conditions can dramatically affect the resulting coordination network. More importantly however, the Account presents a simpler approach to the description and visualisation of complex coordination networks, and gives the reader a noteworthy introduction to network topologies.

Although the review by Kitagawa covers some areas concerning coordination polymers that are also elaborated here in association with other research groups, the article also covers topics such as 'connectors and linkers', 'design and motifs', 'porous structures' and 'functions of coordination polymers'.[5] With respect to 'connectors and motifs', Kitagawa has used the 'pillared layer' to form coordination polymers that 'expand and shrink', and that also show selective guest sorption.[6] Similar studies by Kim and co-workers have employed 'paddle wheels' (zinc carboxylate clusters) with 1,4-diazabicyclo[2.2.2]octane (DABCO) linkers to construct pillared square grid nets.[7,8] These materials show unusual dynamic behaviour depending on guest molecules,[8] and have implications for hydrogen storage, although the H_2 uptake is only $\sim$2 wt% at 78 K.

Recent developments in metal-organic framework chemistry have proven to be particularly important in the use of robust materials for guest storage. Of the many research groups involved in this field, Yaghi and co-workers have arguably been one of the most prolific, and instead of focusing on the synthesis of coordination networks with metal cations and organic ligands such as 4,4′-bipyridine, they employed multidentate ligands such as carboxylates to consistently arrive at more rigid networks. This strategy results in *neutral* frameworks owing to the metal cations and the anionic nature of the ligands and their extensive studies are comprehensively reviewed in an Account on Modular Chemistry with Secondary Building Units (SBU's), as well as a Mini review on strategies for hydrogen storage in MOF's.[9,10]

SBU's—metal carboxylate clusters—can be used to design highly porous and robust MOF's. Simply, SBU's are modelled on the basic copper acetate and zinc acetate motifs (for example) that have D_{4h} and T_d symmetry respectively.[9] These clusters can then readily be linked in any number of ways by varying the organic ligand possessing the carboxylate functionality used in the MOF synthesis (Fig. 2). This modular approach has allowed the authors to synthesise and characterise many tailored MOF's by employing these fundamental shapes in the prediction of topology prior to ligand selection. Additional merits of these materials lie in the typically high percentage yields found during synthesis, and the fact that solvent molecules can easily be removed to afford porosity. The degree of porosity is controllable through catenation (which is also dependent on the modular approach), and this can have implications in guest selection for particular pore sizes.[9] With respect to H_2 storage with MOF's, the authors summarise a number of materials that were studied under various conditions to give the reader an overview of work performed in this area thus far.[10] They also stress that only a fraction of the known 2-D and 3-D MOF's have been examined for properties such as H_2 storage media. Schröder, Champness, Hubberstey and co-workers are also active in this area and have recently reported new MOF's that store 6 wt% H_2 at 78 K and pressures below 80 bar.[11]

More recent developments in the synthetic aspect of this area also include the formation of zeolite-like metal-organic frameworks (ZMOF's) that are built from tetrahedral building units (TBU's).[12] Eddaoudi and co-workers show how these materials have extra-large cavities (significantly larger than MOF's), and that these voids may be used as (host–guest)–guest sensors, for example (Fig. 3). Porous crystalline covalent organic frameworks (COF's) have also recently been synthesised by Yaghi and co-workers. These materials have large pore volumes, can display high thermal stability, and have high surface areas.[13]

Porosity

Before proceeding with a discussion of porosity in van der Waals crystals, it is important to briefly discuss the term and its proper use. Here the reader is directed to a recent Focus Article by Barbour, in which three different kinds of porosity are described: conventional porosity, porosity "without pores" and virtual porosity.[14] Conventional porosity applies to

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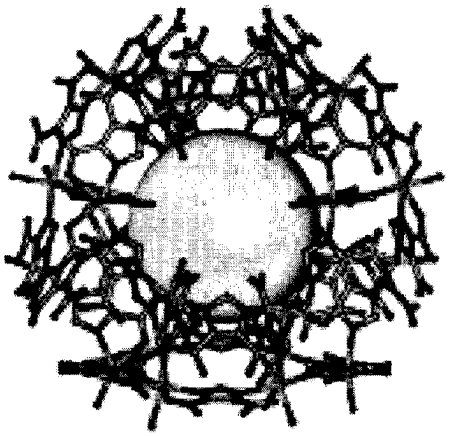
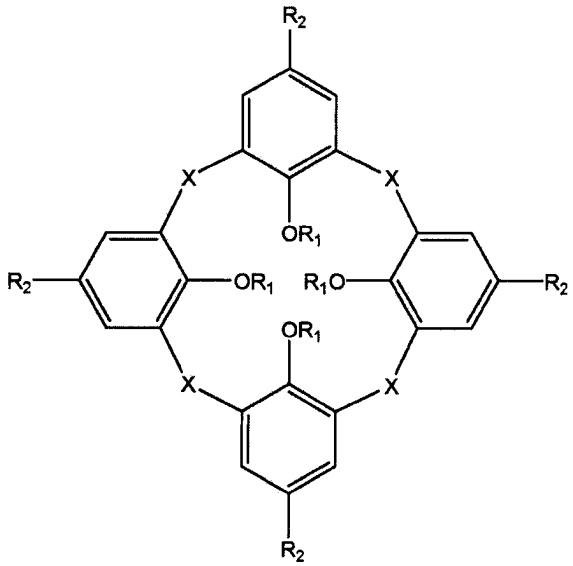


Fig. 3 The *sod*-ZMOF that is constructed from tetrahedral building units (TBU's). The large volume of the structure is represented by the yellow spheroid. (Reproduced with permission from ref. 12. Copyright 2006 the Royal Society of Chemistry.)

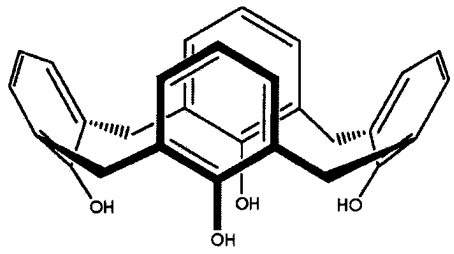
materials such as zeolites or MOF's which retain structural rigidity upon guest removal. Hence, permeability is retained and it is easy to rationalise from the atomic coordinates of the host framework why the material is porous. Porosity "without pores" relates to seemingly non-porous materials that possess void spaces accessible to guest molecules as evidenced by guest uptake experiments; this topic is specifically addressed in the present article in the context of calixarenes that exhibit this remarkable behaviour. The term "virtual porosity" refers to the unfortunate tendency of misrepresenting crystal structures as being porous either by deleting guest molecules from lists of atomic coordinates, or by visualising packing diagrams in the stick or ball-and-stick metaphor. In many of these cases no supporting evidence is presented to demonstrate that the material in question is indeed permeable. Here we wish to re-emphasise that the term should be used in the proper context so as not to detract from the true importance of an apparently extraordinary phenomenon.

Calix[*n*]arenes

One of our main research thrusts involves crystal engineering with calix[*n*]arenes, macrocyclic molecules that are easily functionalised at either the upper or lower rim of the molecular skeleton.[15] Depending on this functionalisation, conformational control over the skeleton can be achieved although the cone conformation is common when the lower rim comprises hydroxyl functionality (Fig. 4). While we use these molecules in many different ways (when functionalised appropriately), we have found the simple calix[4]arenes to display the most remarkable properties in van der Waals crystals. We will therefore limit much of our discussion to five such molecules: calix[4]arene (or *p*-H-calix[4]arene),[16] *p-tert*-butylcalix[4]arene (TBC4),[17–22] *p-tert*-pentylcalix[4]arene,[21] *p-tert*-octylcalix[4]arene,[21] and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14, 20-tetrathiacalix[4]arene[23] (**1–5** respectively, Fig. 4). More recent results by Ananchenko and co-workers,[24–26] that have also focused on this phenomenon (albeit with different calix[4]arenes), will also be discussed in the context of our studies, as will a recent article by Sozzani and co-workers,[27] on methane and carbon dioxide storage in a porous van der Waals crystal.



X = CH_2, R_1 = H, R_2 = H, **1**
X = CH_2, R_1 = H, R_2 = ^{t}Bu, **2**
X = CH_2, R_1 = H, R_2 = ^{t}Pentyl, **3**
X = CH_2, R_1 = H, R_2 = ^{t}Octyl, **4**
X = S, R_1 = Me, R_2 = ^{t}Bu, **5**



1

Fig. 4 Schematic diagrams of calix[4]arenes **1–5**. The typical cone conformation adopted by calix[4]arenes with 'lower rim' OH functionality is also shown for **1**.

Interstitial voids: calix[4]arene (1)

Molecules in the organic solid state are usually closely packed[28] and crystals possessing interstitial lattice voids greater than ~25 Å^3 are generally considered to be rare. Our current interest in crystals that do not always obey the tenets of close-packing originated with a study of simple calix[4]arene solvates.[16] A CSD search reveals that two acetone solvates of **1** are known.[29] One of these solvates (**1a**) is composed of a 1 : 1 host : guest adduct in which the acetone molecule inserts one of its methyl groups into the relatively small calixarene cavity. The packing arrangement is dense but otherwise unremarkable. The second solvate consists of a trigonal 3 : 1 host : guest adduct (**1b**) in which three host molecules form a mutually self-included van der Waals trimer

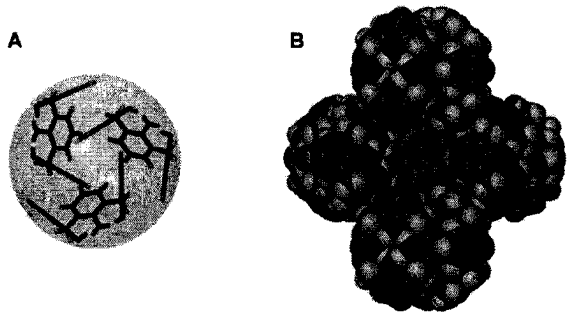


Fig. 5 Two views of the near-spheroidal trimeric arrangement formed by **1** in the solid state ($\mathbf{1}_3$).[16] A) The stick representation shows the self-inclusion of each molecule of **1** within each neighbouring cavity in $\mathbf{1}_3$. B) Space filling representation of the occupation of an interstitial void in the host lattice by CF_3Br. The void (yellow semitransparent surface) is generated by the packing of neighbouring $\mathbf{1}_3$ assemblies and only van der Waals contacts are observable between the host trimers and guest atoms. Colours: gray, C; white, H; red, O; blue, F; brown, Br. (Reproduced with permission from ref. 16. Copyright 2002 AAAS.)

with near-spherical shape (Fig. 5a). Indeed, these trimers pack as a hexagonal close-packed (hcp) arrangement of spheres even though small deviations from perfect spherical geometry exist in the form of protrusions and indentations. Consider the hcp arrangement of only five spheres situated at the vertices of a regular triginal bipyramid: in a lattice composed of perfect spheres this arrangement would form two tetrahedral holes linked by a relatively narrow channel. However, in **1b** the geometrical irregularities of the calixarene trimer result in significant widening of this channel such that the two tetrahedral holes merge to form a single lattice void of approximately 153 $Å^3$. In **1b** the void is occupied by a disordered acetone molecule and a further search of the CSD reveals that the identical host packing mode is adopted by several other simple solvates.

Thermogravimetric analysis (TGA) of **1a** (Fig. 6) shows that two thirds of the acetone molecules can be removed with an onset temperature of *ca.* 70 °C, and that the remaining acetone can only be removed at the surprisingly high temperature of

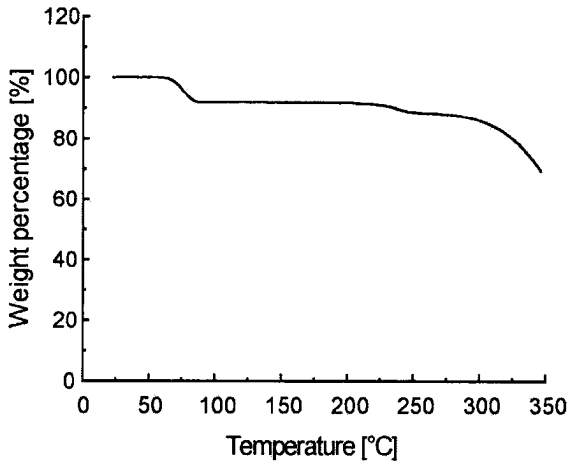


Fig. 6 Thermogram of the acetone solvates of **1** showing loss of two thirds of the acetone guest molecules at *ca.* 70 °C and the remaining third at *ca.* 225 °C.

ca. 225 °C to give the pure apohost phase **1c**. X-ray powder diffraction confirms that loss of two thirds of the acetone from **1a** results in rearrangement of the structure to form **1b**, and that the structure of **1c** is almost identical to that of **1b**. Retention of acetone guest molecules to a temperature of 225 °C implies remarkable stability of the inclusion compound **1b** and similar results were obtained for other solvates with the same host packing mode. We noted from the TGA results that the pure host compound sublimes at *ca.* 270 °C. Since the structure of **1c** had not as yet been determined, we grew crystals of the apohost phase by sublimation of **1** at 270 °C under vacuum. Single-crystal diffraction studies revealed that the structure of **1c** is indeed the same as that of the host lattice of **1b**. Since the crystals were grown under vacuum conditions, the interstitial lattice voids are empty.

The remarkable thermal stability of **1b** and analogous solvates is most likely due to the fact that the host packing arrangement after guest-loss is the same as before. Thus there appears to be no energetic advantage in giving up the guest molecules. We therefore reasoned that, in its trigonal form, **1** should be capable of retaining even highly volatile gas molecules. Although **1** has low solubility in condensed volatile freons and halons, we noted that **1c** could be crystallised from a solution of **1** in toluene (the latter is too large to be accommodated in the lattice void). Consequently, it was possible to incorporate guests such as CF_3Br, C_2F_6 and CF_4 by co-dissolving these gases with **1** in toluene. The presence of freons and halons was observable by single crystal X-ray diffraction studies (*e.g.* Fig. 5b), ^{19}F NMR spectroscopy, and TGA.

It was also possible to effect a solid–solid phase-transformation from the non-hcp acetone solvate to the hcp gas-included phase. This was achieved by heating crushed crystals of the acetone solvate at 50 °C in a steel pressure vessel in the presence of gas. Analysis of the resulting crystalline material confirmed the successful phase transformation and near-stoichiometric incorporation of the freon within the hcp lattice. This method was also used to entrap methane within the lattice voids and thermogravimetric analysis shows stabilisation of this gas in the solid to a temperature of 320 °C above its normal boiling point. Close inspection of the host packing arrangement shows that no pores are present and it is thus easy to rationalise why the guest molecules cannot escape without disassembly of the host lattice, which only occurs at relatively high temperature.

Guest transport in a seemingly nonporous organic solid; *p-tert*-butylcalix[4]arene (TBC4, 2)

TBC4 is well known in supramolecular chemistry not just as a useful host, but also as a key synthetic platform for the synthesis of numerous other functionalised calix[4]arenes.[15] Well over 800 research articles have been reported on **2** and yet it continues to display new, interesting and unique phenomena in the organic solid state. Pure TBC4 forms quite distinct polymorphs, depending on crystallisation conditions.[18,30,31] A high-density polymorph **2a** was grown from a solution of **2** in tetradecane which had been heated for seven hours. The structure of **2a** consists of an efficiently packed (packing

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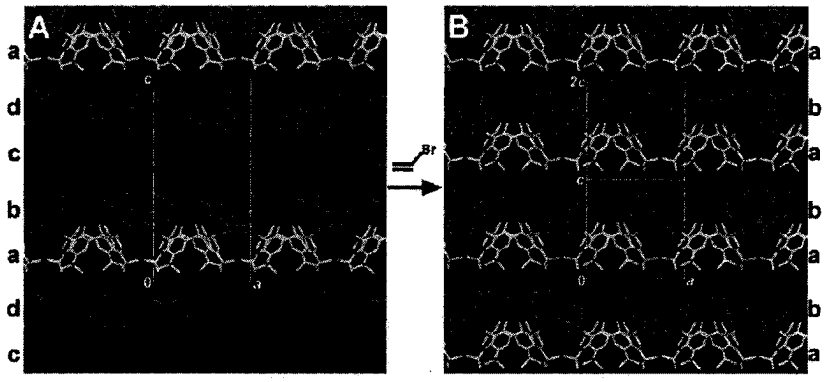


Fig. 7 The single-crystal-to-single-crystal phase transformation observed in a sublimed crystal of **2** after submersion in vinyl bromide.[17] The two forms of the bi-layer arrangement have similar unit cell axes, and the phase transformation results in a change from **ab/cd** to **ab/ab** packing in adjacent bi-layers. (Reproduced with permission from ref. 17. Copyright 2002 AAAS.)

efficiency = 0.67) arrangement of calixarene dimers in which each calixarene inserts one of its *tert*-butyl groups into the cavity of its counterpart.[30]

Sublimation of **2** under vacuum at 280 °C results in the growth of single crystals of a low density polymorph **2b** in which the molecules are arranged to form bi-layers. In this arrangement, the empty cavities belonging to two calixarenes embedded in neighbouring bi-layers overlap partially to form a "skewed capsule" (Fig. 7A)[17] with an approximate free volume of 235 Å^3. This results in a relatively low packing efficiency of 0.59 for the material. Although the two calixarene molecules that primarily form the capsule are not perfectly eclipsed, potential channels leading to the void space are blocked by *tert*-butyl groups of neighbouring molecules. After soaking a single crystal of **2b** in vinyl bromide at −5 °C for 15 minutes, further X-ray diffraction studies show that the material has undergone a single-crystal to single-crystal phase transformation from an **ab/cd** type to **ab/ab** type bi-layer arrangement (Fig. 7B).[17] A remarkable feature of this transformation is that even though neither phase is porous, the cavity of each TBC4 in the **ab/ab** type bi-layer is occupied by a molecule of vinyl bromide, with resulting packing efficiency of 0.64. From this evidence it is clear that cooperative effects between neighbouring TBC4 molecules *must* occur to allow the vinyl bromide to permeate through the seemingly nonporous material, thereby causing adjacent bi-layers to shift by approximately 5.9 Å whilst retaining monocrystallinity. Notably, both phases have closely related unit cell dimensions and it was also shown that both phases can co-exist in the same crystal by halting the diffusion process after approximately 5 minutes. Examination of a 1 : 1 **2** : toluene adduct under controlled heating showed a more remarkable single-crystal to single-crystal phase transformation in which TBC4 layers slide along one another by approximately 9 Å with calixarene molecules rotating by 38° relative to neighbouring bi-layers.

Gas separation and storage with calix[4]arenes: TBC4, 2

In order to probe the energetics of guest uptake by **2b**, nitrobenzene was added to both the sample and reference pans of a differential scanning calorimeter (DSC). After allowing the temperature of the sample chamber to equilibrate, crystals of **2b** were dropped into the sample pan and the heat-flow profile recorded (Fig. 8). The guest-uptake process was expected to yield a large exothermic response in the thermogram. Indeed, the initial trend was exothermic but the exotherm was almost immediately swamped by a large endothermic peak. Although counter-intuitive, these results can now be explained owing to our current understanding of the processes involved.

Upon immersion of the crystals in nitrobenzene, the immediate appearance of bubbles indicated the presence of volatile species (Fig. 9). A single crystal of **2b** was left exposed to the atmosphere for two days, after which X-ray diffraction studies showed significant residual electron density in the TBC4 cavity and that the packing arrangement of the calixarene molecules is no different from that of the freshly sublimed material.[19] Given that the crystals were prepared *in vacuo*, this implies that the material absorbs air into the 235 Å^3 cavities despite the seemingly nonporous nature of the structure. A manometric system was constructed in order to measure sorption isotherms for a range of gases. A systematic study of the sorption of N_2, O_2, and CO_2 introduced to **2b** at an approximate initial pressure of 700 Torr shows that the gases are absorbed to varied extents (Fig. 10A). The sorption

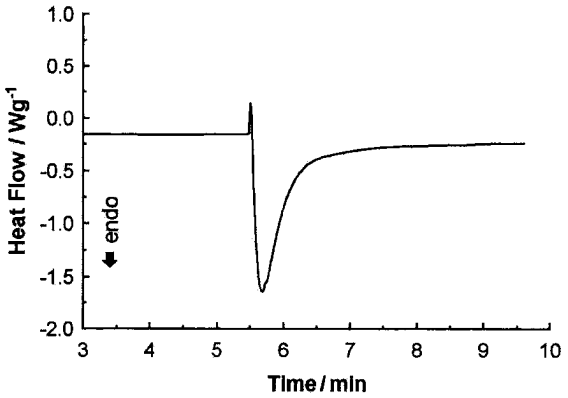


Fig. 8 Isothermal DSC trace for the inclusion of nitrobenzene into the TBC4 lattice. Solutions (30 μl) of nitrobenzene saturated with TBC4 (to minimize contributions from evaporation) were added to both the sample and reference pans and allowed to equilibrate at 23 °C for about 5.5 minutes. Crystals of TBC4 (2.34 mg), also equilibrated at 23 °C, were then added to the sample pan.



