Probing Molecular Motion and Chemical Reactions inside the Chiral Tri-*o*-thymotide Clathrate Cavity by Solid State NMR Techniques†

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Solid state NMR techniques offer a non-destructive alternative to wet chemistry methods in following enantiomeric excess and reactions in chiral clathrates, and show that the two optically distinct populations, one of which cannot be defined by X-ray diffraction, can be characterized by their distinct dynamic behaviour.

The enantioselectivity of tri-*o*-thymotide (TOT) has generated a great deal of interest over the last thirty years or so.[1–5] The ability of single crystals of this material to enclathrate preferentially one enantiomer of a racemic pair has been studied by both X-ray diffraction[3,6,7,8] and polarimetric[2,3] methods. X-Ray diffraction data sometimes fail to locate guest molecules inside the cage structure and are often unable to characterize fully any disorder the guest may exhibit. Polarimetry requires the use of relatively large single crystals of the clathrate which must be destroyed in order to measure the optical rotation of the guest. Solid state ^{13}C CP-MAS NMR has recently been used to study powdered TOT clathrates of chiral molecules.[4] This technique is non-destructive and provides structural as well as dynamic information regarding both the host and guest. It has also been used to estimate the enantiomeric excess of chiral guests inside the cages of powdered samples.

Despite the extensive information on TOT inclusion compounds, the chiral discrimination mechanism is still not well understood. Evidently, the preferential incorporation of one enantiomer over the other involves a dynamic interaction between the guest and host. Hence it is of some importance to define the motional state of the two enantiomers with the ultimate aim of defining exact host–guest potentials. This is especially important in light of the incomplete information obtained from diffraction measurements.

Interest has also been expressed in performing stereospecific chemical reactions involving reactive gases and prochiral molecules trapped within the dissymmetric cages of TOT.[9,10] Such reactions using epoxides and hydrogen halides as reactants have produced chiral reaction products exhibiting enantiomeric excesses. The reaction products have only been characterized after their removal from the host material. There seems to be little direct evidence to show that these reactions do indeed occur inside the cages rather than outside the cages during the course of isolating the guest material from the host.

In this communication we report the use of solid state ^{2}H NMR spectroscopy to distinguish between the favoured and unfavoured enantiomers of (*RS*)-2-bromo[1,1,1-$^{2}H_3$]butane inside the cages of TOT. We also report the use of ^{13}C CP-MAS NMR to follow, non-destructively, the progress of the chemical reaction of enclathrated *cis*-2,3-epoxybutane with HBr gas.

TOT was prepared by methods described previously.[11] (*RS*)-2-Bromo[1,1,1-$^{2}H_3$]butane was prepared by the action of phosphorus tribromide on the labelled alcohol, which in turn was prepared *via* Grignard reaction from propanal with deuterium labelled methylmagnesium iodide (Aldrich).

cis-2,3-Epoxybutane was purchased from Aldrich and used without further purification. TOT clathrates were prepared from small amounts of these solvents by rapid recrystallization of the guest-free host. The reaction of TOT–*cis*-2,3-epoxybutane was conducted by the slow passage of HBr gas (produced by the action of Br_2 on tetrahydronaphthalene) over the finely powdered clathrate.

All solid state NMR spectra were recorded on a Bruker CXP-180 pulse NMR spectrometer operating at 27.6 MHz for ^{2}H and 45.3 MHz for ^{13}C. The ^{2}H spectra were recorded using the quadrupolar echo technique.[12] The ^{13}C CP-MAS spectra were recorded using a pulse sequence to suppress first order spinning sidebands.[13]

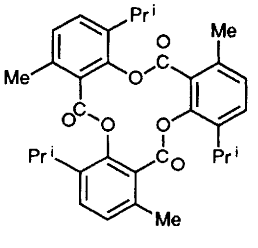
The solid state ^{2}H NMR spectrum of TOT–(*RS*)-2-bromo[1,1,1-$^{2}H_3$]butane at 273 K is shown in Fig. 1*a* along with fast motional limit lineshape simulations[14] in Fig. 1*b*. The spectrum is clearly the sum of two contributions indicating the presence of two distinct populations of the guest molecules, each with differing degrees of mobility. In order to understand the presence of two populations one must take the stereochemistry into account.

