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Toward a Scale of Functional Group Interaction Energies. Equilibrium Control of Functional Group Recognition in Channel Inclusion Compounds of Perhydrotriphenylene

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The notion of the functional group and scales of reactivity are the foundations upon which organic chemists rationalize and systematize reactions. For the supramolecular chemist, whose task it is to organize molecules into assemblies, the functional group again plays a central role. But the absence of a reliable scale of functional group interaction energies leaves one with only a vague notion of the strengths of many weak interactions.

In an attempt to isolate interactions between functional groups and then measure their interaction strengths, we have focused on the "parity" of guest molecule packing in *incommensurate*[1] channel inclusion compounds. Substances such as urea[2] and perhydrotriphenylene (PHTP)[3] form inclusion compounds with a wide variety of linear hydrocarbons and substituted analogues. Within these incommensurate systems, the guests exist in a multitude of roughly equivalent sites. In both types of channels, hydrocarbon guests typically pack in their extended forms,[4] with their methyl groups making van der Waals contact. If terminal methyl groups are replaced with different substituents, then the end-group parity can be "head-to-head" (HH), "tail-to-tail" (TT), or "head-to-tail" (HT). With a statistical distribution of guest orientations, the ratio of (HH + TT) and 2(HT) would be 1.

Most of our efforts have focused on achieving equilibrium control of guest partitioning. This is obviously important for measurement and transferability of functional group interaction energies. Here we show that equilibrium control can be achieved with short-chain guests included within the channels of PHTP, which are wide enough (~5.7–6.7 Å)[5] and flexible enough to allow rapid end-for-end exchange of guests at moderate temperatures. Since the PHTP channel centers are separated by 14.3 Å,[4b] interchannel ordering[6] of guests should be insignificant. Because this system *isolates* the interactions between functional group pairs that are held within van der Waals contact in a nonpolar channel of fixed dimensions, it holds promise as a powerful way of developing a self-consistent scale of interaction energies for a variety of functional group pairs.

The ^{13}C cross-polarization magic angle spinning (CP-MAS) NMR spectra[7] of dozens of unsymmetrically substituted alkanes ($X(CH_2)_nY$) included in urea and PHTP show asymmetric band doubling for terminal functional groups and adjacent carbons but none for internal carbons.[8] For the terminal groups, the doubling ordinarily arises from differences in nearest-neighbor functional groups within the channels, and band intensities reflect the distribution of guest orientations. Figure 1 shows the nitrile region of the CP-MAS spectra[9] of a series of aliphatic nitriles included within PHTP channels.[11,12] At 298 K, the longer chain mononitriles exhibit asymmetric doublets, while 1-cyanopentane gives a broad Lorentzian singlet close to the downfield resonance. The single line for sebaconitrile/PHTP gives the chemical shift of the CN···NC pair (Figure 1f).

All of the α,ω-dinitrile/PHTP inclusion compounds that we have prepared [$NC(CH_2)_nCN$, $n = 6, 7, 8, 10$] give only one nitrile resonance, while all of the 1-cyanoalkanes (except 1-cyanopentane/PHTP) show asymmetric doublets in the approximate ratio of 4:1. Specific host–guest interactions that cause band doubling in the long-chain mononitriles but not in the dinitriles would be fortuitous, and we therefore assign the upfield peak to the CN···Me pair. Shifts in this high-field band (but not the low-field band) with terminally substituted nitriles (e.g., $Br(CH_2)_6CN$, Figure 1e) confirm our assignments. With 1-cyanopentane/PHTP, end-for-end exchange of the guest molecules is thought to be rapid at ~300 K, and a single broad band is observed. Temperature dependence studies of the PHTP inclusion compounds of $CH_3(CH_2)_5{}^{13}CN$ (15% ^{13}C) (Figure 1g–n) and $CH_3(CH_2)_9{}^{13}CN$ (16% ^{13}C) confirm this interpretation. Spectra of 1-cyanohexane/PHTP exhibit reversible broadening and coalescence above 300 K, with the maximum of the averaged band shifting with increasing temperature.[15] With 1-cyanodecane/PHTP, two sharp peaks are observed from 220 to 400 K,

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(1) By incommensurate, we mean that there is no rational fraction with small denominator that relates the host and guest repeat lengths along the channel axis. See: Rennie, A. J. O.; Harris, K. D. M. *Proc. R. Soc. London* **1990**, *430*, 615–640.