Fig. 9 Crystals of sublimed TBC4 are immersed in nitrobenzene. Air bubbles immediately begin to emanate from the crystals as nitrobenzene enters the lattice, expelling the gas.

of CO_2 is more rapid than that of N_2 and O_2, and the CO_2 occupancy in the cavities was found to be 80% at just one atmosphere (atm) of pressure, although this can be increased to 100% at just 3 atm. Disappointingly, no measurable sorption of H_2 gas at pressures reaching 7 atm was observed. However, we noted that the currently employed production process of 95% of the world's H_2 is hampered by impurities such as CH_4, CO, H_2O and, particularly, CO_2. We exposed crystals of **2b** to a 3 : 1 CO_2 :H_2 gas mixture and, using gas chromatography (Fig. 10B), showed that CO_2 can be efficiently removed from such a mixture to afford a hydrogen-rich supernatant gas.

The successful sorption of the above mentioned gases (in sublimed **2**) prompted further examination of such capabilities of the material towards other gases that include methane, hydrogen (at higher pressure) and acetylene.[19–22] It was assumed that, given the 100% occupancy of CO_2 within the TBC4 void, and the approximate dimensions of the gas (5.2 Å long, and 3.4 Å in diameter), such a void space could accommodate at least two molecules of methane based on its near isotropic shape and average diameter of 3.8 Å (Fig. 11). At a similar pressure of ~750 Torr, and at ambient temperature, **2b** was found to absorb methane gas such that 14% of the voids or capsules are occupied by two molecules of methane at 0.54 atm pressure.

Further study of H_2 sorption by sublimed **2** at higher pressure (34.5 atm) showed that under such conditions, the material *was* active and that hydrogen occupancy was

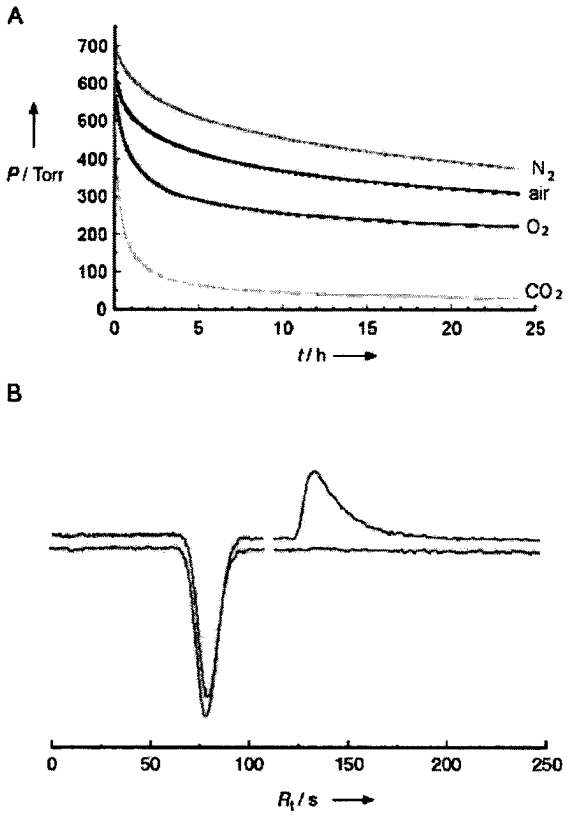


Fig. 10 Diagrams of A) gas sorption isotherms for sublimed **2**, and B) a gas chromatogram showing the purification of a CO_2/H_2 gas mixture using sublimed **2**. In B), the hydrogen peak (in shaded area) is unchanged, whilst the CO_2 peak is completely diminished, thereby demonstrating that sublimed **2** can be used in the purification of H_2 gas mixtures. (Reproduced with permission from ref. 19. Copyright 2004 Wiley.)

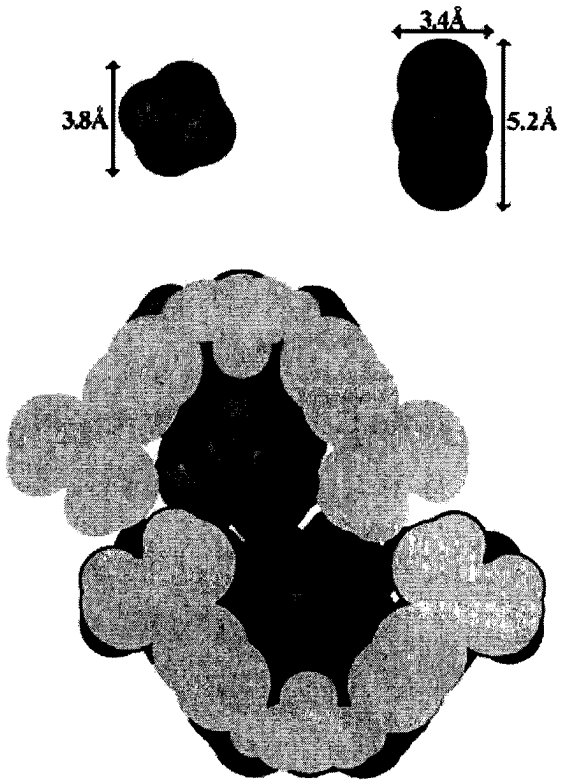


Fig. 11 Figure showing the approximate dimensions of methane (3.8 Å) and carbon dioxide (3.4 × 5.2 Å). A cross-sectioned capsule of sublimed **2** is shown, with two molecules of methane placed in the void space to convey the suitability of the environment for the gas. (Reproduced with permission from ref. 20. Copyright 2005 the Royal Society of Chemistry.)

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0.2 wt%.[21] Although this is slightly disappointing in terms of generating a potential hydrogen storage material based on organic crystals, it does nevertheless demonstrate the principle and encourages future studies in this area.

The absorption of acetylene at an initial pressure ~800 Torr reached equilibrium after 3 h, and an occupancy study (% occupancy *vs* equilibrium pressure) revealed that the uptake of acetylene at STP is ~2% by weight.[22] This value corresponds to the complete filling of the void space in sublimed **2** at ~1 atm pressure, whereas 3 atm are required for the same phenomenon in the case of CO_2. Absorption and desorption isotherms for both CO_2 and acetylene show that at 100% occupancy (at 1 atm for acetylene and 3 atm for CO_2), the process of uptake and release is fast for CO_2 (Fig. 12). For acetylene, a hysteresis loop is observed for this process, indicating that the gas is stabilised in the void space generated in sublimed **2**.

Although it was not possible to observe the acetylene in X-ray diffraction studies, the stabilisation was confirmed when the material (previously subjected to an atmosphere of the gas) was studied using ^{13}C MAS NMR, which showed a characteristic peak for stored acetylene. Most importantly, in the context of guest storage, the calculated density of the stored gas at STP is approximately 0.18 g cm^{-3} which corresponds to stabilising acetylene at 18 MPa (90 times the compression limit for safe storage).

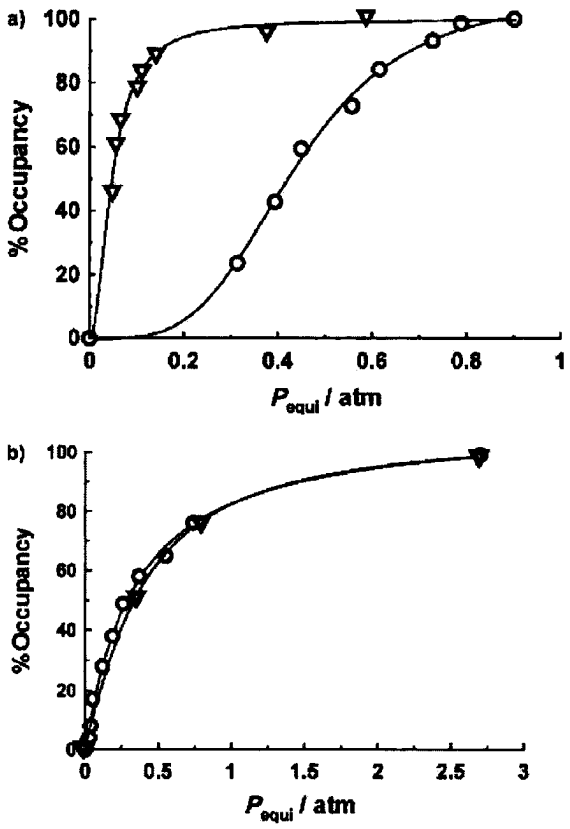


Fig. 12 Adsorption (circles) and desorption (triangles) isotherms of a) acetylene, and b) carbon dioxide. The 100% void occupancy by CO_2 was achieved at 3 atm pressure. (Reproduced with permission from ref. 22. Copyright 2006 Wiley.)

Gas storage by other calix[4]arenes; *p-tert*-pentylcalix[4]arene (3) and *p-tert*-octylcalix[4]arene (4)

Whilst studying the higher pressure absorption of H_2 by **2b**, sublimed samples of **3** and **4** were also examined for similar behaviour.[21] Sublimed crystals of **3** and **4** were studied using single crystal X-ray diffraction, which revealed structures very different to the low density polymorph found for **2**. Although the calixarene molecules **3** and **4** were not found to form guest-free capsules with a large internal void space, the molecular cavities and lattice structures were found to contain discrete void space volumes of ~110 and ~82.5 $Å^3$ respectively (Fig. 13). For **3**, the molecular cavity and interstitial lattice void spaces are connected, while for **4** the "free volume" is composed of two separate void spaces (~23.5 $Å^3$ from the molecular cavity and 59 $Å^3$ from the interstitial lattice void). These structures share a similarity with that of **2b** in that they are seemingly nonporous, but permeable.

The hydrogen storage capacity observed for these materials was similar to that of **2** (~0.2 wt%), but also hints at the potential for the use of organic materials for hydrogen sorption.

Water transport through a nonporous hydrophobic crystal: 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetrathiacalix[4]arene, 5

In keeping with our interest in the transport of guest molecules in single crystals, we extended our studies to the diffusion of water in seemingly nonporous hydrophobic single crystals.[23] Sublimation of **5** results in the formation of two types of single crystal, both of which were studied using X-ray diffraction,

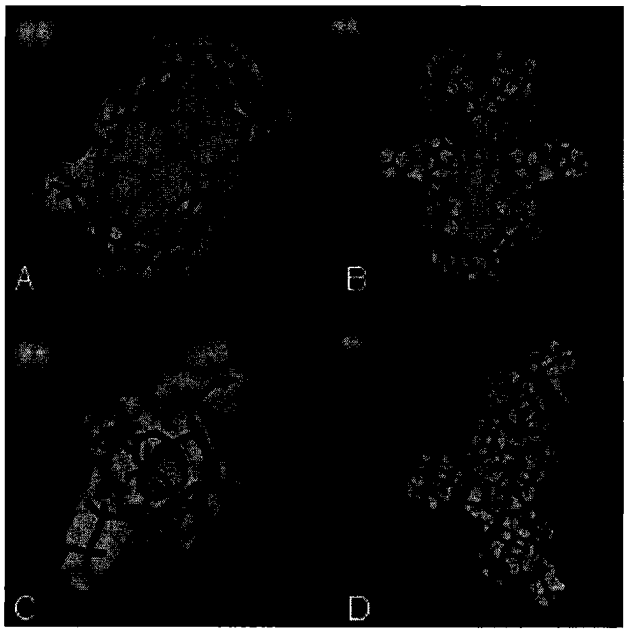


Fig. 13 Visualisations of the free void space present in the crystal structures of sublimed, **2** (A), **3** (B), and **4** (C and D). In order to give an idea of scale relative to each figure, a hypothetical H_2 molecule has been placed in the upper left hand corner of each. (Reproduced with permission from ref. 21. Copyright 2005 the Royal Society of Chemistry.)

and were found to be polymorphs of one another (type I and II), only one of which is of interest in the context of this section (type II). The type II polymorph contains two crystallographically unique molecules of **5** (**5a** and **5b**) which are in the 1,3-alternate conformation owing to the lower rim O–Me substitution (that disrupts the typical cone stabilising hydrogen-bonding motif found in lower rim hydroxyl analogues such as **1–4**). The result of this conformational distortion is that each calixarene possesses two small clefts, each bounded by two distal *tert*-butyl groups and two distal methoxy groups. Owing to crystallographic symmetry, **5a** has two unique clefts, one of which is significantly larger than the other. On the other hand, **5b** has two crystallographically equivalent clefts of equal size. Further expansion of the structure reveals that **5a** and **5b** stack in columns such that the clefts are entirely isolated

Upon immersing a previously studied type II crystal of **5** in water for 8 h, re-collection of X-ray diffraction data and subsequent structural solution reveals residual electron density in the larger of the two clefts of **5a**, and in both clefts of **5b**. The former was modelled with a site occupancy of one while the latter were modelled as being 50 : 50 disordered over the two equivalent sites. The presence of H_2O (in a 1 : 1 H_2O : **5** ratio) was confirmed by IR and TGA analysis.

An interesting point to note is that even though the structure does not appear to be porous, water molecules travel through the crystal and become lodged in the molecular clefts generated by the conformational distortion of **5**. Although it is difficult to arrive at a clear conclusion as to how the water molecules travel through the crystal, it seems plausible that the *p-tert*-butyl groups of **5** may rotate cooperatively to allow the guest transport to occur. This result suggests that classical views of water diffusion processes—through channels large enough to accommodate a water molecule (based on van der Waals diameter)—may be unsuitable at this scale, that crystals are not as impervious and rigid as expected, or that van der Waals forces can act more as accommodating factors rather than rigid barriers.

Guest transport and gas storage in other calix[4]arenes and molecular crystals (respectively)

Ananchenko and co-workers have recently focused their attention on the preparation of a new type of van der Waals dimeric capsule based on functionalised 'upper rim' calix[4]-arenes.[24–26] In their studies, the molecules in the capsule arrangement bear resemblance to the skewed capsule formed by sublimation of **2**, and solvent loss from the interior of the capsules within single crystals is observed (with preservation of monocrystallinity). From this observation, crystals of the capsules placed in a hot (70 °C) solution of dibenzyl ketone (DBK) underwent exchange of DBK for chloroform molecules on the interior of the capsules within single crystals, as monitored by X-ray diffraction and other techniques (Fig. 14).[24] These van der Waals capsules can be used for the phototransformation of stilbene and can be assembled with different alkanoyl functionality at the upper rim.[25–26]

It should be noted that Sozzani and co-workers reported methane and carbon dioxide storage in a conventionally porous van der Waals crystal.[27] The authors show by single-crystal

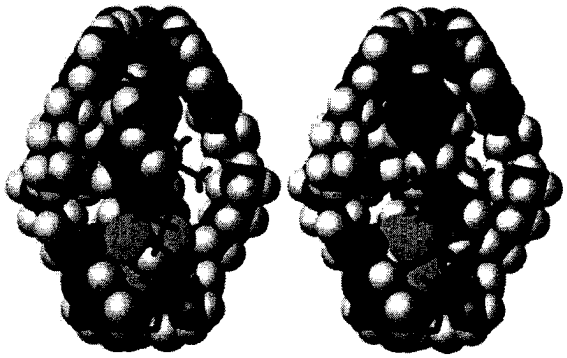


Fig. 14 Illustrations of van der Waals dimeric capsules formed from *p*-hexanoylcalix[4]arene. These views show capsules in which chloroform molecules have left the interior of the assembly, and have been replaced by dibenzylketone. (Reproduced with permission from ref. 24. Copyright 2006 Wiley.)

X-ray diffraction single crystals that molecular crystals of tris-*o*-phenylenedioxycyclotriphosphazene (TPP) contain empty hexagonal pores. The structure possesses significant free void space in the form of nanochannels (with a minimum diameter of 4.6 Å) which are suitable for gas sorption studies. The uptake of Ar, N_2, O_2, H_2, CH_4, and CO_2 was investigated, and the material was found to selectively absorb methane or carbon dioxide. Methane storage was reached up to 0.7 mol of methane per mol of TPP. Indeed, at 195 K and STP, methane uptake was 2.4 and 0.6 wt% respectively. Carbon dioxide uptake was found to be much higher (12 wt% at STP), and ^{13}C MAS NMR of the material exposed to either gas showed characteristic signals for each when stored in the sample. Examination of the NMR signal shifts was indicative of the environment experienced by the absorbed gas and allowed the authors to precisely define the interactions between the guest and the inner surface of the host.

Conclusions

Significant advances have been made towards developing materials that can store or transport guests to varied extents. In the combined areas of crystal engineering and MOF development, this has been realised predominantly by Yaghi and co-workers, but more recently by Schröder and co-workers in their recent work where they show a ~6 wt% H_2 storage at low temperature (77 K).[9–11] Eddaoudi and co-workers are taking the dimensions of these materials to new limits to afford materials with concomitant potential.[12] Although this storage limit is reaching the current target outlined by the DOE (at low temperature and pressures below 80 bar), the temperature issue remains a problem, and one that must be solved with these storage materials to render them suitable candidates for use in the transport industry.

With regard to calix[*n*]arenes, these simple materials show remarkable properties in their ability to cooperate within a single crystal to facilitate guest transport.[17] One of the most surprising examples of this is the notable transport of water molecules through a hydrophobic crystal.[23] Conventional wisdom dictates that this would not be plausible, yet the process is relatively rapid and must therefore be cooperative.

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Recent work by ourselves[32,33] and others[24] in this field further demonstrates the concept, and our work on the storage of gases within cavities in seemingly non-porous TBC4 crystals provide further and continuing evidence for the phenomenon.

Acknowledgements

Owing to space restrictions we have not mentioned many contributions that are related to the topic of this tutorial review. These omissions do not serve as criticism of the work of others. Rather, we have attempted to provide pertinent and concise examples from our own work and these are placed in context by referring the reader to a small selection of reviews that highlight certain features of this fascinating area of research. We would like to thank our colleagues (past and present) for their contributions to this work, with particular thanks to Dr Agoston Jerga.

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Frustrated Organic Solids Display Unexpected Gas Sorption

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The search for new materials that have unique properties, such as gas storage and/or separation, is attracting significant attention due to the impending petroleum shortage.[1] Given this fact, physical adsorption of gases on carbon nanotubes (CNTs),[2a] zeolites,[2b-d] activated carbons,[2c] pillared clays,[2c,d] porous metal−organic or covalent organic frameworks (MOFs or COFs, respectively),[2e-i] and "nonporous" organic solids (calixarenes, for example) is currently an active area of research.[2j-p] Of these materials, those with large surface areas, such as MOFs, CNTs, and activated carbons, have attracted much interest, although limited success has been achieved in storing and separating various gases under ambient conditions. Furthermore, in order to activate these materials for gas storage, the guests or solvent molecules housed by the respective molecular frameworks must be completely removed from the host lattice to afford a porous network with maximized sorptive capability. Notably, these "activation" procedures do not (to our knowledge) involve any kind of solid−solid phase transformations.

Solid−solid phase transformations are rather common, and much of the contemporary polymorphism research into pharmaceuticals and other organic materials typically relates to such phase transitions. The term "frustrated" is frequently used with regard to magnetism.[3] Thus organic solids cannot be frustrated with respect to this definition of magnetism. However, in the process of going from a solvated to desolvated form of the "bowl-shaped" host molecule *p-tert*-butylcalix[5]arene (TBC5, **1**, Figure 1a),[4] we have discovered a new type of material which we believe involves a frustration of the solvate lattice as it moves toward the thermodynamically stable desolvated state.[5] The frustration arises from a reduction in the solvent content within the structure during the desolvation process and results in the formation of a porous material that rapidly sorbs gases under ambient conditions. Here we present two crystal structures of TBC5 (a toluene solvate and a sublimed/desolvated form) that are both nonporous and that represent two inactive phases that are effectively "dead" with respect to gas sorption. We also show that a porous intermediate phase with partial solvent content, formed through a controlled desolvation process, unexpectedly and rapidly sorbs many gases to varied extents.

Recrystallization of pure TBC5 from toluene results in the formation of large single crystals that are suitable for X-ray diffraction studies.[5] Structural solution reveals that the asymmetric unit is comprised of two independent molecules of TBC5 (Figure 1b, types I and II for clarity), two *endo*-cavity toluene molecules (one in each host), and two disordered *exo*-cavity toluene molecules.[5] Symmetry expansion around the cavity of each TBC5 shows the calixarenes to form two distinctly different structural motifs: two type I TBC5s form a near dimeric capsule arrangement, while two type II TBC5s form a partially overlapped dimer (Figure 1b). In both motifs, the *endo*-cavity toluene molecules interact with the aromatic rings of the hosts through a total of five crystallographically unique CH···π interactions, the CH···aryl centroid

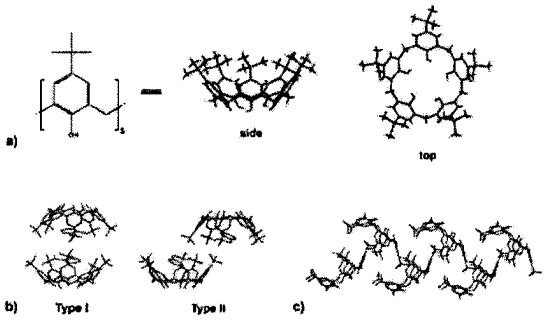


Figure 1. (a) The structure and "bowl-shape" of *p-tert*-butylcalix[5]arene. (b) The two types of TBC5 found in the toluene solvate and their respective "near dimeric capsule" and "partially overlapped dimer" arrangements observed upon symmetry expansion. The toluene guest molecules are shown in the centers of the TBC5 hosts. Note that the type I and II arrangements of TBC5 are shown in orientations irrespective to one another within the actual crystal structure; these views are solely for visualization of the behavior of each independent calixarene from the asymmetric unit. (c) The "self-including" chain found in the sublimed form of TBC5. Hydrogen atoms have been omitted, and disordered *tert*-butyl groups of TBC5 molecules (in both structures) are only shown in one position for clarity in (b) and (c). Atom color code: carbon = blue, oxygen = red, hydrogen = gray.

distances for which all lie in the range of 2.571−2.893 Å.[5] Sublimation of pure TBC5 results in the formation of single crystals that are suitable for X-ray diffraction studies.[5] The structural solution shows that the asymmetric unit is comprised of one-half of a TBC5 molecule, and symmetry expansion shows the molecules to pack in a "self-including" manner to form infinite chains (Figure 1c).