It has long been known that when recrystallized from suitable solvents, TOT is spontaneously resolved into (+) and (−) crystals,[1] providing dissymmetric cages of opposite handedness. With two types of host crystallites in the powdered samples used and both *R* and *S* guests, four combinations are possible (Scheme 1).

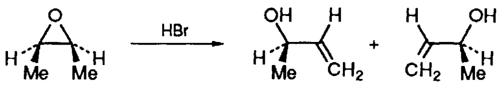
Of these four possibilities there are two diastereoisomeric pairs of enantiomorphs. The members of each pair are indistinguishable by NMR methods; however, the pairs can be distinguished from one another as they are chemically inequivalent. There are two possible environments for a given

(+)Host-*R* Guest
Enantiomorphs
(−)Host-*S* Guest
Diastereomorphs
(+)Host-*S* Guest
Enantiomorphs
(−)Host-*R* Guest

Scheme 1



TOT



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† NRCC No. 32502.

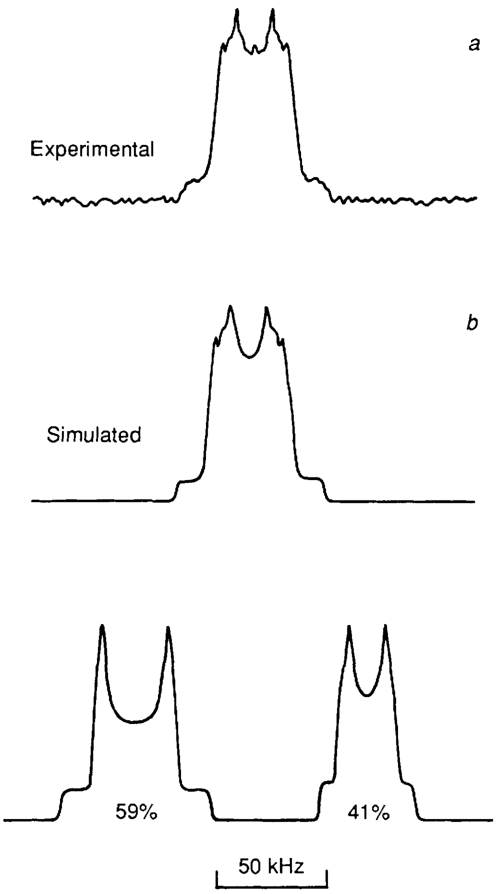

Fig. 1 *a*, Solid state ^2H NMR spectrum of TOT-2-bromo-[1,1,1-$^2H_3$]butane at 273 K. The spectrum was obtained using the quadrupolar echo technique with 90° pulse lengths of 3 μs and echo delays of 35 μs. *b*, Fast motional lineshape simulations used to represent the spectrum in *a*. 1.8 kHz of Gaussian broadening was applied to each contribution before addition. Narrow component: (e^2Qq/h) = 28 kHz, asymmetry parameter = 0.245. Broad component: (e^2Qq/h) = 45 kHz, asymmetry parameter = 0.125.

guest molecule. The population difference in these environments is a reflection of the enantiomeric excess of the guest and the clear lineshape difference for each contribution shows that there are quite distinct degrees of mobility for each type of guest molecule. For a completely rigid methyl group one would expect to observe a quadrupolar coupling constant (e^2Qq/h) of 170 kHz. A rapidly rotating methyl group would be expected to yield a quadrupolar coupling constant of 57 kHz. The quadrupolar coupling constants exhibited by each of the contributions in Fig. 1*b* are 45 and 28 kHz for the broad and narrow components, respectively. Both are lower than expected for a simple methyl group rotation suggesting that the molecules have additional degrees of molecular freedom inside the cavity. The distinct mobility of the two enantiomers probably has its origin in the non-specific van der Waals guest–host interactions, much the same as the chiral discrimination itself.

As opposed to the equilibrium samples produced by slow recrystallization, the samples used in this study, prepared by rapid recrystallization showed an enantiomeric excess of only 18% as the populations are present in a 59 : 41 ratio. This is in agreement with ^{13}C data obtained for the same sample. The reduced discrimination in this case, from those reported previously,[3,4] suggests that the enantiomeric excess can be controlled kinetically and that the finely powdered samples produced in this manner can be studied uniquely by solid state NMR techniques.