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(6) (a) Harris, K. D. M.; Hollingsworth, M. D. *Proc. R. Soc. London* **1990**, *431*, 245–269. (b) Harris, K. D. M.; Smart, S. P.; Hollingsworth, M. D. *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 3423–3429. (c) Hollingsworth, M. D.; Goss, C. R. *Mol. Cryst. Liq. Cryst.* **1992**, *219*, 43–62.

(7) Schaefer, J.; Stejskal, E. O.; Buchdahl, R. *Macromolecules* **1975**, *8*, 291–296.

(8) Hollingsworth, M. D.; Cyr, N. *Mol. Cryst. Liq. Cryst. Inc. Nonlin. Opt.* **1990**, *187*, 135–144.

(9) NMR spectra at 50.3 MHz were obtained with equipment described previously.[8] Temperature was maintained within a 1-deg range with a Bruker BVT-1000, which was standardized against a calibrated copper–constantan thermocouple reading from a Lakeshore Cryotronics DRC-91C temperature controller. Temperature gradients across the sample constitute the largest error in the temperature measurement. Spectra typically consisted of 8*K* data points (6-μs 90° pulses, 8-ms cross-polarization contact time (CT), 204-ms acquisition time during proton decoupling (AQ), 8-s recycle delay), which were zero-filled to 32*K* before transforming with 5-Hz line broadening. Peak positions relative to tetrakis(trimethylsilyl)silane (TTMS) ($\delta = 3.50$ ppm at 298 K)[10] were obtained by simulation. Spectra at 75.305 MHz were obtained with a Chemagnetics CMX-300 spectrometer utilizing a double-bearing zirconium oxide pencil rotor (6-mm i.d.) for which temperature gradients were minimal. Temperature calibration was based on melting transitions of several solids. Spectra consisted of 4*K* data points (4.5-μs 90° pulses, 7.5-ms CT, 136.4-ms AQ, 7.5-s recycle delay), which were zero-filled to 32*K* before transforming without line broadening.

(10) Muntean, J. V.; Stock, L. M.; Botto, R. E. *J. Magn. Reson.* **1988**, *76*, 540–542.

(11) The synthesis and analysis of PHTP and labeled nitriles will be described elsewhere. Macroscopic inclusion compound crystals were grown by dissolving PHTP in the pure liquid guests at 90–100 °C and cooling to 25 °C over 8–10 h. After vacuum filtration, traces of liquid guest were removed from the surface by crushing the crystals between sheets of lens paper. X-ray diffraction (oscillation photographs and powder) showed the correctness of crystal form.

(12) Although the resonances shown in Figures 1a–c,e resemble typical asymmetric doublets observed in CP-MAS spectra of ^{13}C attached to ^{14}N, field dependence experiments show that such residual dipolar splittings between ^{13}C and ^{14}N are averaged by high-amplitude motions of the guest molecules and that the band doubling arises from site differences alone.[13,14] See: Okazaki, M.; Naito, A.; McDowell, C. A. *Chem. Phys. Lett.* **1983**, *100*, 15–18, and references cited therein.

(13) Our ^{15}N labeling and field dependence experiments show that the splitting in the nitrile resonance of stearonitrile/urea is due to site effects (HH vs HT), not residual dipolar interactions, as described in ref 12.

(14) With hydrogen-bonded guests such as 6-aminohexanenitrile, band doubling occurs because of unaveraged residual dipolar coupling between ^{13}C and ^{14}N.

(15) Differential scanning calorimetry (Perkin-Elmer DSC II) showed no phase transitions in this temperature region.