It should be noted that sublimation of TBC5 is troublesome and that much of the starting material is lost due to degradation at high temperature (350 °C under vacuum). Although this is the case, the sublimed form can easily be isolated in bulk by heating a toluene solvate sample to 160 °C overnight, with sample purity/conversion being confirmed by X-ray powder diffraction studies (XRPD).[5] Examination of both the toluene solvate and sublimed TBC5 structures through space filling representation quickly reveals that both are completely nonporous, as shown in Figure 2.[5] Furthermore, when both the solvated and desolvated forms were studied for sorptive capability, both were dead for sorption of O_2, N_2, CH_4, CO_2, and acetylene (Figure 2, left- and right-hand columns).[5]

Careful heating of the TBC5 toluene solvate at 120 °C for 8 h resulted in the formation of material with a partial solvent content (confirmed by NMR spectroscopy) that is consistent with a toluene:TBC5 ratio of 1:23 (compared to 2:1 for the pure solvate form).[5] Unfortunately, this technique afforded opaque material devoid of single crystallinity, thereby precluding the use of single-crystal X-ray diffraction for structural identification purposes. Despite this, XRPD afforded a pattern which has some peaks that are inconsistent with either the toluene solvate or desolvated forms (Figure 2).[5] Gas sorption studies with this material showed remarkably rapid sorptive capability toward CH_4, CO_2, and acetylene, although it is not highly active for H_2 sorption.[5] In comparison with *p-tert*-butylcalix[4]arene,

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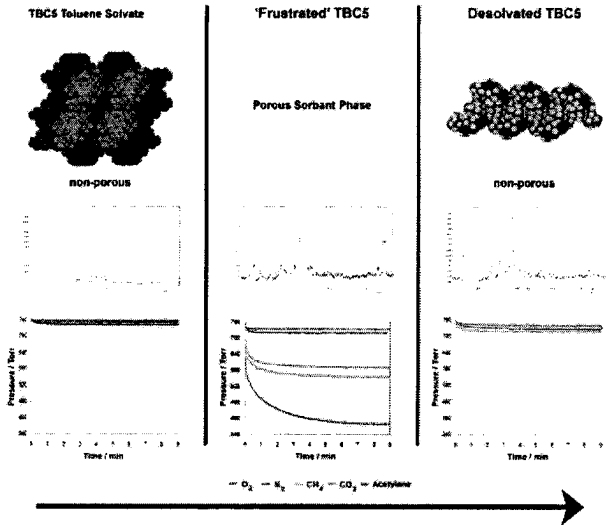


Figure 2. Diagram showing the transition from the nonporous (and inactive) TBC5 toluene solvate, through a porous and rapidly sorbant phase, to the desolvated/sublimed form of TBC5, which is also effectively inactive for sorptive purposes. X-ray powder diffraction patterns are shown for each form, as are the gas sorption curves for O_2, N_2, CH_4, CO_2, and acetylene. The nonporous nature of the toluene solvate is stressed by space filling representation relative to Figure 1b; type I and II TBC5 molecules are shown in green and blue, respectively, for clarity. Similar depiction of the desolvated form also demonstrates complete nonporosity.[5]

a "seemingly nonporous" material, acetylene sorption with this active form of TBC5 is ~75% as efficient.[2p] However, the rate of acetylene sorption is 25 times faster than that of TBC4. This relationship is also generally true when comparing methane and carbon dioxide sorption between the two calixarenes; that is, the amount of gas sorbed is consistently less for this form of TBC5, but the rate of sorption is far greater. Notably, the powder patterns of the frustrated and desolvated phases have some similarities (Figure 2). This suggests that the frustrated phase may be partially composed of the desolvated form while also containing a proportion of active material.

Solid-state ^{13}C NMR spectroscopy performed on samples subjected to 1 atm pressure of CH_4, CO_2, or acetylene gave further proof of the porous nature of the intermediate phase.[5] Methane and carbon dioxide were not retained by the material when removed from the corresponding atmospheres, and their respective spectra resembled that of purely frustrated TBC5. Acetylene *was* retained by frustrated TBC5 and gave a characteristic signal at ~71 ppm, which is close to that of the gas adsorbed in a porous zeolite framework.[5,6] These cases are markedly different to those concerning the sorption of these gases in seemingly nonporous TBC4, the studies for which show dramatically different guest shifts in the solid-state NMR spectra. In particular, the lack of gas retention (CH_4 and CO_2) and the chemical shift of the sorbed acetylene signal all suggest that the frustrated TBC5 phase *is* porous.

Further heating of the active frustrated phase at 160 °C results in conversion to the desolvated form (identifiable by XRPD) with a concomitant halt in sorption for the gases studied here. This phase conversion suggests that perhaps residual toluene molecules hold the extended structure in a frustrated arrangement that is incapable of full collapse into the self-including chains of the desolvated form.



Figure 3. A proposed method for collapse of the "frustrated" organic solid: (1) final evaporation of the last remaining toluene molecules, possibly retained due to strong intermolecular CH···π interactions,[5] results in an opening for structural collapse; (2) the TBC5 molecules can collapse into the fully evacuated cavities, possibly forming a cascade process from which the desolvated "self-including" chains result.

Removal of these residual (and strongly bound[5]) solvent molecules may facilitate such a collapse, which in turn may be followed by a cascade process that results in a complete structural rearrangement to the desolvated form (Figure 3).

Clearly the active frustrated region for TBC5 represents an entire range of partial desolvates that need to be isolated, identified, and studied for gas sorption properties. The fact that the XRPD of one active phase (reported here) contains peaks for the desolvated form suggests that perhaps only a percentage of the material studied is indeed active for sorption. If this is the case, and the percentage is small, it is plausible that greatly enhanced gas sorption may be found for a pure sample of the active form.

Acknowledgment. This work was supported by the National Science Foundation.

Supporting Information Available: Materials and experimental methods, solid-state ^{13}C NMR spectra, crystal data, full structural descriptions for the crystal structures of TBC5·toluene and sublimed TBC5, description of CH···π interactions, and additional views of the nonporous nature of both crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Comparison of porous and nonporous materials for methane storage†‡§

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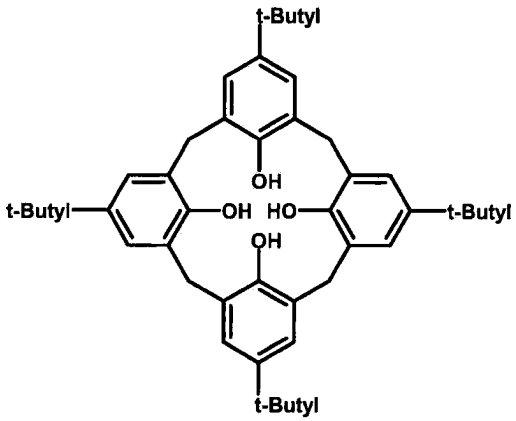
Sublimed, low-density *p-tert*-butylcalix[4]arene absorbs methane more readily at room temperature and 1 atm pressure than do either single wall carbon nanotubes (SWNT) or a comparative porous metal–organic framework (MOF-1).

Materials which store a high gravimetric density of hydrogen or methane are crucial for the development of alternatives to oil-based fuels. Target goals of 7 wt% hydrogen and 35 wt% methane have been set.[1] Several methods have been proposed for on-board hydrogen storage[2] based on compressed gas cylinders, chemisorption, and physical adsorption on porous and nonporous materials, but no ideal method has emerged. Parallel work on methane is being pursued.[3] In this regard physical adsorption of methane on porous materials with large surface area such as metal-organic frameworks and carbon nanotubes has attracted much interest, although limited success has been achieved in storing methane under ambient conditions. In our laboratory, we have focused on 'nonporous' materials for gas storage and separation.[4] In this communication we compare the methane uptake of nonporous, low-density *p-tert*-butylcalix[4]arene, **1**, with a porous metal–organic framework (MOF-1), **2**, and with single walled carbon nanotubes (SWNT), **3**, at room temperature and 1 atm pressure (Scheme 1).

The low density polymorph of **1** obtained at 280 °C under reduced pressure shows that the calixarene molecules are arranged in an up–down fashion to form skewed capsules, each with an estimated free volume of 235 Å^3 (Fig. 1). We have previously shown that the low-density polymorph of **1** absorbs N_2, O_2, CO and CO_2 under ambient conditions.[5] This polymorph has also been used to separate the hydrogen from a mixture of hydrogen and carbon dioxide.[5] Further, immersion of crystals of the low-density polymorph in liquid vinyl bromide results in a single-crystal to single-crystal phase transformation in which vinyl bromide diffuses completely through the crystal, filling each calixarene cavity and effecting the transformation from the monoclinic crystal system to the tetragonal one.[6]

In order to compare the gas sorption properties of **1–3** we prepared **2** using the literature procedure.[7] Heating a diethylformamide solution containing 1,4-benzenedicarboxylate and zinc nitrate hexahydrate for 24 h afforded the crystalline metal–organic framework **2**.[8] The crystal structure of **2** shows that the oxide-centered Zn_4O tetrahedron is edge-bridged by six carboxylates to give an octahedral arrangement, which reticulates into a three dimensional cubic network after removal of the solvent guests (Fig. 1). SWNT's were obtained from Carbon Nanotechnologies Inc. This material was converted into a gel in benzene and then freeze-dried to remove the benzene to give guest-free **3**. The first reports on gas sorption by MOF's claimed 4.5 wt% of H_2 (77 K and pressure of 1 atm) and 135 cm^3 (STP)/cm^3 of CH_4 (room temperature and 34 atm pressure). These sorption values have since been revised to 1.5 wt% of H_2 at same conditions. There have also been reports that SWNT's store 8.0 wt% of H_2 (77 K and pressure of 1 atm) but recent studies have revised the value down to 1 wt%.[9]

Sorption isotherms were recorded volumetrically on **1–3** using 80 mg of sample in each case. The sample of **1** (or **2** or **3**) was placed in the pressure chamber (V = 10.9 cm^3), and the chamber was evacuated for two hours to remove any trace of gas trapped in the host lattice. Fig. 2 presents the absorption isotherms of **1–3** in which methane was introduced with an initial pressure of 1 atm. The pressure in the sample chamber decreased with time and equilibrium was established after 4 h for the sample of **1**. At this pressure the molar ratio of the calixarene to methane was calculated to be 0.14 : 1. This result



Scheme 1

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† Dedicated to Professor George Gokel on the occasion of his 60th birthday.

‡ The HTML version of this article has been enhanced with colour images.

§ Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b610321a

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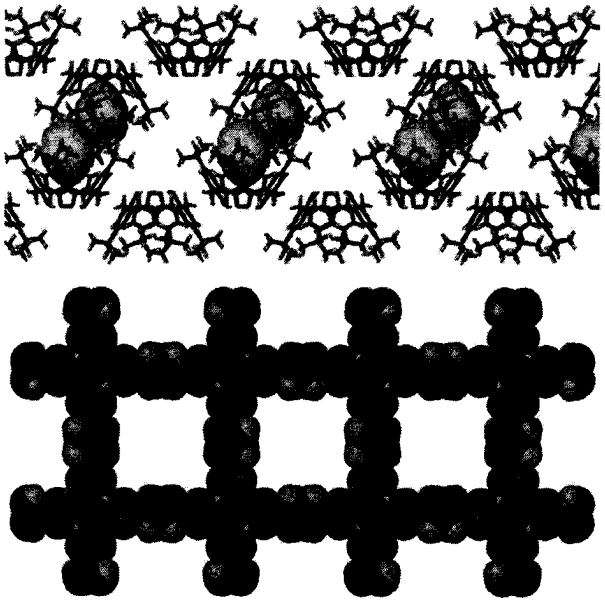


Fig. 1 X-Seed[13] representation of a bilayer packing of calixarene molecules in **1** (Top). The surface was generated using Connolly Molecular Surface.[14] Space fill representation of porous metal–organic frame work for clarity solvent molecules are removed (Bottom).

indicates 28% of the dimeric capsules are filled with methane at 1 atm pressure, a value which agrees well with that previously reported.[10] It has been shown that **1** is capable of accommodating two methane molecules within each dimeric capsule.[10]

Samples of **2** and **3** were activated by removing the guest molecules from the host lattice under reduced pressure with heating (sample **2** and **3** were evacuated at 150 °C and 60 °C for over 24 h under vacuum, respectively). The X-ray powder diffraction patterns of sample **2** before and after removing the solvent are identical, indicating that the MOF-1 framework is stable upon desolvation (see supplementary information, Fig. S1, S2 and S3). Methane was introduced into the chamber containing samples **2** and, subsequently, **3** with an initial

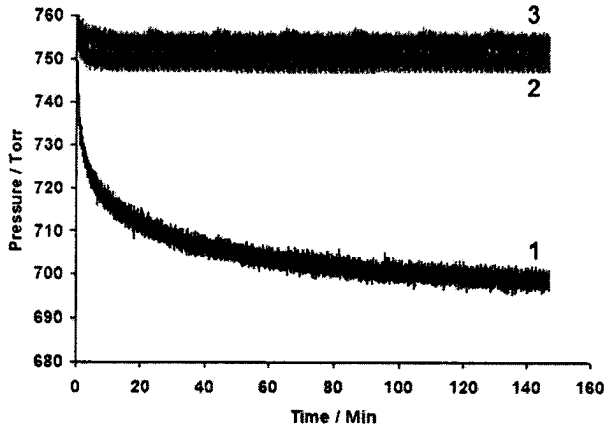


Fig. 2 Methane isotherms of samples **1–3** at room temperature.

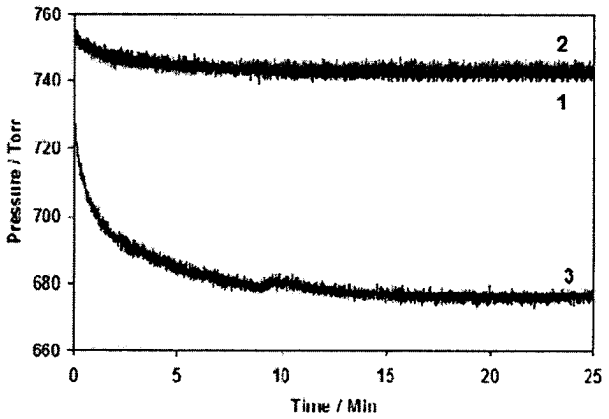


Fig. 3 Low temperature isotherms of methane in samples **1–3**.

pressure of 1 atm. For **2** and for **3**, no significant uptake of methane was observed (Fig. 2). In order to further investigate samples **1**, **2**, and **3** with regard to methane sorption, the sample chamber was cooled to −70 °C and methane was again introduced at a pressure of 1 atm. Under these conditions, methane uptake by samples **1** and **2** was marginal, but significant amount of methane uptake was observed in sample **3** (Fig. 3).

At room temperature the uptake of methane by nonporous material **1** is high compared to that of porous metal-organic framework MOF-1 (surface area ~4000 $m^2 g^{-1}$) and SWNT's (~2000 $m^2 g^{-1}$). It appears that large cavities with high surface area are not required to enhance the storage capacity and, In fact, the larger cavities lead to a decrease in the strength of the interaction between the adsorbent surface and the methane.[11]

Unlike conventional porous materials such as **2** and **3**, which uptake and release guest molecules, no channels or cavities are found in **1**. However, gas molecules diffuse through the seemingly nonporous lattice without disrupting the arrangement of the host molecules. As described earlier, at room temperature the aromatic and hydroxyl groups at the lower rim of the calixarene appear to be rigid, while the *tert*-butyl groups of the upper rim may rotate about the C(ar)–C(sp^3) bond, as evidenced by crystallographic disorder. We speculate that the cooperative rotation of the *tert*-butyl groups allows the gas molecules in **1** to diffuse through the crystals. The 'nonporous' nature of **1** was further supported by measuring the dinitrogen adsorption isotherms at 77 K and 1 atm pressure. The low BET surface area of 15 $m^2 g^{-1}$ for **1** indicates that **1** is nonporous at 77 K (see supplementary information, Fig. S4). X-Ray crystallographic results on the structure of **1** at 295 K show that all *tert*-butyl groups are disordered, while at 195 K only one *tert*-butyl group is disordered. Thus, both the X-ray crystallographic work and BET measurements are consistent with **1** being nonporous at 77 K, and with the porosity of **1** at room temperature being linked to the motion of the *tert*-butyl groups which guard the cavities.

Several attempts to collect single crystal X-ray diffraction data on **1** with methane revealed only diffuse electron density.

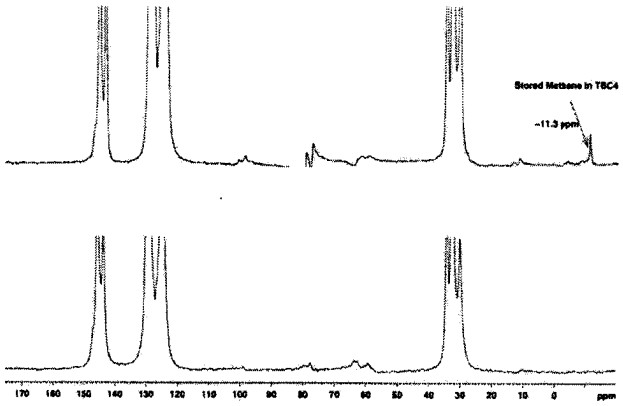


Fig. 4 ^{13}C MAS NMR of sample **1** (Bottom). The sharp signal at −11.3 ppm indicates the stored methane in **1** (Top).

However, solid-state NMR techniques¶ proved effective in the detection of the absorbed methane in calixarene cavity **1** under ambient conditions. Fig. 4 shows a comparison of the solid-state NMR spectra of pure host and host with absorbed methane. The ^{13}C resonance of the guest methane is found at −11.3 ppm. A few reports of methane stored in zeolites and porous cyclotriophosphazene derivatives have appeared in the literature, with ^{13}C chemical shifts ranging from −5 to −9 ppm. The exceptional upfield shift in nonporous **1** (−11.3 ppm) may be due to stronger binding of the methane in **1** compared to the previous reports for binding in porous materials.[12]

The results presented herein emphasize three important points. First, large pores do not necessarily lead to sorption of gases such as methane. The tight fit imposed by calixarene **1** provides van der Waals stabilization for methane, even at room temperature. Second, nonporous organic solid **1** exhibits a thermal window for methane sorption. At −70 °C, the thermal motion of the host molecules (most important for the *tert*-butyl groups guarding the entrance to the cavities) is reduced and the crystals are nonporous with regard to methane sorption. Third, while the details of the mechanism for the evolution of porosity in seemingly nonporous organic solids such as **1** is not yet known, it is clear that any such mechanism must involve communication among host molecules in the crystalline lattice, leading to transport of small molecules from one cavity to another and, ultimately, throughout the crystalline solid.[4,5,10,15]

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¶ Solid state NMR was done on a Bruker DRX300 wide bore spectrometer equipped with a 7 mm CP-MAS probe. The operating frequencies are 300.13213 (^1H) and 75.47359 (^{13}C). About 200 mg of finely ground powder was used to fully pack a 7 mm Zirconia rotor. For all the samples proton decoupled ^{13}C CP-MAS (Cross Polarization1 with Magic Angle Spinning) was performed at spinning rate of 5 KHz. TOSS (Total Suppression of Sidebands) was applied to remove the sidebands caused by spinning. The total time for data collection ranges from a few hours to overnight. The spectra were collected with 2K data points with a 34 ms acquisition time and 2 s of relaxation delay. Data was zero-filled to 8 K and a 5 Hz line-broadening was also applied. The external chemical shift reference was CO carbon of glycine at 176.03 PPM.

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Preface

Current research in chemistry and materials science is now vigorously pushing the boundaries of the components studied firmly into the multi-nanometer length scale. In terms of traditional "molecules" a nanometer (10^{-9} m) is relatively large. As a result, it is only relatively recent advances in analytical instrumentation capable of delivering a molecular-level understanding of structure and properties in this kind of size regime that have allowed access to and the study of such large molecules and assemblies. The key interest in multi-nanometer-scale structures (nanostructures) is the fact that their size allows them to exhibit a significant degree of functionality and complexity – complexity that is mirrored in biological systems such as enzymes and polynucleotides, Nature's own nanostructures. However, this functionality is compressed into a space that is very small on the human scale, sparking interest in fields such as molecular computing and molecular devices. Thus one of the great opening frontiers in molecular sciences is the upward synthesis, understanding of structure and application of molecules and molecular concepts into the nanoscale.