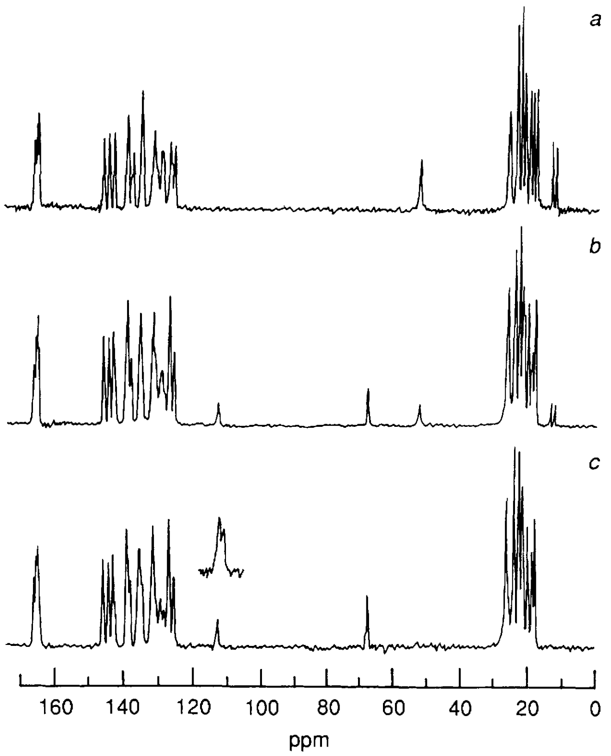

Fig. 2 *a*, Solid state ^{13}C CP–MAS spectrum of TOT-2,3-epoxybutane. *b* and *c*, Spectra taken after the clathrate in *a* was exposed to HBr gas for 15 and 120 min respectively. The spectra were acquired using a pulse sequence to suppress first order spinning sidebands. 3K data points were collected using a sweep width of 20 kHz. The 90° pulse length was 3.8 μs, and contact times of 3 ms were used. Spinning rates were typically 3.6 kHz.

The ^{13}C CP–MAS NMR spectrum of TOT-*cis*-2,3-epoxybutane is shown in Fig. 2*a*. The guest resonances appear at δ 52.4, 13.5 and 12.4 ppm ($SiMe_4$ at 0 ppm). The enantiotopic methyl carbons[15] of the guest molecule which are normally equivalent in solution are nonequivalent inside the chiral environment provided by the TOT cages. As the reaction with HBr proceeds (Fig. 2*b* and 2*c*) new guest resonances at 67.6 and 112 ppm appear at the expense of the original ones. These are consistent with the C-2 and C-4 carbons of but-3-en-2-ol,[16] respectively, the C-1 and C-3 resonances being buried by the host spectrum.

The ^{13}C spectra confirm the reaction product identified previously[9] by wet chemistry techniques and also provide proof that the reaction takes place inside the clathrate cages. The sharpness of the TOT spectral lines indicates that even the short range order in the lattice is preserved during the reaction. On close inspection it can be observed that the resonance at 112 ppm is actually a doublet, analogous to those observed in the ^{13}C CP–MAS spectra for the TOT clathrates of the 2-substituted butanes.[4] The doublet is asymmetric indicating that the reaction is stereoselective. The chirality of the cavity must therefore have an effect on which one of the two C–O bonds is cleaved during the course of the reaction.

In conclusion, it has been shown that solid state ^2H NMR can successfully be used to distinguish between the two inequivalent populations of chiral guest molecules inside the dissymmetric cages of TOT. Studies are currently under way to characterize fully the molecular motion exhibited by each of the populations of enclathrated 2-bromobutane. It has also been shown that ^{13}C CP–MAS NMR can be used to follow, non-destructively, the reaction of TOT clathrates with reactive gases. The data unambiguously show that reactions are indeed able to occur within the cavities and that the stereochemistry of the reaction of enclathrated *cis*-2,3-epoxybutane is influenced by the chirality of the TOT cages.

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