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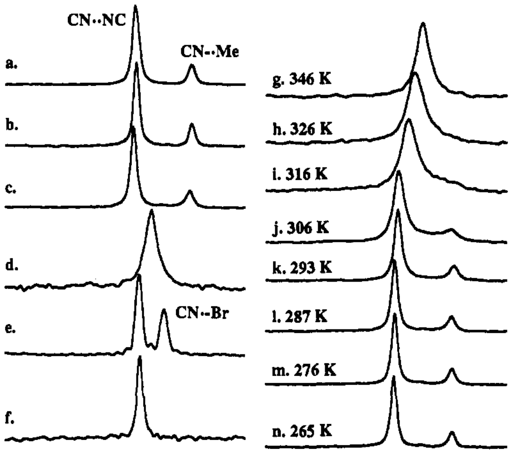


Figure 1. ^{13}C CP-MAS NMR spectra (50.3 MHz) of nitrile/PHTP inclusion compounds. (a) $CH_3(CH_2)_9{}^{13}CN$ (15% ^{13}C)/PHTP (297 K); (b) $CH_3(CH_2)_7CN$/PHTP (297 K); (c) $CH_3(CH_2)_5{}^{13}CN$ (16% ^{13}C)/PHTP (291 K); (d) $CH_3(CH_2)_4CN$/PHTP (297 K); (e) $Br(CH_2)_6CN$/PHTP (287 K); (f) $NC(CH_2)_8CN$/PHTP (297 K); (g–n) variable-temperature spectra of $CH_3(CN_2)_5{}^{13}CN$/PHTP (15% ^{13}C).

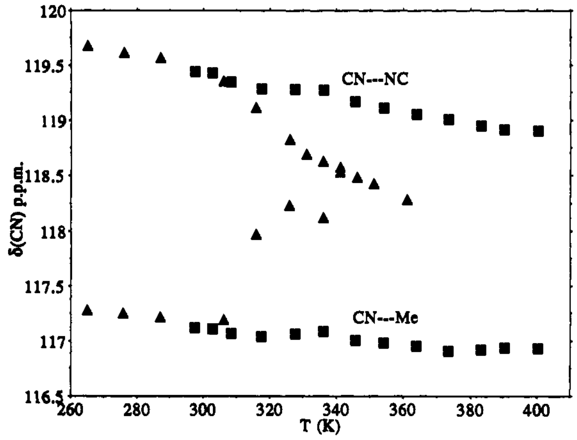
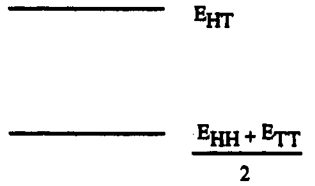


Figure 2. Temperature dependence of δ(CN) for CN···NC (upper) and CN···Me (lower) and rapidly exchanging pairs in $CH_3(CH_2)_9{}^{13}CN$/PHTP (■) and $CH_3(CH_2)_5{}^{13}CN$/PHTP (▲).

showing that rapid exchange does not occur, even at 400 K. The nitrile peaks in the spectrum of $Br(CH_2)_6CN$/PHTP show broadening and coalescence above ~350 K. Temperature dependence studies of α,ω-dinitriles in PHTP show only single, narrow bands for the nitrile carbons.

To measure the equilibrium partitioning for 1-cyanohexane/PHTP in the fast exchange limit, we require the temperature dependence of "intrinsic" peak positions for HH and HT pairs that are not shifted by rapid exchange. Apart from dynamic exchange effects and shifts in K_{eq}, several factors could, in principle, contribute to the temperature dependence of δ(CN) for 1-cyanohexane/PHTP.[16] These include changes in the equilibrium structures of HH and HT pairs (e.g., increasing separation with increasing T) and structural changes in the host that influence the local or bulk susceptibility.[15] Fortunately, plots of δ(CN) vs T have extremely shallow slopes and are nearly collinear for 1-cyanodecane/PHTP and for 1-cyanohexane/PHTP in the slow exchange regime (Figure 2).[16a] If we assume[18] that the same linear relationships hold for the "intrinsic" chemical shifts of 1-cyanohexane/PHTP at higher temperatures, we can estimate the "intrinsic splitting" for each temperature and calculate K_{eq}[19] for the following two-level[20] system:



A plot of ln K vs $1/T$ yields a straight line (r = 0.992, N = 7, T = 326–361 K) in the fast exchange regime for 1-cyanohexane/PHTP. For this process, the enthalpic term favors the lower state by 5.2(3) kcal mol^{-1}, whereas the entropy term disfavors the same state by 14(3) cal mol^{-1} K^{-1}, presumably because of restricted motional freedom for the CN···NC pairs, which are thought to be overlapped significantly[21] and tethered strongly by dipole–dipole interactions.

The system described here is unique in that it approaches the spatial constraints of a molecular crystal while exhibiting the equilibrium control of partitioning that is characteristic of liquids and gases. Thus, measurements such as these should be important for our understanding of phenomena as diverse as enzyme–substrate interactions, solvent effects on chemical reactions, and the process of crystallization and will provide a challenge for molecular modeling simulations. Further energetic and structural studies of this and other functional group pairs, including weakly hydrogen-bonded systems and donor–acceptor pairs, will appear in forthcoming publications.

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(16) For cases in which motional properties of HH and HT pairs are very different,[17] changes in cross-polarization efficiencies of HH and HT pairs might give rise to shifts in the averaged band position in the fast exchange regime. However, differential temperature dependences in cross-polarization efficiencies for HH and HT pairs were not significant for the contact times used in our experiments. (a) Because the spectra of 1-cyanodecane/PHTP and 1-cyanohexane/PHTP were taken on different spectrometers, the slopes of chemical shift vs T for the CN···NC pair are slightly different for these two samples. As the data given here show, agreement was significantly better when the same probe and spectrometer were used for the temperature dependence measurements. The "intrinsic" slopes were therefore taken to be the slopes in the slow exchange regime for 1-cyanohexane/PHTP. Slopes (M, δ(ppm) K^{-1}), intercepts at 298 K (I, δ(ppm)), correlation coefficients (R), temperature range (T in K), and number of points (N) were as follows (standard errors in parentheses). CN···NC: 1-cyanodecane/PHTP, M = –0.0053(1), I = 119.42(5), R = 0.996, T = 212–400, N = 15; 1-cyanohexane/PHTP (slow exchange regime), M = –0.0078(10), I = 119.44(8), R = 0.956, T = 266–306, N = 4; $NC(CH_2)_8CN$/PHTP, M = –0.007(1), I = 119.38(2), R = 0.987, T = 295–333, N = 6; $NC(CH_2)_6CN$/PHTP, M = –0.0070(4), I = 119.33(2), R = 0.991, T = 291–348, N = 7. CN···Me: 1-cyanodecane/PHTP, M = –0.0022(1), I = 117.12(3), R = 0.977, T = 212–400, N = 15; 1-cyanohexane/PHTP, M = –0.00019(2), I = 117.25(8), R > 0.999, T = 266–306, N = 4. Because of the temperature dependence of the chemical shift of TTMS, a correction of 0.002 54(5) ppm/K should be added to each of the slopes above. (So as to avoid another source of statistical error, this correction was not applied for each chemical shift during evaluation of the different least-squares lines.)

(17) Alemany, L. B.; Grant, D. M.; Pugmire, R. J.; Alger, T. D.; Zilm, K. W. *J. Am. Chem. Soc.* **1983**, *105*, 2133–2141.

(18) This assumption is probably the largest possible source of systematic error, but the linearity of plots of δ(CN) vs T for several dinitriles indicates that extrapolation is warranted.

(19) For a detailed discussion, see: Szymanski, S.; Witanowski, M.; Gryff-Keller, A. In *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: New York, 1978; Vol. 8, pp 227–289.

(20) Note that one end-for-end exchange requires an energy of $2E_{HT} - (E_{HH} + E_{TT})$. A description of the Ising treatment of this system will appear in a forthcoming publication.

(21) The C_2 resonance is doubled, with the taller HH component shifted downfield from the smaller HT band.