In compiling this book we have sought to bring together chapters from leading experts working on the cutting edge of this revolution on the nanoscale. Each chapter is a self-contained illustration of the way in which the nanoscale view is influencing current thinking and research across the molecular sciences. The focus is on the "organic" (loosely applied) since it is generally carbon-based building blocks that are the most versatile molecular components that can be induced to link into nanoscale structures. As chapters by Mohammed Eddaoudi and Lee Cronin show, however, hybrid organic–inorganic materials and well-defined inorganic building blocks as just as capable of assembling into well-defined and well-characterized discrete and polymeric nanostructures.

Crucial to the whole field of nanochemistry is the cross-fertilization between researchers from different disciplines that are approaching related structures from very different perspectives. It is with this aspect in mind that we have deliberately mixed together contributions from the solid-state materials community as in Dario Braga's perspective on the crystal engineering or organic nanostructures and from experts in discrete molecular assemblies such as Dimitry Rudkevich, Kay Severin, Thomas Rauchfuss and Bruce Gibb. Of course, nanostructures are not

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always so well defined and so these aspects are balanced nicely by David Smith's chapter on gel-phase materials – in some respects a "halfway house" between solution-phase and solid-state assemblies. We also felt it of key importance to illustrate ways to use small-scale molecular concepts in order to "synthesize-up" nanostructures. Chapters by Paul Beer, Steve Loeb and Len MacGillivray provide very different perspectives on templation and assembly in the field, while Makoto Fujita and Mike Ward deal with larger-scale self-assembly. Finally, all-important functional nanostructured devices are illustrated by Vincenzo Balzani's chapter.

Although a book of this size can only be illustrative of such a burgeoning field, it is our sincere hope that the juxtaposition of these different perspectives and systems in one place will stimulate and contribute to the ongoing process of cross-fertilization that is driving this fascinating and emerging area of molecular science. It has certainly been a fascinating and pleasurable experience to work on this project and we thank all of the authors wholeheartedly for their enthusiastic contributions to this project. We are grateful also to Manfred Köhl and Steffen Pauly at Wiley-VCH for their belief in the book and for their help in making it a reality. As this book went to press we learned of the sad and untimely death of Dimitry Rudkevich. We would like to dedicate this book to his memory and legacy to science.

December 2007

Jonathan W. Steed, Durham, UK
Jerry L. Atwood, Columbia, MO, USA

INCLUSION COMPOUNDS

VOLUME 5

INORGANIC AND PHYSICAL ASPECTS OF INCLUSION

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Preface

The principal aim of *Inclusion Compounds*, published in 1984 in three volumes, was to provide a comprehensive and up-to-date survey of the field of Inclusion Chemistry. However, as a natural consequence of rapid growth in this exciting area, much important new work has appeared in the past six years. This subject was highlighted by the award of the Nobel Prize for Chemistry to D. J. Cram, J.-M. Lehn, and C. J. Pedersen in 1987. It is, therefore, not difficult to understand the enthusiasm with which the editors planned the present two volumes. In order to maintain in-depth coverage, the policy of inviting leading international authorities to write on their particular fields of interest has been retained. It may be noted that certain subjects which previously received, at most, scant coverage have now developed to such an extent as to demand separate chapters, as evidenced by the examples of the diol hosts, calixarenes, clathrasils, cyclidenes, and solid state NMR spectroscopy. Having again been able to secure eminent contributors, the editors are confident that the present volumes are of the same high standard as that of the previous volumes which have been well received and widely cited.

We have pleasure in thanking the staff of Oxford University Press for their efficient production of Volumes 4 and 5.

Tuscaloosa, Lancaster,
and Glasgow
May 1991

J. L. A.
J. E. D. D.
D. D. M.

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INCLUSION PHENOMENA AND MOLECULAR RECOGNITION

Edited by

Jerry L. Atwood

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PREFACE

The Fifth International Symposium on Inclusion Phenomena and Molecular Recognition was held September 18-23, 1988 at Orange Beach, Alabama. This followed previous very successful symposia in Warsaw (1980), Parma (1982), Tokyo (1984), and Lancaster (1986). The overall tone of the event at Orange Beach was expressed elegantly by Fraser Stoddart at the close of his lecture:

"At a meeting like this, I think we should be asking ourselves more openly where we have come from and where we are going to. I am certainly willing to put my head on the block. Chemistry, as I see it, is entering a golden age of opportunity and those of us here who respond to the multidisciplinary challenge of the subject will perhaps start the movement to reunite the chemical sciences for the first time in more than a century. Given the recognition granted through Charles Pedersen, Donald Cram, and Jean-Marie Lehn to our field from Stockholm last year, there are many here who are surely poised – if they have not already done so – to capture the academic high ground and intellectual leadership of our subject. And what is more – it will be on the back of our fundamental science that many of the exciting technological advances of the twenty-first century will be forged."

In order to capture the flavor and excitement of the symposium, herein we present reviews by thirty-eight of the invited lecturers.

The program was shaped by the Program Committee: Jerry L. Atwood, Richard A. Bartsch, George W. Gokel, Fredric M. Menger, Yukito Murakami, and Galen D. Stucky. The local arrangements were overseen by Jerry L. Atwood, Duane C. Hrncir, William E. Hunter, Gregory H. Robinson, and Robin D. Rogers. The accompanying persons program was set up by Tracey M. Atwood. Financial support was generously provided by:

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and The University of Alabama.

General guidance for the symposium was in the hands of the International Organizing Committee: G. D. Andreetti, J. L. Atwood, R. Breslow, J. E. D. Davies, Yu. A. Dyadin, T. Iwamoto, J.-M. Lehn, J. Lipkowski, D. D. MacNicol, W. Saenger, J. Szejtli, F. Vögtle, and R. L. Wife.

Special thanks go to my Assistant Editor for this volume, Dr. Simon G. Bott, who oversaw all phases of the production of the camera-ready copy.

November, 1989 Jerry L. Atwood

NOTE: Asterisks appear in the author listings of certain chapters to designate the author to whom correspondence should be addressed.

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HIGH RESOLUTION SOLID STATE NMR STUDIES OF THE EFFECT OF TEMPERATURE AND ADSORBED ORGANIC MOLECULES ON ZEOLITE LATTICE STRUCTURES

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INTRODUCTION

Zeolite Catalysts and Molecular Sieves

Zeolites are an important class of inorganic materials which are widely used as sorbents, ion exchangers, catalysts and catalyst supports [1-6]. The unique feature of zeolites which makes them so useful in catalytic reactions and sorption processes is their selective accessibility to organic molecules due to host-guest interactions. Their lattice structures are very open three dimensional frameworks with extremely uniform pore systems which control the size and shape of the organic molecules which can enter and diffuse through the lattice. When catalytic reactions take place within the structure, control is exerted on both the reactant and the product molecules. The general formula for an aluminosilicate zeolite system is as given in Equation (1) where the stoichiometry of the elements present is usually presented in terms of the ratios of the oxides. Because Si and Al differ in atomic charge, an extra-lattice cationic charge M^x must be present for each aluminum in the lattice to preserve electrical neutrality (these cations may be easily ion exchanged). In addition, water of hydration will usually be present but is not part of the aluminosilicate lattice framework.

$$(M^x)_{y/x}[(AlO_2)_y(SiO_2)_{1-y}].nH_2O \qquad (1)$$

The catalytic activity of zeolites is generated by converting them to an "acid form" by heating the "ammonium" form of the zeolite (where the cations are NH_4^+) to 450°C which causes decomposition of the ammonium ions as in Equation (2) to yield a material where the

$$NH_4^+ \rightarrow NH_3\uparrow + H^+ \qquad (2)$$

Inclusion Phenomena and Molecular Recognition
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MOTION OF ORGANIC SPECIES OCCLUDED OR SORBED WITHIN ZEOLITES [1]

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SUMMARY

Containment of organic species within microporous materials such as zeolites influences their modes of molecular motion. This manifests itself in a range of ways, including a reduction in the volume that is readily accessible to the molecules by translation, constraints upon the molecular conformational space, restricted modes of molecular reorientation, or altered vibrational frequencies. The perspectives on certain of the motional properties of sorbates and of tetramethylammonium cations within zeolites provided by simple molecular modelling, neutron powder diffraction, ^{13}C and $^{2}H(D)$ NMR, and inelastic and quasielastic neutron scattering are outlined and illustrated by selected recent results.

INTRODUCTION

Interest in the behavior of organic species within zeolites [2-7] arises from several different perspectives. Zeolites as catalysts and catalyst supports enjoy a dominant role in heterogeneous catalysis, particularly in petroleum and petrochemical processing [8]. Zeolites as sorbents and molecular sieves offer unique selectivities [3,9]. In addition, from a more fundamental standpoint, zeolites provide a medium in which the properties and phase behavior of organic or inorganic species can be studied in constrained environments of defined shapes, sizes and dimensionalities. Containment of sorbates or organic cations within microporous materials influences their modes of molecular motion. This manifests itself in a range of ways, including a reduction in the volume that is readily accessible to the molecules by translation, constraints upon the molecular conformational space, restricted modes of molecular reorientation that reflect the nature of interactions with internal surfaces, or alteration of the vibrational frequencies. Each of these aspects can be studied and exploited experimentally.

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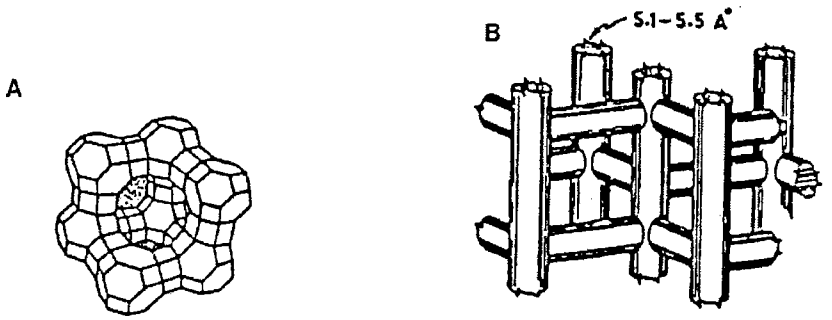
PHOTOCHEMISTRY IN ZEOLITE CAVITIES

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INTRODUCTION

Although the use of zeolites as catalysts has been fairly well established [1], their utility as molecular reaction vessels has not attracted wide attention [2]. It is this less explored aspect of zeolites that is of interest to us and forms part of this presentation [3]. Zeolites may be regarded as open structures of silica in which aluminum has been substituted in a fraction (X/X+Y) of the tetrahedral sites [4]. The framework thus obtained contains pores, channels and cages. As the trivalent aluminum ions replace tetravalent silicon ions at lattice positions, the network bears a net negative charge which must be compensated by other counter ions. The latter are mobile and may occupy various exchange sites depending upon their radius, charge and degree of hydration. They can be replaced, to varying degrees, by exchange with other cations. If zeolite water is removed, many other organic and inorganic molecular entities can be accommodated in the intracrystalline cavities.

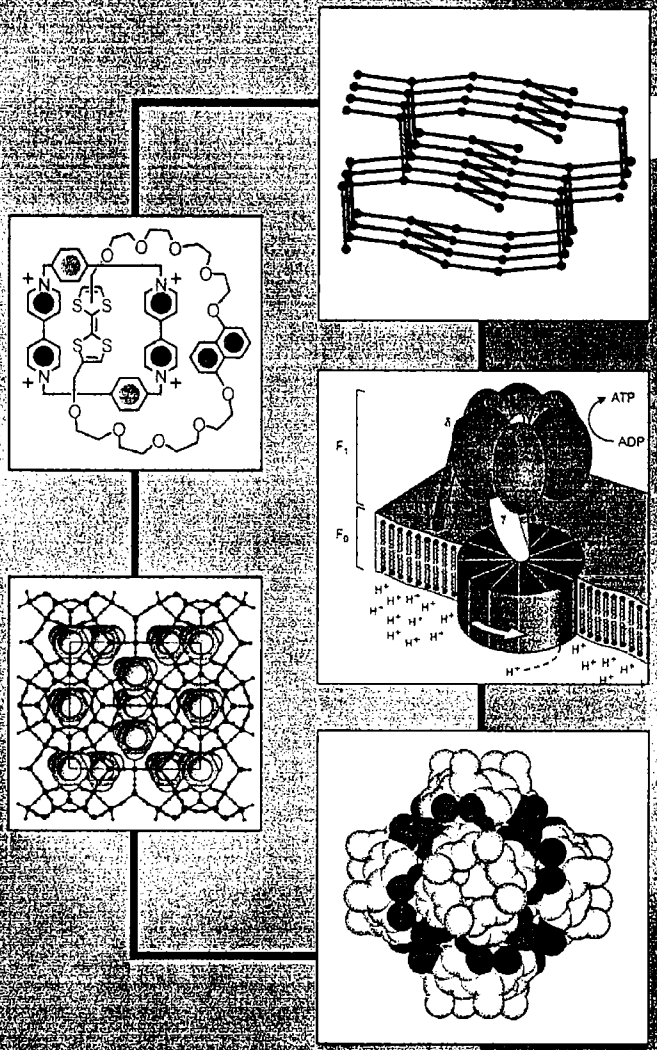


Zeolite X and Y
Pore entrance 7.4 Å

Silicalite and ZSM-5
Cage size 6.6 and 11.8 Å

Figure 1. Differences in structure between faujasites (A) and pentasils (B).

Inclusion Phenomena and Molecular Recognition
Edited by J. Atwood
Plenum Press, New York, 1990



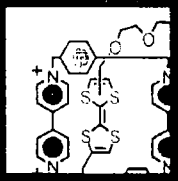
Volume Two

ENCYCLOPEDIA OF SUPRAMOLECULAR CHEMISTRY

EDITED BY
JERRY L. ATWOOD
JONATHAN W. STEED

Volume Two

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Solid-State Nuclear Magnetic Resonance Spectroscopy

S

John A. Ripmeester
Christopher I. Ratcliffe
National Research Council Canada, Ottawa, Ontario, Canada

INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy evolved into a major technique for the characterization of materials in just about all areas of chemistry. Most researchers and students will be familiar with solution applications, where chemical shifts and J couplings of spin $^1/_2$ nuclei can be used for simple spectral analysis of reaction products as well as the complex multidimensional techniques used to determine the structure and conformation of molecules as complex as proteins. A fundamental strength of NMR spectroscopy is that there is one-to-one correspondence between a chemically distinct nucleus and a chemically shifted line in the resonance spectrum; thus, spectra are quantitative fingerprints of the material under investigation.

DIFFERENCES BETWEEN SOLIDS AND LIQUIDS

In the solid state, NMR spectroscopy differs from solution spectroscopy in a number of ways. The main one is that in solution spectroscopy, all anisotropic interactions are averaged by rapid molecular motion, so that usually only the two aforementioned interactions, chemical shifts and J couplings, survive at their isotropic averages. However, because in the solid state molecular motion is seldom isotropic, all spin interactions behave as second-rank tensors. This means that interactions such as the chemical shift depend on the orientation of a molecular fragment with respect to the magnetic field, and on the details of the motion of the fragment. In single crystals, this then gives rise to an orientation-dependent chemical shift spectrum, and for powdered samples, where all orientations are allowed, a powder pattern results. Overlapping powder patterns cause obvious problems in resolving contributions from inequivalent nuclei, so much effort is spent on developing methods that give better-resolved spectra.

Another factor in solid-state spectroscopy is that some interactions not encountered in the spectral analysis of liquids contribute to the solid-state spectrum. These include the through-space coupling of magnetic spins, known as the nuclear dipolar interaction, and the quadrupolar interaction between the nuclear electric quadrupole moment and the electric field gradient. Although both complicate the spectra, each contributes unique information and different possibilities for probing the solid state.

NMR SPECTRA IN SOLIDS

Below, we present a brief account of solid-state NMR spectroscopy that will point the interested researcher to more detailed accounts. General references are given[1–8] that will give the interested reader a detailed account of a variety of solid-state NMR topics. Refs. [1,2] give an encyclopedic overview of NMR spectroscopy that is updated regularly.

Spin—1/2 Nuclei

Carbon and hydrogen are of particular importance in supramolecular chemistry, as both organic and metal–organic components are in prominent use. A closer examination of these two nuclei provides a good starting point for discussion of all spin $^1/_2$ nuclei.

The proton (^{1}H) is an abundant nucleus (99.8%), it has a large magnetic moment, and hence, a high NMR frequency. The dipolar coupling between protons is the main broadening interaction and varies as $\gamma^2(3\cos^2\theta - 1)/r^3$ (where γ = magnetogyric ratio of the proton, r = internuclear distance, and θ = angle between the internuclear vector and the magnetic field direction), so that the ^{1}H spectrum of most organic compounds is a line, usually featureless, as broad as 10–50 kHz. Because the chemical shift range is small ($\sim$20 ppm), if fine structure is seen, it almost always arises from dipolar couplings. For certain geometries, this allows for the analysis of internuclear distances. Sufficiently rapid molecular motion averages the dipolar couplings, thus narrowing the resonance line. Only center-of-mass diffusion reduces the dipolar coupling to zero. Molecular motions also affect the rate at which nuclear magnetization is lost, and from studies of the relaxation time as a function of temperature, the activation energy E_a for a motion can be obtained. Chemical shift information for ^{1}H, therefore, is difficult to

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obtain directly, and recourse must be taken to specialized techniques. The ^{1}H spins can be manipulated by multiple pulse cycles that remove homonuclear dipolar couplings. The chemical shift tensors that result can then be averaged to their isotropic values (plus a set of spinning side bands that are separated from the main resonance by the spinning frequency) by application of magic angle spinning (MAS). This involves rotating the sample rapidly about an axis that is inclined to the magnetic field at 57.3°, known as the "magic angle," the angle where $(3\cos^2\theta - 1)$ vanishes. The CRAMPS experiment (Combined Rotation and Multiple Pulse Sequence) combines the two approaches to produce high-resolution ^{1}H spectra in solids.

If the dipolar couplings are not too large, or if they were partially averaged by molecular motion, fast MAS (~35 kHz) used by itself can be employed to obtain a high-resolution spectrum. In such cases, many of the complex experiments designed for liquids can be applied to these "soft" solids.[2]

The ^{13}C nucleus, on the other hand, at 1% natural abundance, is considered to be a "rare" nucleus. The main line-broadening mechanisms are the anisotropic chemical shift and dipolar couplings to protons. In order to observe a high-resolution spectrum, it is necessary to apply high-power ^{1}H decoupling (50–100 kHz, values that are considerably larger than the dipolar coupling) and to apply MAS to average the chemical shift tensors to their isotropic values. The usual way of recording ^{13}C-NMR spectra is to transfer polarization from an abundant nucleus, usually ^{1}H to the rare ^{13}C nucleus. This double-resonance experiment is referred to as CP/MAS (cross-polarization with magic angle spinning). Although it is usually easier to generate a spectrum this way rather than by generating ^{13}C magnetization directly by applying a single pulse at the ^{13}C frequency and decoupling the ^{1}H, quantitation is more difficult, as the spectral line intensities depend on the strength of dipolar coupling, the length of the cross-polarization sequence applied, and the ^{1}H spin-lattice relaxation time in the rotating frame, which all must be taken into account when performing a CP/MAS experiment.

Other "rare" nuclei for which spectra can be recorded in the same way as for ^{13}C include ^{29}Si, ^{15}N, ^{31}P, ^{77}Se, ^{125}Te, ^{113}Cd, and ^{129}Xe.

Quadrupolar Nuclei (Spin>1/2)

By far, the majority of nuclides with spin are quadrupolar nuclei ($I > 1/2$). It should be remembered that for a spin I, there are $2I + 1$ energy levels and $2I$ allowed transitions. Of those with spin $I = 1$, ^{2}H is by far the most popular. The magnetic moment of ^{2}H is a factor of 7 smaller than that of ^{1}H, resulting in a lower resonance frequency and much smaller homonuclear dipolar couplings. The quadrupolar interaction, usually 300 KHz or less, is then a small perturbation on the Zeeman energy levels, giving rise to a quadrupolar fine structure. In a single crystal, each inequivalent ^{2}H nucleus gives rise to a doublet with a separation that depends on the orientation of the quadrupolar coupling tensor in the magnetic field.

In a powder, because all orientations are allowed, the spectrum is broadened into a characteristic powder pattern that can be analyzed in terms of a quadrupole coupling constant (C_Q) and an asymmetry parameter (η). One attractive feature is that at low-to-medium magnetic fields, the quadrupolar coupling is the only interaction required to interpret the spectra; at higher fields, the chemical shift anisotropy must be taken into account as evident from asymmetry in the spectrum. The main use of ^{2}H-NMR is to study dynamics of molecules or molecular fragments, usually as a function of temperature. Dynamics cause narrowing of the line shapes as the quadrupolar coupling tensor reorients in the magnetic field, and details of the motion can be worked out from the shapes of the narrowed lines. The rate of motion and, thus, the line shape depend on temperature, and by fitting line shapes to dynamic models at specific rates, activation energies (E_a) can be obtained from Arrhenius plots of rate versus $1/T$. Another property of ^{2}H-NMR, which can be of use in supramolecular chemistry, is that C_Q is a sensitive indicator of the strength of hydrogen bonds: the stronger (and hence, shorter) the bond, the smaller C_Q is for the ^{2}H atom in the bond.

Most quadrupolar nuclei are half-integral spins, and these have a central transition, affected by the second-order quadrupolar coupling, plus a set of satellite transitions with splittings related to the first-order quadrupolar coupling. A full discussion of the spectroscopy of half-integral quadrupolar nuclei is beyond the scope of this article, but the key features of the second-order central line shape are its inverse dependence on the magnetic field strength, a second-order shift (from the isotropic shift), and the fact that MAS alone will not completely remove the anisotropy.

SOLID-STATE NMR SPECTROSCOPY AND SUPRAMOLECULAR CHEMISTRY

Structure, Disorder, and Dynamics

Why should a supramolecular researcher be interested in solid-state NMR spectroscopy?[7,9] After all, with advances in diffraction methods, it would appear that many if not most problems can be solved by crystallographic methods. A chief distinction between NMR and diffraction is that the former is a local-order technique, whereas the latter is a long-range-order technique. One

piece of information related to long-range symmetry in crystalline materials obtainable from NMR is that not only chemical inequivalence but also crystallographic inequivalence give rise to splittings in the spectrum. In this way, it is often possible to get a snapshot of the unit cell contents, and this has, on occasion, been used to guide the choice of space group.

In many complex supramolecular systems, usually still considerably less complicated than biological systems, there may be problems of disorder that are often dynamic. It must be remembered that for diffraction models, all disorder is projected back into the unit cell, whereas NMR spectroscopy will be sensitive to the local symmetry in all parts of the crystal. Thus, it is possible that the lattice symmetry for a diffraction-derived structural model can be higher than that indicated by NMR, as the former is affected by space averaging. For example, in Dianin's compound with *p*-xylene[10] (Fig. 1), with the x-ray structural solution, a spatially averaged sixfold symmetry of the host and disordered guest can be seen. If this were the true local symmetry, then each chemically (and crystallographically) distinct C should have only one resonance in the ^{13}C-NMR, whereas at room temperature, these resonances show splittings, indicating a static *p*-xylene disorder. The splitting pattern shows that each cavity lost its threefold axis and the center of symmetry; the high x-ray symmetry coupled with the observed disorder indicates that the distortions are not correlated through the lattice. The splittings disappear at higher temperatures as the disorder becomes dynamic, and on

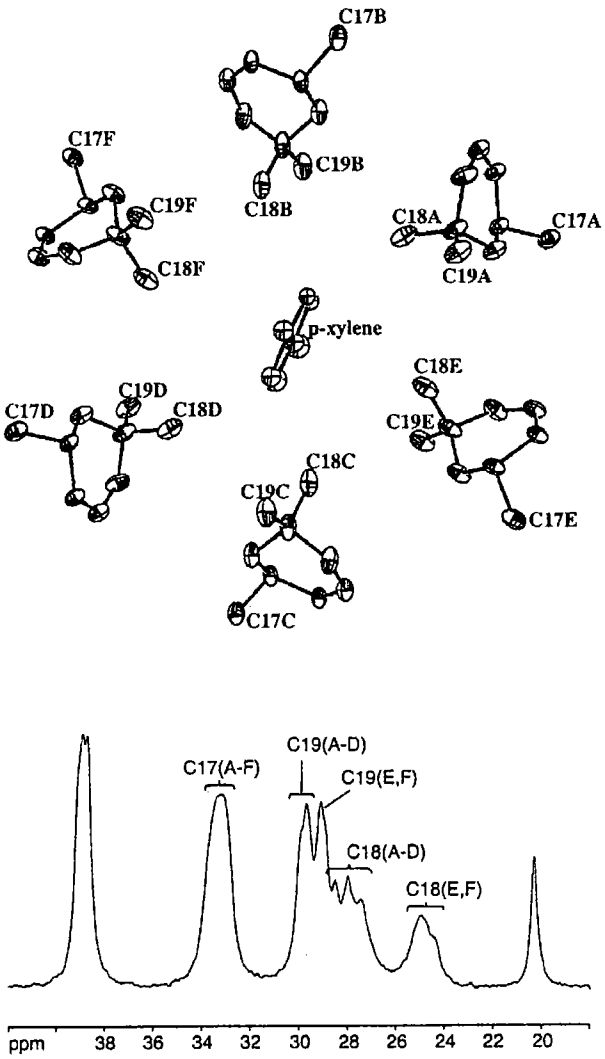


Fig. 1 Dianin's compound with *p*-xylene guest. (From Ref. [10].) (Top) Packing of six Dianin's host molecules around a *p*-xylene molecule, looking down the sixfold axis of the x-ray diffraction model (only part of each Dianin's molecule is shown). (Bottom) Room-temperature ^{13}C-CP/MAS spectrum showing the multiple splittings for the methyl groups (18 and 19, pointing into the cavity) that arise because the *p*-xylene molecule is static, and the sixfold symmetry is lost.

time average each set of carbons becomes a sixfold equivalent. On the other hand, it is possible for the symmetry indicated by NMR to be greater than that derived from crystallography. This is often the case if there is sufficiently rapid molecular motion, and the NMR spectrum is affected by time averaging. For example, the ^{13}C-NMR of *n*-pentane in *t*-butyl-calix[4]arene shows only a single methyl resonance, rather than the two lines expected for the two distinct methyls seen in the crystal structure, one inside the calix cavity and the other outside.[11,12] The NMR, therefore, indicates dynamic exchange of the two ends of the pentane.

A great deal can be gained through the combined use of NMR and crystallography in a synergistic approach to refining structures. With NMR, we can determine if the disorder is static or dynamic and often define the exact nature and activation energies of the motions of both guest molecules and components of the host. Another contribution of NMR is in the detection of phase transitions and the possible involvement of dynamics and disorder in the transition process. Another example of where the combined use of NMR and x-ray diffraction led to a better understanding of the material and to an improved refinement of the structure is the toluene calix-[4]-arene inclusion compound.[13,14] At room temperature, the structure refines as P4/*n* in which the calix has a fourfold axis, and the toluene is disordered. Below a phase transition at 248 K (initially detected by NMR), the ^{13}C-NMR

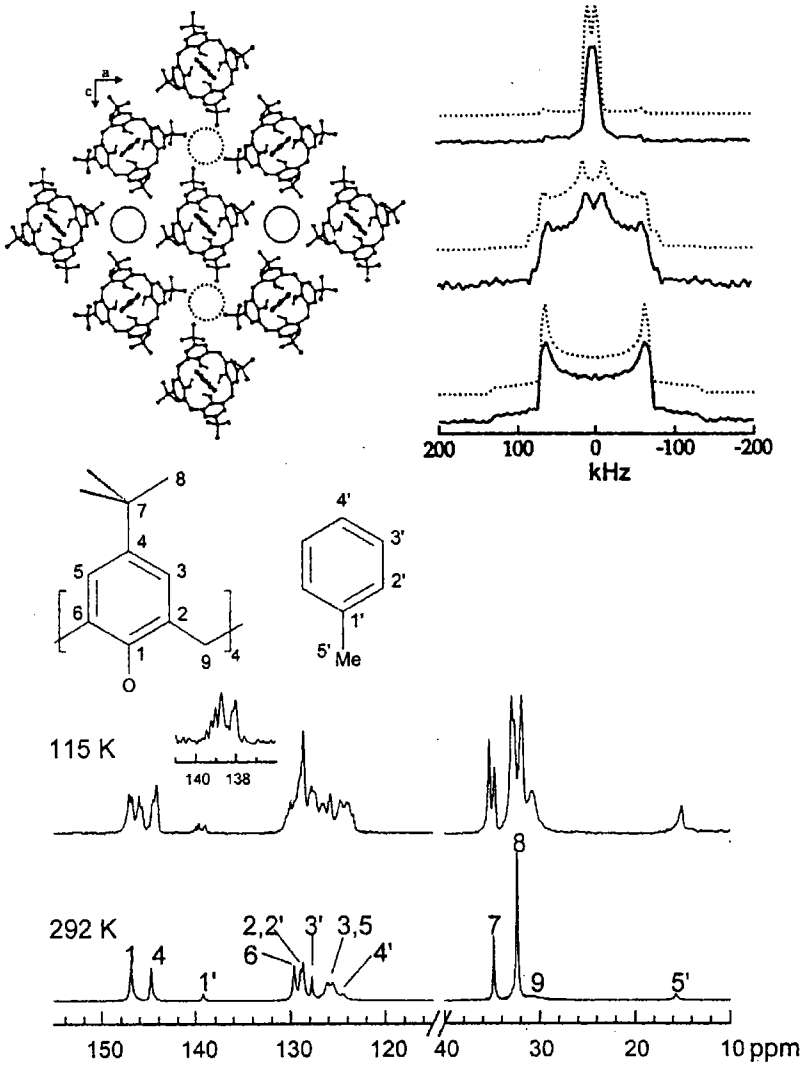


Fig. 2 (Top left) The 173 K P2/*c* structure of toluene-*t*-butyl-calix-[4]-arene, showing guest-induced twofold distortion of the host molecules. (From Ref. [14].) (Top right) ^{2}H-NMR line shapes, showing, from the bottom up, static (129 K), twofold flip (179 K), and fourfold rotation (337 K). (From Ref. [13].) (Bottom) The increased multiplicity of lines in the ^{13}C-CP/MAS spectra between 292 K and 115 K. (From Ref. [13].)

lines show splittings indicating a lowering of symmetry. Shown by ^{2}H-NMR is that the toluene is static at 129 K, undergoes rapid twofold reorientation at 179 K and only goes into fourfold reorientation above the phase transition. An initial x-ray structure determination of this low-temperature phase appeared to show no difference from the room temperature phase (P4/*n*), but clearly this was not compatible with the NMR results. Further investigation of fine details in the diffraction data, including a set of superlattice lines, revealed a more complex structure in which the calix has twofold symmetry, P2/*c* (Fig. 2). Also of interest in this system and shown by x-ray and ^{13}C-NMR is the observation that 90–95% of the toluenes have their methyl groups inserted into the cavity, versus 5–10% out. For the external methyl, a weak line is observed close to the resonance seen for liquid toluene, whereas a stronger line is observed for the methyls in the cavity shifted by ~6 ppm to lower frequency, due to ring current effects from the aromatic rings of the calix.

To demonstrate static disorder in numerous cadmium cyanide host structures,[15,16] ^{113}Cd-NMR was used, because the number of resonances observed depends on whether the CN groups are ordered, statically disordered, or dynamically disordered (Fig. 3). The ^{13}C- and ^{15}N-NMR helped to establish or confirm connectivities in other mixed-metal cyanide frameworks, where it is more difficult to probe the metal nuclei directly, by making use of dipolar and J-couplings.[7,17] Likewise, ^{27}Al, ^{29}Si, and ^{31}P were used to establish connectivities in zeolite and aluminophosphate frameworks.[5,18,19]

Static line shapes arising from chemical shift anisotropy (CSA) and quadrupolar coupling also reflect the local symmetry of the nucleus. Isotropic lines occur for high-symmetry sites, such as tetrahedral, cubic, or octahedral, where these interactions are zero [e.g., in the ^{63}Cu-NMR of tetrahedral copper centers in $N(CH_3)_4$-$CuZn(CN)_4$ and $N(CH_3)_4CuCd(CN)_4$·guest frameworks],[6,17] whereas the lines have characteristic shapes for sites with axial symmetry or for lower-symmetry sites. In the case of ^{129}Xe, the sign of an axial CSA line shape also indicates whether the cavity is oblate or prolate.[20,21]

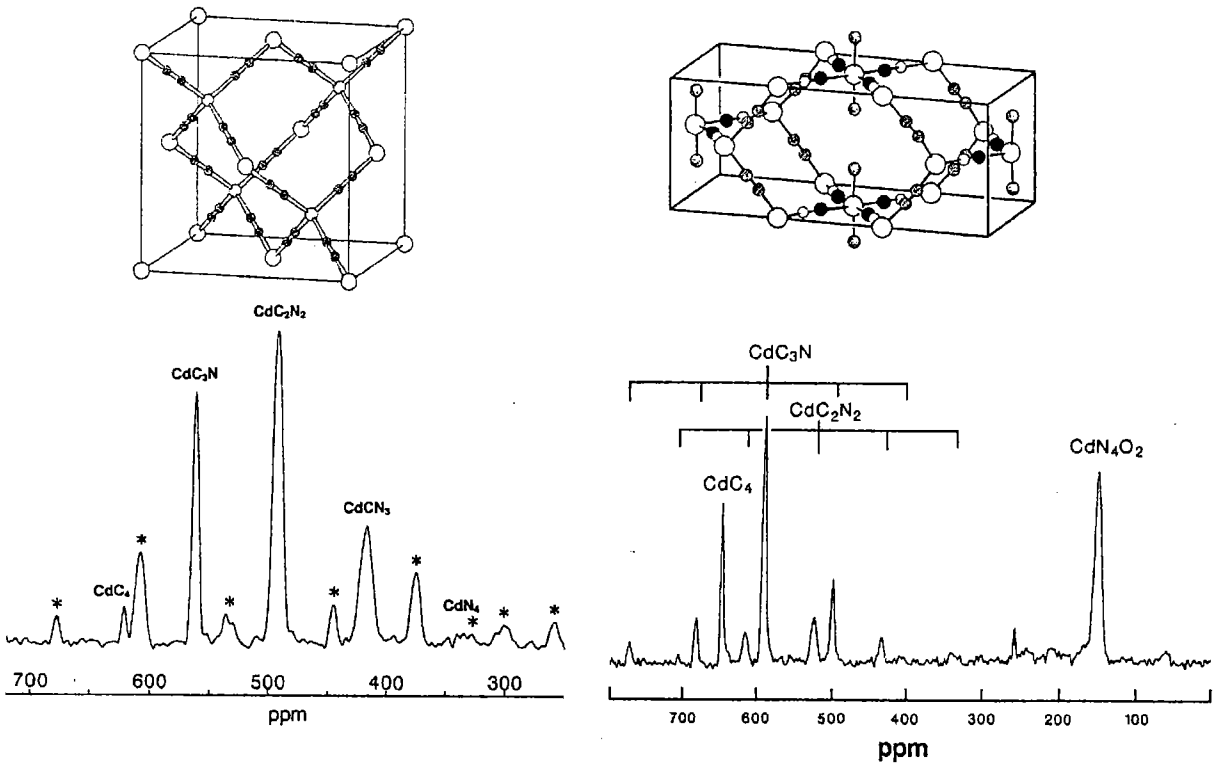


Fig. 3 (Left) The ^{113}Cd-NMR MAS spectrum of $Cd(CN)_2 \cdot C_6H_{12}$. The five lines arise from tetrahedral Cd attached to C_4, C_3N, C_2N_2, CN_3, and N_4, and indicate static disorder of the CN in the Cd–C–N–Cd linkages (* indicates spinning side bands). (From Ref. [15].) (Right) The ^{113}Cd-NMR CP/MAS spectrum of $Cd(CN)_2 \cdot 2/3\ H_2O \cdot$t-BuOH is shown, indicating ordering of the CN connecting the Oh Cd site to Td Cd sites (all N on the Oh Cd), with static disorder of the CN between Td Cd sites (the combs indicate the spinning side bands for CdC_3N and CdC_2N_2). (From Ref. [16].) X-ray structural studies previously established that this material could fall into one of five space groups, and a choice was made on the basis of the lowest *R*-factor. The NMR showed that this choice was not tenable and narrowed the choice to three of the five space groups. The structures of the frameworks are shown above the spectra: large open circles are Cd atoms; hatched circles are disordered C/N; and black circles are N atoms.

^{2}H-NMR is used extensively in studies of dynamics and disorder of guests and hosts in numerous supramolecular systems. These include clathrate hydrates, *t*-butylcalixarenes, cyclodextrins, metal cyanide clathrates, *tri-ortho*-thymotide, crown ethers, Dianin's compound, urea, thiourea, and numerous others. The benzene and pyridine *t*-butylcalixarenes provide an example where there is agreement between the orientations of the guest molecules with respect to the calix axis determined by NMR and diffraction, and where two guest molecules of similar shape have distinct differences in their dynamics.[22] It often comes as a surprise to the uninitiated that there can be large-scale motions in solids, yet solid-state NMR spectroscopy provided ample evidence of this over the years; a fine example being 18-crown-6, a large host macrocycle consisting of a ring of 18 atoms, which reorients rapidly in many of its solid complexes at room temperature.[23,24] In the malononitrile complex, the ring is

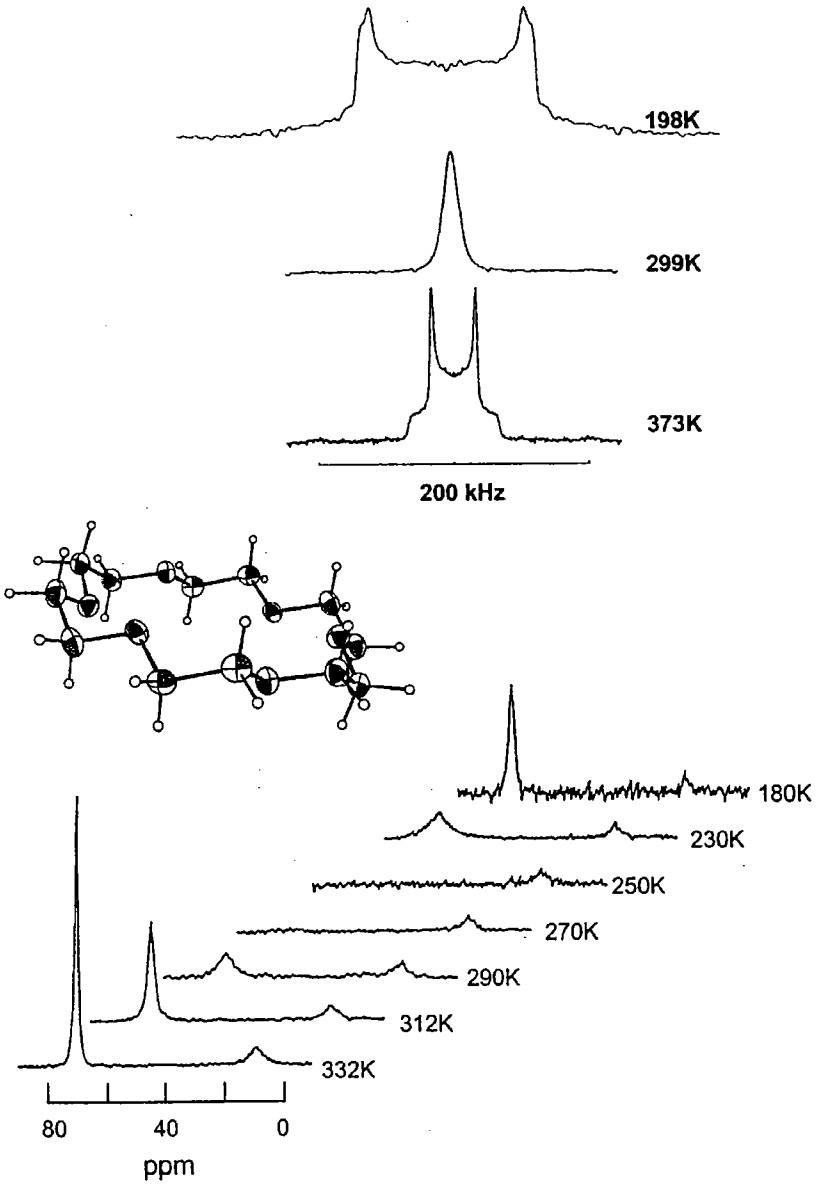


Fig. 4 The molecular merry-go-round in the solid complex 18-crown-6·$2CH_2(CN)_2$. (Middle) The ring adopts an almost D_{3d} symmetry. (Bottom) The ^{13}C-CP/MAS spectra as a function of temperature, showing fade-out of the resonance of the macrocycle carbons at 69.5 ppm near 250 K due to interference of incoherent reorientational motion with the coherent ^{1}H decoupling. (From Ref. [23].) (Top) The ^{2}H-NMR line shapes of the deuterated macrocycle as a function of temperature, indicating reorientation around the ring with a concomitant flip in orientation of each C–D bond between equatorial and axial. (From Ref. [24].)

in a D_{3d} conformation, and each $O—CH_2—CH_2$ unit rotates among adjacent sites around the ring. In the process, the CH_2 groups flip up and down, performing a motion resembling that of a merry-go-round (Fig. 4).

Similarly, effects of dynamics on line width and line shape can be observed for static NMR spectra of the following:

1. The chemical shift anisotropy, e.g., ^{13}C in CO_2 clathrate hydrate (which shows a line considerably narrowed from that of a static CO_2 molecule,[25]), likewise for ^{77}Se in H_2Se clathrate hydrate[26] and ^{15}N in pyridine in *t*-butyl-calixarene.[22]
2. Noninteger quadrupolar nuclei, e.g., the central transition line shapes
   a. Of ^{17}O in water in THF clathrate hydrate, which narrows from a broad static quadrupolar line shape at 140 K to a line shape indicating rapid pseudoisotropic reorientation just below the melting point.
   b. Of alkali metals, such as ^{23}Na and ^{87}Rb in zeolites, which show isotropic lines that retain a field-dependent second-order shift, which indicates that these lines arise from dynamic averaging over sites with significant quadrupolar coupling.

The changes in line shape can often be used to derive details of the motions.

Evidence of dynamics can also be found in ^{13}C-CP/MAS spectra, where modulation of the $^{13}C—^1H$ dipolar coupling due to reorientation can interfere with the ^1H decoupling, causing broadening and a fade out of the signal over a specific temperature range (i.e., at specific rates of reorientation) (Fig. 4),[23,27] or prevent complete elimination of the resonances of carbons with attached ^1H in interrupted decoupling (also known as dipolar dephased or nonquaternary suppression) experiments.

Many supramolecular systems have pore spaces, usually, but not always, occupied by guest species. The ^{129}Xe-NMR can be applied to study the pore spaces or the exchange or competitive adsorption of guest species.

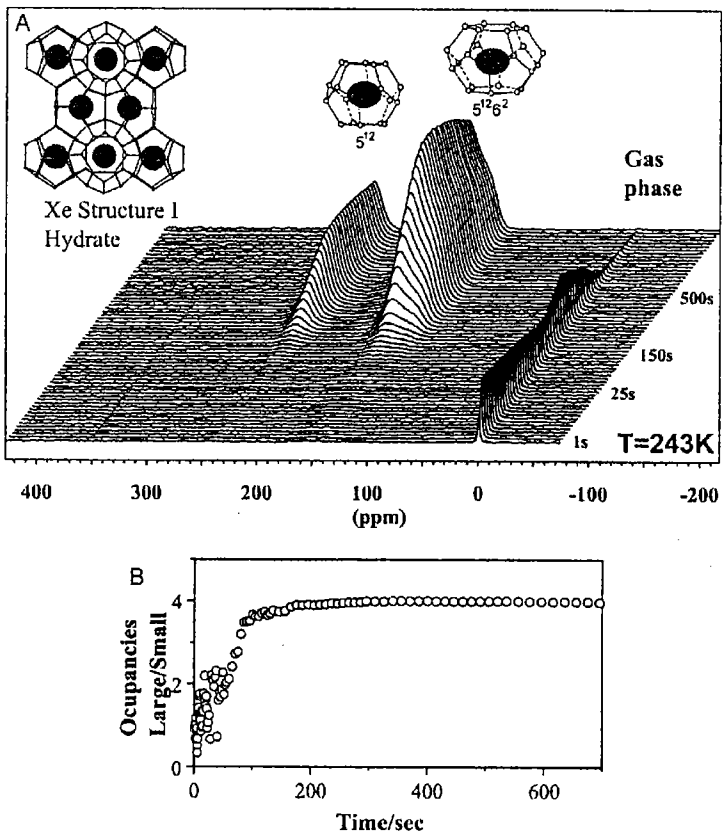


Fig. 5 Hyperpolarized ^{129}Xe-NMR spectroscopy of the formation of xenon hydrate on ice. (From Ref. [28].) (A) Single-scan spectra taken as a function of time, showing the development of Xe clathrate hydrate when HP Xe is admitted to powdered ice at 243 K. There is an initial induction period where only the gas line is observed, followed by a rapid rise of the lines due to Xe in the small and large cages of the clathrate hydrate. (B) The Xe-NMR intensity ratio of large:small cages shows an initial relative excess of Xe in small-cage environments, before eventually approaching the ratio in equilibrium Xe hydrate.

Although ^{129}Xe ($I = 1/2$) is a low-boiling gas under normal conditions, most of its NMR applications are in porous solids. The Xe atom is inert but highly polarizable, and as such, its chemical shift is sensitive to changes in its local environment: smaller cavities give larger chemical shifts, and the chemical shift anisotropy is sensitive to cavity shape. Thus, its signal, with the isotropic and anisotropic chemical shifts, is often diagnostic of whether the Xe atom behaves more like a trapped solid or adsorbed gas inside the pore system. The ^{129}Xe can also be hyperpolarized using optical pumping techniques such that its spin polarization is several orders of magnitude larger than the normal thermal spin polarization. This results in a greater NMR sensitivity, allowing for time-resolved studies of formation and decomposition processes, diffusion processes, and competitive adsorption between Xe and other guest molecules in supramolecular systems.[28,29] An example is shown in Fig. 5.

Of course, there are numerous other more sophisticated and hence less routine NMR experiments (refer to more specialized reviews[1,2,5,8] that can be applied to give information about supramolecular systems, such as the following:

1. The ^{1}H spin-counting technique can be used to determine the number of ^{1}H in a local cluster, and thus count the number of molecules in a cavity.[30,31]
2. Solid-echo double resonance (SEDOR) and rotational-echo double resonance (REDOR) techniques can be used to determine the proximity of the two types of nuclei, e.g., to determine which Na ions are closest to Al atoms in the framework of a zeolite, or to determine internuclear distances, or to help locate the position of a guest molecule relative to the host framework.[2,8]
3. MQMAS (Multiple Quantum MAS) is used to resolve resonances of noninteger quadruplar nuclei: complete narrowing of the second-order quadrupolar line shape cannot be achieved by MAS alone, but this is feasible when MAS is combined with multiple quantum pulse sequences.[2,5,8] This was used extensively in studies of zeolites.
4. Magnetic resonance imaging (MRI) can be used for diffusion measurements in porous systems, by monitoring the distribution of such nuclei as ^{1}H and ^{129}Xe as a function of time.[1,32]

CONCLUSION

It is clear that solid-state NMR has developed into a powerful tool for the supramolecular chemist who is interested in developing a true understanding of systems that are complicated and that, in fact, need to be flexible, responsive, or have dynamic components in order to be functional. On examining the development of NMR spectroscopy, it is remarkable that periodically there were major developments in hardware, software, or some fundamental aspects of spectroscopy. All of these led to increased prospects for spectroscopy as a research tool for the sciences. This is also the case for solid-state spectroscopy as it is applied to supramolecular chemistry, where the technique has now diffused from a few specialized labs into the mainstream. There is no reason to suppose that such developments will stop. Soon the impact of the general availability of higher fields to solid-state spectroscopists will give unprecedented sensitivity, thus giving access to smaller samples as well as nuclei that have lower sensitivity or low gamma. The wide range of fields will also allow for the development of complex spectroscopy of half-integral quadrupolar nuclei, thus giving the researcher a whole new range of probes for material studies as well as dynamic processes.

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Volume 8

PHYSICAL METHODS IN SUPRAMOLECULAR CHEMISTRY

Volume Editors

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PERGAMON

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EXHIBIT 13

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	Case No. 06-438-GMS

DECLARATION OF JERRY ATWOOD IN SUPPORT OF ABRAXIS'S MOTION IN LIMINE NOS. 1 AND 2

I, Jerry Atwood, declare as follows:

1. I am a Curators' Professor at the University of Missouri-Columbia. I have been retained by Abraxis as an expert in this case. I submit this Declaration in Support of: (1) Abraxis's Motion in Limine No. 1 to Strike Portions of Elan Expert Harry Brittain's Expert Report Regarding Testing of Abraxane And To Bar Related Testimony And Argument; and (2) Abraxis's Motion in Limine No. 2 to Exclude Evidence of Elan's SSNMR Testing of Abraxane. Except where otherwise stated, I have personal knowledge of the matters set forth herein, and if called upon to do so, I could and would competently testify thereto.

2. I filed an Opening Expert Report on September 28, a Rebuttal Expert Report on October 29, 2007, and a Supplemental Report on February 29, 2008 in this matter. Among other things, these reports discuss the amorphous nature of the paclitaxel in Abraxane, X-ray powder diffraction ("XRPD"), and solid-state nuclear magnetic resonance ("SSNMR"). These reports are attached as Exhibit A. A copy of my Curriculum Vitae is attached as Exhibit B.

Summary of Critical Information Not Provided By Elan's Experts Regarding the SSNMR Testing

3. As I will discuss in more detail below, Elan's experts did not disclose many critical aspects of their testing that would be necessary for me to reproduce their experiments and analyses, and completely assess any potential issues with the data. This missing information includes:

- Laboratory notebooks or other records summarizing all of the experts' work
- The physical paclitaxel control samples
- The purity of the paclitaxel control samples
- The physical characteristics of the paclitaxel control samples
- The precise methods used to prepare the paclitaxel control samples
- The chain of custody and storage conditions for the paclitaxel control samples
- The physical Abraxane samples used to prepare the air- and freeze-dried manipulated samples
- The purity of the air- and freeze-dried manipulated samples
- The physical characteristics of the air- and freeze-dried manipulated samples
- The precise methods used to prepare the air- and freeze-dried manipulated samples
- The chain of custody and storage conditions for the air- and freeze-dried manipulated samples
- The parameters employed to convert the time domain SSNMR data into the frequency spectra, for example:
    - The parameters employed to apodize the data

- The parameters employed to phase the data
- The peak width

- The reason why Dr. Munson chose to attach to his expert report only 6 out of the 34 spectra generated, and how those 6 were chosen
- Why some of the spectra for the same sample were different
- The parameters used for the deconvolution of the SSNMR peaks, for example
  - The size, width, and exact placements of the peaks
  - Whether the shape assigned was Lorentzian, Gaussian, or some mixture of the two
  - Whether SpinSight was used to refine these parameters
- How Dr. Munson made a third peak "appear" in the manipulated air- and freeze-dried samples
- The basis for Dr. Munson's determination of the area of the "third peak" in the manipulated air- and freeze-dried samples
- The basis for Dr. Munson's determination that the area of the "third peak" in the manipulated air- and freeze-dried samples should be doubled
- The basis for Dr. Munson's 50% error

Expert Reports Failed to Reveal Those Who Did the Experimental Work

4. In their reports, Elan's experts gave the impression that they did the experimental work themselves. I have learned through deposition transcripts, however, that Dr. Barich did the experimental work for Dr. Munson; Dr. Shi did the work for Dr. Berkland; and Drs. Bihovsky and Tsuji did the work for Dr. Winkler. Elan's experts did not disclose any of this information in their reports.

Elan's Experts Failed to Keep Laboratory Notebooks

5. Many of Elan's experts did not keep laboratory notebooks or other records of their experiments for this litigation. For example, in his deposition, Dr. Munson stated:

"Q. I'm asking you as applies to the experiments you do in your laboratory.

A. . For many of the experiments in our laboratory what we will do is take a particular sample, place it into a rotor and then spin that particular sample to acquire solid-state NMR data.

Q. Where are the details of how you do that experiment recorded?

A. The procedure is very well established. So because it's the same procedure that we do time and again, we typically don't record those details."

(Declaration of Emily A. Evans in Support of Abraxis's Motion in Limine No. 1 and No. 2 ("Evans Decl."), Ex. 22 at 25:5-15 (Munson Dep.).)

6. It is clear from Dr. Munson's deposition testimony that he kept no records of the procedures utilized in the SSNMR experiments that form the basis for his deconvolution work in his expert report. It is also clear that Dr. Barich, not Dr. Munson, actually performed all the SSNMR experiments for this litigation. In fact, Dr. Munson did not know what manipulations were done on the SSNMR data which led to the SSNMR spectra given in the exhibits to his expert report.

7. It is clear from Dr. Barich's deposition testimony that he also kept no records of the procedures utilized in the SSNMR experiments. (Evans Decl., Ex. 26 at 71:16-20 (Barich Dep.).)

8. Dr. Shi also did not keep a laboratory notebook; neither did Dr. Berkland. (Evans Decl., Ex. 21 at 143:18-144:13 (Shi Dep.); Ex. 18 at 72:15-17 (Berkland Dep.).) Dr. Winkler did not keep a laboratory notebook, and only one of his two assistants did. (*Id.*, Ex. 14 at 79:22-80:9 (Winkler Dep.).)

9. The failure of Elan's experts to keep laboratory notebooks or other records containing experimental details is unacceptable scientific practice. Even undergraduate students at all major colleges and universities are taught and required to keep a laboratory notebook. For example, the widely used textbook "Quantitative Chemical Analysis," by Harris (Fifth Ed., 1998, Freeman, New York) has a section in the introductory chapters entitled "The Lab Notebook." The full section is attached as Exhibit C. The first paragraph states:

> "The critical functions of your lab notebook are to state *what you did* and *what you observed*, and it should be *understandable by a stranger*. The greatest error, made even by experienced scientists, is writing incomplete or unintelligible notebooks. Using *complete sentences* is an excellent way to avoid incomplete description."

Harris further states in this same section:

> "The measure of scientific 'truth' is the ability of different people to reproduce an experiment. A good lab notebook will state everything that was done and what you observed and will allow you or anyone else to repeat the experiment."

Other scientific textbooks have similar sections on the importance of recording experiments in a laboratory notebook. Sections from these textbooks are attached as Exhibits D and E.

10. Dr. Winkler agrees. For example, he testified:

"Q. Is it scientifically-accepted practice to not write down experiments in a lab notebook? ***

A. We try to write all of our experiments down in a laboratory notebook."

(Evans Decl., Ex. 14 at 315:14-19 (Winkler Dep.).) Even Dr. Munson testified to the importance of keeping laboratory notebooks:

"Q. Do you know what a laboratory notebook is, Doctor?

A. Yes. I know what a laboratory notebook is.

Q. What is it?

A. Laboratory notebooks are oftentimes kept in the case of where additional information is required for recalling certain experimental procedures.

Q. Do you instruct your postdoctoral fellows and graduate students in your lab to keep laboratory notebooks to record the details of the experiments they perform?

A. I encourage my students to keep sufficient records so that they can reproduce their results and explain their results."

(Evans Decl., Ex. 22 at 23:15-24:3 (Munson Dep.).)

11. The absence of written records is not merely a case of an omitted formality. Neither Dr. Munson nor Dr. Barich could remember critical details from the SSNMR experiments because it had been almost a year since the experiments were performed. (Evans Decl., Ex. 26 at 149:1-151:3 (Barich Dep.).) For example, Dr. Barich and Dr. Munson could not remember the parameters used for the deconvolution. (*Id.* at 197:8-198:13 (Barich Dep.); Ex. 22 at 197:21-200:1, 226:10-25; (Munson Dep.).) As another example, Dr. Shi could not remember whether he lyophilized the manipulated Abraxane sample for 24 hours or 1 week. (*Id.*, Ex. 21 at 96:9-97:24 (Shi Dep.).) As yet another example, Dr. Winkler could not remember who did the

key sample preparations on certain paclitaxel standards, when they did them, and what they actually did. (Evans Decl., Ex. 14 at 69:25-70:5 (Winkler Dep.).) This lack of memory with time is the major reason why accepted scientific practice demands that a laboratory notebook or other detailed records be kept.

12. The failure of Drs. Munson, Barich, Shi, Berkland, and Winkler to keep records of the experiments they performed for this litigation is contrary to standard scientific practice. Due to their lack of proper record keeping, Elan's experiments are not reproducible. As explained by Harris, experiments that are not reproducible lose their scientific value. For example, an experiment that is not reproducible may not be used as a method testing a scientific hypothesis. To test a hypothesis, a scientist must be able to replicate an experiment and observe consistent results.

13. This lack of reproducibility is compounded by other unique circumstances relating to Elan's experiments. Elan's SSNMR stands in stark contrast against an array of evidence that the paclitaxel in Abraxane is completely amorphous. For example, Abraxis conducted numerous X-ray Powder Diffraction tests, all of which show that there is no crystalline paclitaxel in Abraxane. Moreover, XRPD, as opposed to SSNMR, is the gold standard for measuring crystallinity. In addition, Dr. Munson's own analysis of his SSNMR spectra reveals only a very small amount of crystallinity - measured only at 4%, then doubled, and halved again by assigning an error rate. A scientist would generally be skeptical of an experiment that showed any crystallinity, where the great weight of other experiments showed that the drug was completely amorphous. Against this backdrop, accepted scientific practice would demand that Dr. Munson perform further analysis before he could conclude that the paclitaxel in Abraxane contained a small portion of crystallinity.

Samples Were Improperly Analyzed and Handled

14. Dr. Winkler stated in his declaration that he prepared three samples: paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel. These samples were transferred to Dr. Berkland and then to Dr. Munson or Dr. Barich. It must be emphasized that the SSNMR analysis of these "standard" samples forms the basis for Dr. Munson's crystallinity arguments with regard to his deconvolution studies. At his deposition, Dr. Winkler revealed three important facts: (1) Dr. Winkler did not keep a laboratory notebook; (2) Dr. Winkler did not prepare the paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel, nor was he present when others carried out the preparations; and (3) Dr. Winkler did no analysis to test the purity of any of the several samples of paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel.

15. Experimental data, such as Dr. Munson's SSNMR data, can be no better than the sample from which the experimental data is measured. The quality of the samples of paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel should have been determined by analysis. Dr. Winkler should have tested the paclitaxel which was used in the preparation of the paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel samples. He did not do so.[1] (Evans Decl., Ex. 14, 93:7-13 (Winkler Dep.).) Dr. Winkler should have confirmed that the final control samples of paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel were actually what they purported to be. He did not do so. (*See, e.g., id.*, Ex. 14, 121:25-122:3, 122:6, 186:3-4, 7-14; 230:18-20, 23-24, 231:2 (Winkler Dep.).)

16. As his sole method of "analysis" of paclitaxel dihydrate, Dr. Winkler relied on his assistants following the method of preparation published by a Korean group. (*Id.*, Ex. 14, 72:10-

[1] Dr. Winkler did test the purity of one of the starting paclitaxel materials, but he threw away the results. (Evans Decl., Ex. 14, 225:21-226:17 (Winkler Dep.).)

73:20 (Winkler Dep.) .) His method of "analysis" of the amorphous paclitaxel was to again rely on the method of preparation published by the Korean group, followed by FTIR (Fourier Transform Infrared) spectroscopy. (*Id.*, Ex. 14, 121:25-122:15 (Winkler Dep.).) Following a literature preparation is not a scientifically accepted method of analysis. In the FTIR work, Dr. Winkler testified that he only considered one peak out of very many in the spectrum of amorphous paclitaxel. (*Id.*, Ex. 14, 65:21-67:22 (Winkler Dep.).) Dr. Winkler could not remember any details regarding the recrystallized anhydrous paclitaxel. (*Id.*, Ex. 14, 69:25-70:5 (Winkler Dep.).)

17. Dr. Winkler testified that the paclitaxel control samples were prepared from three different paclitaxel starting materials: one from Sigma, one from Biomall, one from Upjohn. (*See, e.g.*, *id.*, Ex. 14, 90:21-25, 172:8-173:9 (Winkler Dep.).) Dr. Winkler did not disclose this in his report, and he attached only the certificate of analysis from the Sigma starting material. (*Id.*, Ex. 16, ¶ 6 (Winkler Decl.).) Dr. Winkler also testified that his assistants prepared these controls several times, from approximately January to September 2007 (*id.*, Ex. 14, 85:9-87:8 (Winkler Dep.)); this was also not disclosed in Dr. Winkler's report. Dr. Winkler could not remember where he sent several of these samples; he could only remember that he sent one set of samples to Dr. Berkland. (*Id.*, Ex. 14, 87:22-88:15 (Winkler Dep.).)

18. Dr. Winkler attached two FTIR spectra to his declaration that purported to be spectra from the samples of dihydrate and amorphous paclitaxel that he sent to Dr. Berkland in February 2007. Other FTIR spectra produced by Dr. Winkler suggest that the spectra attached were not those corresponding to the samples he discussed in his declaration. (*See, e.g.*, *id.*, Ex. 14, 214:14-217:3 (Winkler Dep.).)

19. Dr. Winkler's failure to do adequate analysis of the samples of paclitaxel dihydrate, anhydrous paclitaxel, and amorphous paclitaxel which his assistants prepared is not acceptable science. Dr. Barich has collected SSNMR data on "standards" of unknown purity. Dr. Munson has deconvoluted a peak from SSNMR data and made an interpretation based on "standards" of unknown purity.

20. As I have stated in my expert reports, I disagree with the way in which Dr. Munson treated the SSNMR data and with the conclusions he reached. However, from Dr. Winkler's deposition testimony, I have now learned that the standards for the SSNMR data were of unknown purity. (*See, e.g., id.*, Ex. 14, 121:25-122:3, 122:6, 186:3-4, 7-14; 230:18-20, 23-24, 231:2 (Winkler Dep.).) Therefore, no reliance should be placed on the SSNMR data much less on the interpretation thereof.

Dr. Munson's Expert Report and Opinion

21. Dr. Munson's Expert Report discusses his analysis of certain ssNMR experiments on Abraxane, manipulated Abraxane samples, and the paclitaxel products created by Drs. Tsuji and Bihovsky. (*Id.*, Ex. 9, ¶¶ 14-16 (Munson Rep.).) Dr. Munson used the dihydrate, anhydrous, and amorphous paclitaxel standards as controls. Dr. Munson first compared the manipulated air-dried and freeze-dried samples of manipulated Abraxane to the amorphous control, opining that a peak at 204 ppm in the manipulated Abraxane samples had a "shoulder." (*Id.*, Ex. 9, ¶¶ 18-19 (Munson Rep.).) Dr. Munson then deconvoluted the three spectra, and states in his report that a "third peak appeared" in both manipulated samples at approximately 207 ppm. (*Id.*, Ex. 9, ¶¶ 21-22 (Munson Rep.).) According to Dr. Munson, the amorphous sample only deconvoluted into two peaks. (*Id.*, Ex. 9, ¶ 20 (Munson Rep.).)

22. To determine the nature of this "third peak," Dr. Munson then looked to the dihydrate sample, which he claims has two crystalline peaks at approximately 207 and 209 ppm. (*Id.*, Ex. 9, ¶¶ 23-24 (Munson Rep.).) He states that the 207 ppm peak "strongly suggests that the dihydrate sample is not pure dihydrate, but rather is a mixture of two different crystalline forms." (*Id.*, Ex. 9, ¶ 23 (Munson Rep.).)

23. I agree with Dr. Munson with regard to the impurity of the paclitaxel dihydrate sample. I cannot agree with his bald assumption of a previously undiscovered crystal form of paclitaxel dihydrate based on a rogue peak at 207 ppm. Dr. Munson could have performed a spiking experiment (with paclitaxel dihydrate) to try to verify that the phantom peak at 207 ppm was indeed paclitaxel dihydrate. Instead, he offers only speculation.

24. Dr. Munson then makes the unwarranted assumption that the small phantom peak at 207 ppm in the deconvolution exercise is only half the intensity of the carbon atom from which it originates, with the other half coming from the large peak at about 203 ppm.[2] (*Id.*, Ex. 9, ¶ 24 (Munson Rep.).) In Dr. Munson's argument, the very small peak at 207 ppm and the large peak at 203 ppm each represent half of one carbon atom in terms of intensity. This argument is unsupported. As Dr. Munson stated in the last sentence of his paragraph 14, "One way to diagnose the presence of two crystallographically-inequivalent molecules in the crystal lattice is to determine the relative peak areas of each carbon, as **both peaks for each carbon should have roughly equal intensity**." (*Id.*, Ex. 9, ¶ 14 (Munson Rep.) (my emphasis).) As shown in Appendix D of Dr. Munson's report, the peaks at 203 and 207 ppm clearly do not have nearly equal intensity. (*Id.*, Ex. 9, App. D (Munson Rep.).)

[2] In Dr. Munson's report, he labels this peak at 204 ppm, rather than at 203 ppm.

25. What Dr. Munson has done is to make up a peak at 203 ppm, which he could not find using deconvolution. He then made up an intensity of 3.5% for that peak he could not find. Next, he added that imaginary 3.5% to the dubious 3.5% of the peak he did see through deconvolution, to get 7%. (*Id.*, Ex. 9, ¶ 24 (Munson Rep.).) This approach is devoid of scientific merit and runs counter to Dr. Munson's own data.

26. Further into paragraph 24, Dr. Munson states "the error associated with measurement is estimated to be 50% of the determined value." (*Id.*, Ex. 9, ¶ 24 (Munson Rep.).) Dr. Munson apparently pulled this number out of thin air; nowhere is a reference of a means of making such an estimate given. He confirmed this fact in his deposition, referring to the 50% error rate as a "best guess estimate." (*Id.*, Ex. 22, 234:10-235:11 (Munson Dep.).) According to Dr. Munson, the phantom peak, which resulted from the flawed deconvolution, has led to his conclusion that the lyophilized Abraxane sample contains a range of crystalline paclitaxel "of 3.5 to 10.5%"! In other words, Munson used his error rate to further inflate his numbers. Munson's calculations are devoid of scientific support.

SSNMR Data Not Included in Dr. Munson's Expert Report

27. Dr. Munson's expert report contains the results of only 6 ("SSNMR") experiments. (Evans Decl, Ex. 9 at Appendices C-H (Munson Rep.).) In his report, Dr. Munson presented one spectrum on each of the six following samples: (1) paclitaxel dihydrate, (2) anhydrous paclitaxel, (3) amorphous paclitaxel, (4) Abraxane, (5) manipulated (centrifuged, separated, and freeze-dried) paclitaxel from what was originally Abraxane, and (6) manipulated (centrifuged, separated, and air-dried) paclitaxel from what was originally Abraxane. (*Id.*) Dr. Munson's report did not mention any other SSNMR experiments.

28. Through discovery, I learned that 34 SSNMR experiments were done on these same six samples. These experiments were carried out by a man named Dr. Dewey Barich; not Dr. Munson. (Evans Decl., Ex. 22 at 33:3-4 (Munson Dep.).) For the original Abraxane sample, Dr. Barich conducted 9 separate SSNMR runs, from January 19 to January 24, 2007. (*Id.*, Ex. 28 (Munson Data Summary from Elan).) For the manipulated air-dried sample, Dr. Barich conducted 4 separate SSNMR runs, spanning from March 21 to April 29, 2007. (*Id.*) For the manipulated freeze-dried sample, Dr. Barich conducted 13 separate SSNMR runs, spanning from January 30 to May 1, 2007. (*Id.*) For the dihydrate paclitaxel sample, Dr. Barich conducted 2 separate SSNMR runs, both on April 20, 2007. (*Id.*) For the anhydrous paclitaxel sample, Dr. Barich conducted 3 separate SSNMR runs, from March 2 to May 2, 2007. (*Id.*) Finally, for the amorphous paclitaxel sample, Dr. Barich conducted 3 separate SSNMR runs, from March 3 to April 30, 2007. (*Id.*)

29. Elan's experts did not disclose the existence of the 28 other experiments in their reports. Further, no Elan expert explained why Dr. Munson chose the 6 spectra that he attached to his report.

30. Over these 34 experiments, the same sample produced quite different spectra, depending apparently on the condition of the sample and methods used for the SSNMR experiments. It must be emphasized that the condition of the sample and the methods used for analysis were not disclosed, recorded, or remembered by Dr. Munson or Dr. Barich. Dr. Barich did recall that at least one sample received from Dr. Berkland was packed into the rotor (the sample container for the SSNMR instrument) and left in an open laboratory hood for more than three months. (Evans Decl., Ex. 26 at 212:25-213:20 (Barich Dep.).) Such a practice does not lead to reliable scientific results.

31. As an example of the different results from the same sample, I have appended as Exhibit F spectra obtained for the freeze-dried paclitaxel on February 2 and April 29, 2007. The spectra are different, especially in the 195-210 ppm range, which is the range on which Dr. Munson bases his entire argument about crystallinity. I am concerned about the failure of Dr. Munson to disclose the spectrum taken on February 1. I am also concerned about Dr. Munson's selective reliance on spectra that are not representative of all the spectra generated for the same sample.

32. To meet the standards that any scientist would demand, accurate records should have been kept concerning all the samples prepared and analyzed by the various Elan experts. Further, all studies performed on these samples should have been disclosed and discussed in the expert reports of the Elan experts. For example, Dr. Munson should have explained why: (1) he chose the spectra he did, and (2) certain spectra for the same sample were so dramatically different. Finally, the fact that Dr. Barich recorded different spectra for the same samples additionally calls Dr. Munson's conclusions about the existence of crystallinity in Abraxane into question.

Dr. Munson's Production

33. In his productions, Dr. Munson provided two types of data in association with Elan's SSNMR testing: hard-copy and electronic. Both forms are insufficient to allow analysis of the data.

Munson Hardcopy SSNMR Data

34. Dr. Munson produced hardcopy SSNMR data associated with the 34 runs that Dr. Barich conducted in this case. A chart summarizing the production of this data is contained in the Declaration of Emily Evans (Ex. 28.) I understand that Elan had not produced any of the data by the time my Rebuttal Report was due, and had only produced 1/11th of the data prior to Dr. Munson's deposition. Elan was still producing this data as late as January 24, 2008 – more than one month after I understand expert discovery closed.

35. A representative example of the hardcopy data produced by Dr. Munson is attached as Exhibit G.

36. The first few pages and the last few pages of this three hundred and sixty page file represent some of the parameters used during operation of the SSNMR machine. (*See, e.g.*, Ex. G at MUNSON 2526-8 and MUNSON2886-91.)

37. The 300 pages in between appear to be related to the actual data collected by the SSNMR machine. (*See, e.g.*, Ex. G at MUNSON2529-2885.) This data is completely unintelligible. Dr. Barich testified at his deposition that Dr. Munson requested that Dr. Barich create a special software program to convert the testing data into text files. (Evans Decl., Ex. 26 at 231:25-234:1 (Barich Dep.).) Dr. Barich further testified that he found Munson's request to convert the data both "unusual" and "a little surprising." (*Id.* at 234:22-235:18.) Dr. Barich also testified that the hard copy documents of the data files were not produced to Abraxis as they were kept in the ordinary course of business. (*Id.* at 232:5-23.)

38. The results of an SSNMR experiment are customarily presented as a frequency spectrum. This is how Dr. Munson presented data from 6 of his 34 runs in his Expert Report. Representative examples of how this data is normally presented are attached to Dr. Munson's Expert Report as Appendices C-H.

39. I understand that Elan sent Abraxis a chart summarizing its hardcopy production of the SSNMR data. (Evans Decl., Ex. 28.) According to this chart, Elan produced only 11 of the 34 frequency spectra associated with Elan's NMR testing, 6 of which had already been attached to Dr. Munson's Opening Report. In other words, Dr. Munson has yet to produce in hardcopy form more than 2/3^{rds} of the data that he evaluated. Without these frequency spectra, it is not possible to understand the scope of the experiments evaluated by Dr. Munson.

Munson Electronic Data

40. Dr. Munson also produced electronic data associated with the experiments. The initial SSNMR data produced by Dr. Munson apparently was what is referred to as "time domain" NMR data. Of the 34 files produced, fully half of them could not be opened using such standard software as the GRAMS/32 package. It must be noted that even for the "time domain" data which could be opened using the GRAMS/32 package, I had no way of knowing what manipulations Dr. Barich or Dr. Munson had employed in converting the "time domain" data into the spectra which appear as appendices to Dr. Munson's expert report.

41. At Dr. Munson's deposition, he testified that he and Dr. Barich used SpinSight software to manipulate the raw SSNMR data and view it as spectra. (Evans Decl., Ex. 22 at 184:22-185:2 (Munson Dep.).) Dr. Munson did not disclose this critical information in his report. (*Id.*, Ex. 9.) Different software packages can produce spectra that appear different, even

when generated from the same raw time domain data. Had Dr. Munson explained the exact parameters used in generating the spectra from his SSNMR experiments, I could have used different software to attempt to reproduce his results. However, Dr. Munson also did not disclose this information in his report.

42. I was therefore forced to obtain the SpinSight software package that Dr. Munson and Dr. Barich used. The SpinSight software could be used only with a Sun computer and a Solaris 9 operating system. Dr. Munson also did not disclose this information. Both the software and the hardware used by Dr. Munson and Dr. Barich are legacy products that are no longer supported by the manufacturers.

43. Elan's other cxperts were surprised that Dr. Munson did not reveal in his expert report the software he used for the SSNMR data collection and peak deconvolution. For example, Dr. Brittain testified as follows:

"Q. Dr. Brittain, what software did Dr. Munson use for deconvolution?

A. I must be missing - I don't see it mentioned.

Q. It surprises you, doesn't [it]?

A. I[t] would have been something that I would have written in."

(Evans Decl., Ex. 8 at 119:8-14 (Brittain Dep.).)

Critical Dctails of the SSNMR Data Using SpinSight: Apodizing

44. After I obtained the SpinSight software and set up the Sun computer with the Solaris 9 operating system (which are outdated hardware and software), I opened the files on which the exhibits in Dr. Munson's expert report are based. In order to process the raw, "time domain" data, many choices of parameters were required. For example, the SpinSight software

requires that the data be apodized. Apodize is defined in the Allwords.com English Dictionary as "to remove or smooth a sharp discontinuity in a mathematical function." The choices for apodization using the SpinSight Software are as follows:

"Exponential

Gaussian

Sinebell

Sinebell Sq

Trapezoidal

Kaiser

Hamming

Hanning

Hanning Enhanced"

Table 6-1 from the SpinSight Software manual that contains the apodization choices is attached as Exhibit H.

45. One must choose one of these nine methods of data manipulation in order to process the raw data provided by Dr. Munson. The choice of apodization affects the shape of the peaks in the SSNMR spectra.

46. Dr. Munson's Report does not reveal which of the 9 parameters he used. He should have done so. For example, Dr. Brittain testified as follows:

"Q. What algorithm did Dr. Munson use for deconvolution?

A. That would have been in the details of the program, but it is, all he says is he has deconvoluted it."

(Evans Decl., Ex. 8 at 119:15-19 (Brittain Dep.).)

47. Based on analyzing the Munson SSNMR data and attempting to match my results with those Dr. Munson provided in the exhibits to his expert report, it is my opinion that Dr. Barich chose the "Exponential" function for apodization. This means that Dr. Barich thought the SSNMR peaks would be best represented by an exponential shape, rather than, for example, by a Gaussian shape. (An exponential line shape is usually referred to as a Lorentzian line shape.) This choice means that Dr. Barich predisposed the SSNMR peaks to be exponential (Lorentzian) rather than Gaussian in shape.

48. Dr. Munson apparently did not understand that Dr. Barich had chosen the exponential or Lorentzian apodization function. In his deposition, Dr. Munson stated: "Gaussian lines are oftentimes found in solid-state NMR spectroscopy." (Evans Decl, Ex. 22 at 198:22-23 (Munson Dep.).) In summary, the apodization function affects the shape of the peaks in the SSNMR spectra. Dr. Munson's conclusion that the manipulated Abraxane samples contain a small percentage of crystalline paclitaxel is based on the shape of the peaks in his SSNMR spectra. Given that apodization does alter the shape of peaks, Dr. Munson's conclusions are called into question.

Critical Details of the SSNMR Data Using SpinSight: Phasing

49. Another step in the processing of the raw data is referred to as phasing. As can be seen in Exhibit I, the SSNMR operator has choices to make with regard to the phasing of the spectrum. Phasing is another critical parameter in determining the shape of the SSNMR peaks. For example, in Exhibit J, I have phased the Barich data for the run associated with file name "formul_AsRec_vacp5.5k_pd2" (Abraxane total composition) in two ways. First, I phased the

spectrum so as to obtain a smooth baseline at the extremities of the pattern. Second, I phased the spectrum so as to obtain a smooth baseline with regard to the peak at approximately 203 ppm. As one may observe, the shape of the peaks changes dramatically based on this choice.

50. I do not know how Dr. Barich and Dr. Munson phased the spectra which ended up as exhibits to Dr. Munson's expert report. Again, this information is not provided in Dr. Munson's report. It must be emphasized that it is not scientifically acceptable to base an opinion on a spectrum without providing the critical details of the collection of the data and the presentation of the spectrum.

Critical Details of the SSNMR Data Using SpinSight: Deconvolution

51. Dr. Munson deconvoluted one peak from each of 3 of the 34 spectra generated from Barich's SSNMR runs. Dr. Munson's report does not explain why he chose to deconvolute only 3 of the 34 spectra.

52. An essential step in Dr. Munson's report is that in the deconvolution analysis a third peak "appcared," and that this third peak represented a new crystalline form of paclitaxel. Without the presence of this third peak, there is no basis for his opinion that any of the paclitaxel in the manipulated Abraxane samples was crystalline. As will be explained below, a review of the evidence demonstrates that Dr. Munson himself manufactured the third peak, contrary to accepted scientific practice.

53. It is well known that one deconvolutes a peak into the minimum number of peaks necessary for a good fit. Dr. Brittain agrees with my opinion (Evans Decl., Ex. 8 at 119:20-120:7 (Brittain Dep.)):

"Q. Did Dr. Munson input the desired number of peaks?

A. My understanding about the deconvolution routines is that's part of the input - you put in the number of peaks. You then see how the program matches up some of those peaks, basically minimizing the differences between the calculated sum and the experimental, and then the proper result is the one that can satisfactorily ***fit the peak with the smallest differences, but with the least number of peaks***." (my emphasis)

54. When two peaks fit just as well as three in both the air-dried and freeze-dried manipulated Abraxane samples, it is scientifically improper to choose a three peak fit, as Dr. Munson did.

55. In order to deconvolute a peak using the SpinSight software, the user must first decide on the number of peaks. Dr. Munson's description in paragraphs 21 and 22 of his report of a third peak "appearing" in the manipulated Abraxane samples seems strange, as the SpinSight software requires a user to manually input the number of peaks desired. Indeed, Dr. Munson and Dr. Barich both testified to the fact that Dr. Munson manually inputted the third peak. (Evans Decl., Ex. 26 at 186:25-189:1 (Barich Dep.); Ex. 22 at 214:2-221:18 (Munson Dep.).) Not only does the user choose the number of peaks, the user can also choose: 1) the peak position 2) the peak width; and 3) the peak shape. In other words, this process is subjective. After a user enters these parameters, the user can then chose to have the SpinSight software "refine" the results. Refining may involve, for example, modification of the placement of the peaks, the peak widths, and the percent Gaussian/Lorentzian of the peaks.

56. Dr. Munson's report is again silent as to the deconvolution procedure used, let alone the exact details one would need to reproduce Dr. Munson's deconvolution.

Dr. Munson Improperly Deconvoluted the SSNMR Peak at about 203 ppm

57. I attempted to recreate Dr. Munson's deconvolution of the peak at around 203 ppm using the SpinSight software. As Elan's experts have not disclosed any of the deconvolution parameters used, I have chosen parameters with the objective of reproducing Dr. Munson's spectra.

58. First, I deconvoluted the peak at approximately 203 ppm in the spectrum for the amorphous sample. The spectrum is attached as Exhibit K. This spectrum was generated from the same run that Dr. Munson discloses in his report as Appendix E. My deconvolution into two peaks refines to give an acceptable fit.

59. Then, I deconvoluted the peak at approximately 203 ppm in the spectrum for the manipulated sample of Abraxane that was freeze-dried. The spectrum is attached as Exhibit L. This spectrum was generated from the same run that Dr. Munson discloses in his report as Appendix G. My deconvolution into two peaks refines to give an acceptable fit. In fact, the fit of two peaks for this spectrum was even better than for the two peaks in the amorphous sample spectrum.

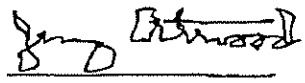
60. I also deconvoluted the peak at approximately 203 ppm in the spectrum for the manipulated sample of Abraxane that was air-dried. The spectrum is attached as Exhibit M. This spectrum was generated from the same run that Dr. Munson discloses in his report as Appendix H. My deconvolution into two peaks refines to give an excellent fit. In fact, the fit of two peaks for this spectrum was even better than for the two peaks in the amorphous sample spectrum. For the air dried sample, I also entered a third peak. This spectrum is attached as Exhibit N. The result, in terms of fit, was no better for the three peaks than for the two peaks.

Moreover, the third peak that I entered, after the SpinSight software refined the peak parameters, is a different shape and position than the third peak in Dr. Munson's Appendix L.

61. Dr. Munson, in his attempt to find crystallinity, has used the SpinSight deconvolution software in a manner for which it is not intended. I note in the SpinSight manual, page 7-20, Figure 7-9 which is "An expanded region before deconvolution", and Figure 7-10 which is "An expanded region after deconvolution." (Exhibit O.) One may observe that all nine of the peaks found in the deconvoluted pattern are observable in the pattern before deconvolution. (*Id.*) This stands in stark contrast to Dr. Munson's deconvolution in which he manufactures a small third peak which is buried under the two main peaks. Deconvolution is not meant to be used for the purpose of manufacturing peaks. There is no third peak in a proper deconvolution of the peak at about 203 ppm using the SpinSight software routine for deconvolution. It is not scientifically proper to use deconvolution to conjure up a peak where none exists.

I declare under penalty of perjury of the laws of the United States of America that the foregoing is true and correct.

Executed this 27th day of March, 2008 at Orange Beach, Alabama.



Jerry Atwood

EXHIBIT 14

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	Case No. 06-438-GMS

DECLARATION OF EMILY EVANS IN SUPPORT OF ABRAXIS'S MOTION IN LIMINE NOS. 1 AND 2

I, Emily A. Evans, declare as follows:

1. I am an attorney admitted to practice law in the State of California, and I am admitted *pro hac vice* in the above-captioned action. I am a Partner in the law firm of Morrison & Foerster LLP, attorneys for Abraxis BioScience, Inc. ("Abraxis") in the above-captioned action. I submit this Declaration in Support of: (1) Abraxis's Motion in Limine No. 1 to Strike Portions of Elan Expert Harry Brittain's Expert Report Regarding Testing of Abraxane And To Bar Related Testimony And Argument; and (2) Abraxis's Motion in Limine No. 2 to Exclude Evidence of Elan's SSNMR Testing of Abraxane. I have personal knowledge of the matters set forth herein, and if called upon to do so, I could and would competently testify thereto.

October 2, 2007 Hearing

2. At the October 2, 2007 hearing before the Court, Abraxis moved to compel production of certain documents and interrogatory responses related to Elan's testing of

Abraxane. Abraxis's counsel argued, among other things, that the Federal Rules required Elan to produce all testing conducted by Elan's testifying experts:

> We have their expert report now, with some testing data. But they only want to show the jury the testing data that they like. We don't really think much of their testing data. But we think the jury ought to have the whole story.

(Exhibit 1 at 85:20-24.)

3. In response, Elan's counsel represented to the Court that Elan had "preserved all the walls between consultants and testifiers." (Exhibit 1 at 90:8-14.) Attached as Exhibit 1 is a copy of relevant portions of the transcript.

4. At the hearing, Abraxis also requested that Elan log all testing documents it contended were protected by privilege or work-product immunity. In response, Elan's counsel represented to the Court that these testing documents had already been identified on Elan's privilege log, an amended version of which had been served on August 31, 2007. (Exhibit 1 at 90:15-21; *see also id.* at 89:22-90:3.)

5. Below is a summary of events that occurred during the course of expert discovery relating to Elan's testing, organized for the Court's convenience by the expert at issue.

Dr. Harry Brittain

6. On September 28, 2007, Elan submitted an Opening Expert Report from Dr. Brittain. In this Report, Dr. Brittain opines, among other things, that Abraxane meets the "crystalline" limitation of the '363 patent. A copy of his Opening Expert Report (without exhibits) is attached as Exhibit 2. Elan has placed Dr. Brittain on its list of witnesses it "may call" during trial. (Exhibit 3.)

7. On October 19, 2007, Abraxis subpoenaed Dr. Brittain, requesting "Documents, including laboratory notebook entries, raw data, reports, memoranda, or other communications, including electronic mail messages or other electronic information, regarding laboratory manipulation or testing of Abraxane or derivatives of Abraxane." (Exhibit 4 at 5, No. 12.) Elan lodged objections under the privilege and the work-product doctrines. (Exhibit 5 at 10.)

8. On November 15, 2007, Elan produced a privilege log to Abraxis with documents withheld from Dr. Brittain's files. This log was produced less than 24 hours in advance of Dr. Brittain's deposition. The log contained 466 entries, all but 10 of which were described as "test data" or "laboratory notebook[s] reflecting tests." All of the entries are dated before July 31, 2007. Elan's privilege log served on August 31 does not have any entries in which Dr. Brittain is identified.[1] A copy of the Brittain log is attached as Exhibit 6. Elan's representation at the October 2 hearing that Elan had already furnished Abraxis with a complete privilege log was thus incorrect.

9. In mid- to late-November 2007, Abraxis's counsel requested the withheld documents, stating that the "Federal Rules and case law make clear that Elan has waived any privilege or work product over Brittain's documents, as Brittain is a testifying expert." Relevant correspondence is attached as Exhibit 7 (11/15/07 email from Kruze to Elan; 11/28/07 email from Kruze to Glover; 11/29/07 email from Glover to Kruze).

[1] Elan's privilege log contains approximately 30 entries with a "Consulting expert" listed in the "to" or "from" field. It is impossible to ascertain whether any of these entries overlap with Dr. Brittain's log, as many of Dr. Brittain's entries do not have a date, the descriptions are vague, and none of the "consulting experts" are identified by name in Elan's log.

10. To date, Elan's counsel has refused to produce its withheld testing documents. In a meet and confer, Elan stated that its basis for withholding these documents was that Brittain was retained as a consulting expert prior to the litigation by Elan counsel William Sipio. Elan maintains that the work done by Brittain for Sipio was separate and distinct from this lawsuit. (*See id.*)

11. A copy of excerpts from the transcript of Dr. Brittain's deposition, which took place on November 16, 2007, is attached as Exhibit 8. At his deposition, Elan's counsel instructed Dr. Brittain not to answer questions regarding his testing of Abraxane, again claiming privilege. (*See, e.g.*, Exhibit 8 at 6:13-7:13.)

Dr. Jeffrey Winkler

12. On September 28, 2007, Elan served an Opening Expert Report from Dr. Munson, which is attached as Exhibit 9. The Winkler Declaration was part of Dr. Munson's Report. Dr. Winkler's Declaration discusses the paclitaxel samples used as controls in Elan's SSNMR testing of Abraxane. (Exhibit 9 at Appendix M.) Dr. Munson relied on the Winkler Declaration in forming the opinions expressed in his expert report. (Exhibit 9 ¶¶ 8 & 14.) Elan has placed Dr. Winkler on the list of witnesses it "may call" during trial. (Exhibit 3 at 4.)

13. On October 19, 2007, Abraxis subpoenaed Dr. Winkler, requesting "Documents, including laboratory notebook entries, raw data, reports, memoranda, or other communications, including electronic mail messages or other electronic information, regarding laboratory manipulation or testing of Abraxane or derivatives of Abraxane." (Exhibit 10 at 5, No. 12.) Elan lodged objections under the privilege and work-product doctrines. (Exhibit 11 at 11.)

14. After an exchange of correspondence, on November 28, 2007 attorneys for Abraxis and Elan held a telephone conference regarding Elan's withholding of testing documents in the files of Elan's experts. During that call, Elan's counsel stated that Elan was withholding testing documents only from Dr. Brittain's files. (Exhibit 12.)

15. On February 12, 2008, Elan produced a privilege log listing documents withheld from Dr. Winkler's files. This log was produced less than 24 hours before Dr. Winkler's deposition. There were eleven entries described as "report discussing infringing product." (Exhibit 13.) Elan's counsel represented on the record at the deposition that these entries "relate to privileged information documents involving Dr. Winkler." (Exhibit 14 at 305:14-25.) Dr. Winkler confirmed that the entries "relate[d] to testing of Abraxane." (*Id.*)

16. To date, Elan's counsel has refused to produce these withheld testing documents.

17. Elan also resisted Abraxis's requests to depose Dr. Winkler for several months. Abraxis's subpoena, dated October 19, 2007, instructed Dr. Winkler to appear for a deposition on November 30, 2007. (Exhibit 10.) Elan refused to produce Dr. Winkler until it "reconsidered its objections" on January 4, 2008. Relevant correspondence is attached as Exhibit 15 (10/25/07 email from Walters to Glover and 1/4/08 email from Glover to Walters).

18. Dr. Winkler signed his Declaration under penalty of perjury. (Exhibit 16 at 3.) In his declaration, Dr. Winkler stated that "***I prepared*** amorphous [and crystalline dihydrate] paclitaxel. (*Id.* at 2-3 (emphasis added).) At his deposition, finally held on February 13, 2008, Dr. Winkler admitted that he did not personally prepare the samples; rather, Riichiro Tsuji and Ronald Bihovsky prepared the samples. (Exhibit 14 at 47:4-48:8.) Attached hereto as Exhibit 14 is a copy of excerpted pages from Winkler's deposition transcript.

19. Elan and Elan's experts did not disclose that Riichiro Tsuji and Ronald Bihovsky prepared the paclitaxel standards used in Elan's testing until Dr. Winkler revealed this at his deposition.

20. At his deposition, Elan's counsel instructed Dr. Winkler not to answer questions regarding his testing of Abraxane, again claiming privilege. Elan's counsel did allow Dr. Winkler to confirm that he conducted at least 3 additional tests on Abraxane. (*See, e.g.*, Exhibit 14 at 333:3-4, 9-20.) Elan's counsel would not, however, allow questioning into what specific types of tests Dr. Winkler conducted.

Drs. Cory Berkland and Lianjun Shi

21. On September 28, 2007, Elan submitted Dr. Berkland's Opening Expert Report. In this Report, Dr. Berkland opines, among other things, about infringement of the '363 patent by Abraxis. Dr. Berkland's Opening Report states that "the nanoparticle components of samples of Abraxane were isolated in our lab." (Exhibit 17 ¶ 14.) A copy of his expert report (without exhibits) is attached as Exhibit 17. Dr. Berkland's Report does not mention Dr. Lianjun Shi. (*Id.*)

22. During his deposition, Dr. Berkland testified that he did not prepare the nanoparticle fractions of Abraxane; rather, Dr. Shi did. (Exhibit 18 at 200:12-201:10.) A copy of relevant portions of Dr. Berkland's deposition transcript is attached as Exhibit 18.

23. Abraxis subpoenaed Dr. Shi. A copy is attached as Exhibit 19.

24. Elan initially resisted producing Dr. Shi for deposition and filed a motion to quash on December 18, 2007 in the Federal District Court for the Southern District of New York. Elan's motion is attached as Exhibit 20. Elan finally agreed to present Dr. Shi for deposition on

January 7, 2008. Attached hereto as Exhibit 21 is a copy of excerpted pages from the deposition of Dr. Lianjun Shi. At deposition, Dr. Shi testified that he prepared the Abraxane test samples, but that he had not maintained records of the preparation conditions or kept the test samples themselves. (Exhibit 21 at 42:1-43:16; 143:18-144:25.)

25. At his deposition, Dr. Shi confirmed that he personally prepared the manipulated Abraxane samples that Elan conducted testing on. (Exhibit 21 at 42:1-43:2.)

26. Dr. Shi did not produce a single document in connection with his work on Elan's testing of Abraxane.

27. Elan has placed both Drs. Shi and Berkland on its list of witnesses it "may call" during trial. (Exhibit 3.)

Dr. Dewey Barich

28. Dr. Munson's report stated that "solid-state NMR spectroscopy . . . was used to investigate the samples provided to me." (Exhibit 9 ¶12.) Dr. Munson's report does not mention Dr. Barich. (*See generally* Exhibit 9.)

29. At Dr. Munson's deposition, Dr. Munson revealed for the first time that Dr. Barich conducted the actual NMR experiments Munson reported and relied on. (Exhibit 22 at 33:3-4.) Attached hereto as Exhibit 22 is a copy of excerpted pages from the deposition of Dr. Eric Munson taken on November 29, 2007.

30. On November 30, 2007, Abraxis subpoenaed Dr. Barich for deposition on December 13, 2007. Attached as Exhibit 23 is a copy of Dr. Barich's original subpoena, along with Elan's objections.

31. Dr. Barich did not appear at his deposition as noticed on December 13, 2007. A transcript of his non-appearance is attached as Exhibit 24.

32. The next day, on December 14, 2007, Elan filed a motion to quash Dr. Barich's subpoena in the Federal District Court for District of Kansas. The motion, without exhibits, is attached as Exhibit 25.

33. After resisting production of Dr. Barich, Elan's counsel finally made him available on January 25, 2008. Attached hereto as Exhibit 26 is a copy of excerpted pages from the deposition of Dr. Dewey Barich. Dr. Barich confirmed at his deposition that he personally conducted the NMR runs on the paclitaxel samples, Abraxane, and manipulated Abraxane samples. (Exhibit 26 at 23:11-15.)

34. Elan has placed Dr. Barich on its list of witnesses it "may call" during trial. (Exhibit 3.)

Dr. Munson

35. Elan also engaged in obstructive practices to hide much of the SSNMR data that Dr. Munson evaluated in rendering his opinions.

36. In his Opening Report, Dr. Munson relied on certain SSNMR data to reach his conclusion that the paclitaxel in Abraxane contains a small portion of crystallinity. Dr. Munson attached six SSNMR spectra to his Opening Report. Dr. Munson's report did not reveal many underlying facts related to his testing, including the software he used, and the fact that Dr. Barich conducted 34 SSNMR runs total in connection with this case. (*See generally*, Exhibit 9 (Munson

Report).) These 34 tests were conducted between January 2007 and May 2007. (*See, e.g.*, Exhibit 26 at 65:8-13 (Barich Dep.).)

37. Abraxis served Dr. Munson with a subpoena, requesting "Documents, including laboratory notebook entries, raw data, reports, memoranda, or other communications, including electronic mail messages or other electronic information, regarding laboratory manipulation or testing of Abraxane or derivatives of Abraxane." Attached hereto as Exhibit 27 is a copy of Abraxis's subpoena to Dr. Eric Munson dated October 19, 2007, and Elan's objections.

38. Dr. Munson "produced" several sets of both hardcopy and electronic raw data in connection with his SSNMR testing of Abraxane. The following is a summary of Munson's hard copy and electronic productions.

Hardcopy "Production"

39. The following is a chart listing the dates of production for all hard-copy documents produced:

Date Produced to Abraxis's Counsel	Document Production Number
November 7, 2007	MUNSON 1-1865
November 8, 2007	MUNSON 1866-2202
November 20, 2007	MUNSON 2204-2463
November 29, 2007	MUNSON 2264-2325
December 13, 2007	MUNSON 2464-7282
December 14, 2007	MUNSON 7283-9882
January 22, 2008	MUNSON 9883-10128

January 24, 2008	MUNSON 10129-10663

40. Attached as Exhibit 28 is a chart sent to Abraxis by Elan summarizing the exact dates Elan produced hardcopy documents regarding the 34 NMR experiments conducted. ("Munson Data Summary")

41. Elan had produced data from only 3 runs (out of 34) by November 8, 2007. (Exhibit 28.) These 3 runs, according to Elan's chart, did not represent any of the data used in Munson's final report. (Exhibit 28.) As of Dr. Munson's deposition, which occurred on November 29, Elan had produced only 1/11th of Munson's testing data.

42. Elan produced hardcopy data associated with 16 out of the 34 runs on December 14, 2007, the day expert discovery closed, and two weeks after Dr. Munson's deposition. On December 18, Elan produced hardcopy data associated with 8 more runs. Finally, on January 22 and 24, one year after the SSNMR tests began, Elan produced the hardcopy data relating to the remaining 7 experiments.

43. As the accompanying declaration of Dr. Atwood explains, much of this hard copy data was unintelligible. (*See, e.g.*, Atwood Decl. at ¶¶ 34-39.)

44. Dr. Barich testified at his deposition that Dr. Munson requested that Dr. Barich create a special software program to convert the testing data from their native format into text files. (Exhibit 26 at 231:25-234:1 (Barich Dep.).) Dr. Barich further testified that he found Munson's request to convert the data both "unusual" and "a little surprising." (*Id.* at 234:22-

235:18.) Dr. Barich also testified that the hard copy documents of the data files were not produced to Abraxis as they were kept in the ordinary course of business. (*Id.* at 232:5-23.)

Electronic "Production"

45. On November 19, 2007, Elan produced a disc containing electronic data and bates labeled MUNSON 2203.

46. The files containing the actual time domain data from the SSNMR runs would not open on a Morrison & Foerster computer.

47. On November 21, 2007, a paralegal at Morrison & Foerster uploaded a copy of the electronic files to Dr. Atwood, Abraxis's expert. (Exhibit 29.)

48. Dr. Munson's report did not reveal the type of software or computer he used to generate his data files. (*See generally*, Exhibit 9 (Munson report).)

49. During his deposition on November 29, 2007, Dr. Munson revealed that he used a software called "SpinSight." (Exhibit 22 at 184:22-185:2.)

50. My colleague, Frank Wu of Morrison & Foerster, contacted Kevin Geohring at Varian about obtaining the SpinSight software on December 3, 2007. I understand from Mr. Wu that Mr. Geohring told him that the software was available from Debra Mulder at Varian, but would require the Sun operating system to run and payment of a licensing fee.

51. On December 7, 2007, Morrison & Foerster hired an outside consultant (Mr. S. Whitehead) to prepare a computer with a Sun Solaris 9 operating system. On December 10,

2007, Mr. Whitehead began working on the project, and returned a Morrison & Foerster HP laptop loaded with the Solaris 9 software on December 17, 2007.

52. Also on December 17, 2007, Morrison & Foerster LLP signed a license with Varian for the SpinSight software for $1100. The software was sold to us "as is," with no technical support, as Varian informed me that this was a legacy product. A copy of the license is attached as Exhibit 30.

53. We received a copy of the SpinSight software on January 8, 2008. Also on January 8, 2008, the SpinSight software was loaded onto the laptop with the Sun operating system and forwarded to Dr. Atwood.

54. In mid-January, Dr. Atwood informed me that the SpinSight software was not functioning correctly. Dr. Atwood also informed me that he had hired an IT specialist to assist him with the software/hardware problems. I understand from Dr. Atwood that this IT specialist informed Dr. Atwood on January 23, 2008 that the software would not operate unless it was loaded onto an actual Sun Microsystems workstation, as opposed to the Intel-based laptop we had originally provided. Shortly thereafter, Dr. Atwood told me he had acquired a Sun workstation.

55. Morrison & Foerster communicated with Elan's counsel several times regarding Elan's failure to produce the SSNMR documents in usable format. The relevant correspondence is attached as Exhibit 31 (12/4/07 email from Evans to Sullivan; 1/23/08 email from Kruze to Sullivan; 1/24/08 email from Sullivan to Kruze; 2/8/08 e-mail from Kruze to Sullivan; 2/22/08 e-mail from Sullivan to Kruze.)

56. As explained by Dr. Atwood in his declaration, Drs. Munson and Barich did not reveal several critical parameters regarding their SSNMR work. Without these parameters, Abraxis still cannot accurately replicate the SSNMR spectra that Dr. Munson considered when forming his opinions. For a further description, please see the Declaration of Dr. Jerry Atwood.

I declare under penalty of perjury of the laws of the United States of America that the foregoing is true and correct.

Executed this 27th day of March, 2008 at Palo Alto, California.

Emily A. Evans

EXHIBIT 15

ISI's 50 Most Cited Chemists, 1981-June 1997, ranked by total citations:

David A. Pendlebury

Name	Papers 81-June 97	Citations 81-June 97	Cites/Paper (Impact)
1-10			
A.Bax	152	21,655	142.47
J.A.Pople	176	14,044	79.80
P.V.Schleyer	525	13,559	25.83
R.R.Ernst [N]	182	13,069	71.81
G.M.Whitesides	318	12,310	38.71
H.F.Schaefer	515	11,921	23.15
J.C.Huffman	577	11,654	20.20
A.L.Rheingold	830	11,317	13.63
D.Seebach	349	11,275	32.31
J.M.Lehn [N]	307	10,823	35.25
11-20			
T.J.Meyer	267	10,490	39.29
R.E.Smalley[N]	96	10,456	108.92
A.J.Bard	333	10,365	31.13
D.G.Truhlar	328	10,310	31.43
J.J.P.Stewart	39	10,179	261.00
E.J.Corey [N]	303	10,129	33.43
F.A.Cotton	634	9,911	15.63
P.A.Kollman	140	9,703	69.31
M.J.S.Dewar	119	9,701	81.52
W.L.Jorgensen	154	9,695	62.95
21-30			
R.N.Zare	290	9,617	33.16
B.M.Trost	332	9,302	28.02
C.W.Bauschlicher	351	9,139	26.04
A.H.White	866	9,107	10.52
R.Taylor	221	9,020	40.81
R.J.Bartlett	251	8,984	35.79
G.A.Somorjai	328	8,958	27.31
K.N.Houk	287	8,654	30.15
T.J.Marks	217	8,366	38.55
S.J.Lippard	230	8,342	36.27
31-40			
K.Raghavachari	123	8,272	67.25
R.Hoffmann [N]	248	8,269	33.34

A.H.Zewail	211	8,208	38.90
J.L.Atwood	348	8,109	23.30
M.B.Hursthouse	659	8,008	12.15
J.M.White	367	7,961	21.69
K.B.Sharpless	148	7,931	53.59
R.Freeman	151	7,961	52.32
D.J.Williams	656	7,761	11.83
R.R.Schrock	235	7,725	32.87
41-50			
H.W.Kroto [N]	140	7,514	53.67
M.Karplus	141	7,459	52.90
G.M.Sheldrick	441	7,453	16.90
D.A.Evans	148	7,409	50.06
L.A.Paquette	529	7,402	13.99
G.Ertl	242	7,347	30.36
K.C.Nicolaou	228	7,337	32.18
R.Noyori	183	7,281	39.79
W.A.Herrmann	387	7,337	18.57
D.H.R.Barton[N]	407	7,183	17.65

[N] = Nobel laureate.

From:

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Notes and Elaborations

The following data are offered for your interest. I recently searched the ISI database, 1981-June 1997, for all chemistry papers and their citation counts (how many times they were cited) through 1997. I then summarized the data by author name (ISI indexes all authors on a paper, not just first author). Thus, the statistics below represent so-called all-author counts.

It is important to recognize what I surveyed and what I did not. The data represent citations recorded over 1981-June 1997 to ISI-indexed chemistry papers 1981-June 1997, and do not represent citations to books, to pre-1980 papers indexed by ISI, or to any papers not indexed by ISI during 1981-June 97. We have defined chemistry as any paper appearing in journals that ISI has classified as chemistry, organic chemistry, physical chemistry, chemical

engineering, analytical chemistry and all chemistry subfields used for Current Contents.

There were some 627,871 unique author names found in the set. **Only 10,858 (1.7%) were cited 500 times or more**. The 50 names below appear on the top of the first page of a printout of the authors cited 500 times or more that runs about 100 pages. These 50 highly cited chemists represent the top .01% worldwide in terms of total citations.

Seven Nobel laureates appear (marked by [N]), and I bet another 6-10 listed here are Nobel laureates-to-be (time will tell if this forecast is accurate). Lists like this one compiled over the last few decades have contained the names of many laureates-to-be. See E. Garfield and A. Welljams-Dorof, "Of Nobel Class: A Citation Perspective on High Impact Research Authors," Theoretical Medicine, 13:117-35, 1992, for an overview.