J. Org. Chem. **1997,** *62,* 2619−2621

Observation of Diastereomers of the Hydrogen-Bonded Aggregate Hub(M)$_3$·3CA Using ^{1}H Nuclear Magnetic Resonance Spectroscopy When CA Is an Optically-Active Isocyanuric Acid

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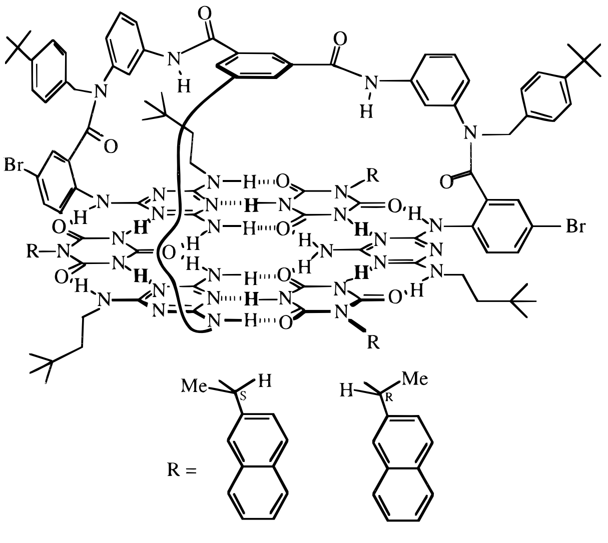
Received August 8, 1996

Diastereomers of the hydrogen-bonded aggregate hub(M)$_3$·3CA (Chart 1) are observed in the ^{1}H NMR spectrum when the isocyanuric acid component (CA) is optically-active. The trismelamine component, hub(M)$_3$, contains no chiral centers but exists as a pair of enantiomers due to the orientation that the three melamine groups adopt when complexed to molecules of CA (Scheme 1).[1] That is, for the C_3 symmetric aggregate, the melamines can be arranged in a clockwise (M) or counterclockwise (P) arrangement.[2] The C_1 symmetric aggregate —generated conceptually by rotation around the indicated spoke—also exists as an enantiomeric pair. Aggregates incorporating optically-inactive CA show degenerate lines for their enantiomers in the ^{1}H NMR spectra. Two hydrogen-bonded imide lines (appearing between 16 and 13 ppm) are observed for the C_3 aggregate, and six lines are observed for the C_1 aggregate.[3]

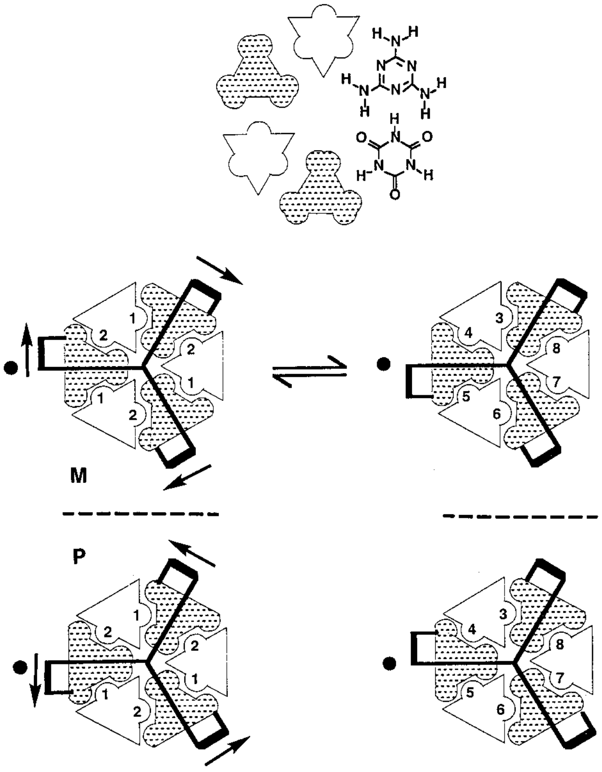
Using an optically-active CA, we observe experimentally mixtures of diastereomers (Scheme 2). Figure 1 shows the variable temperature ^{1}H NMR (VT) spectra of the imide region of **1-M**. Aggregate **1-P** shows indistinguishable VT spectra. The spectrum recorded at 258 K shows two pairs of two lines corresponding to the two diastereomers of the C_3 isomer and some of the lines of the diastereomeric C_1 isomers. The C_3 diastereomers exist in a 3:1 ratio; that is, one diastereomer is 0.3 kcal/mol more stable than the other. The difference in energies between the C_1 isomers is much smaller, and is difficult to estimate due to uncertainty in assignment of these lines to different diastereomers. Choice of solvent affects both the resolution of these isomers and their relative populations (Figure 2).

Chart 1. Aggregates Used in This Study[a]



Aggregate = **1-S** **1-R**

Scheme 1. Aggregates (Viewed from above) Showing an Alternating Arrangement of CA (White triangles) and Melamine (Darkened triangles)[a]



[a] Unique hydrogen-bonded imide protons are shown as numbered bulges on the CA. When CA is optically-inactive, hub(M)$_3$·3CA exists as a C_3 isomer (and its enantiomer) and a C_1 isomer (and its enantiomer). These isomers differ in the orientation of the attachment of the trismelamine spoke (darkened line) to the melamine group. We refer to these enantiomers as M and P depending on the orientation of the spokes as illustrated by the arrows. The dashed line denotes the mirror plane relating the M and P isomers. The C_1 and C_3 isomers can be interconverted conceptually by rotation of the indicated (●) spoke.

Similar geometric isomers have been observed in other systems: initial investigations of medium-sized rings based on tri-*o*-thymotide in solution by Stoddard[4−7] —and the support of these findings using single-crystal X-ray diffraction[8,9] and ^{13}C NMR spectroscopy[10] —revealed the presence of isomers. Recently, conformational diastereomers of a related trianthranilide have been isolated.[11] The incorporation of chiral centers into the covalent

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(1) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 905.

(2) We have adopted the M/P nomenclature to describe the cyclic arrangement of the melamine groups; see: Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567.

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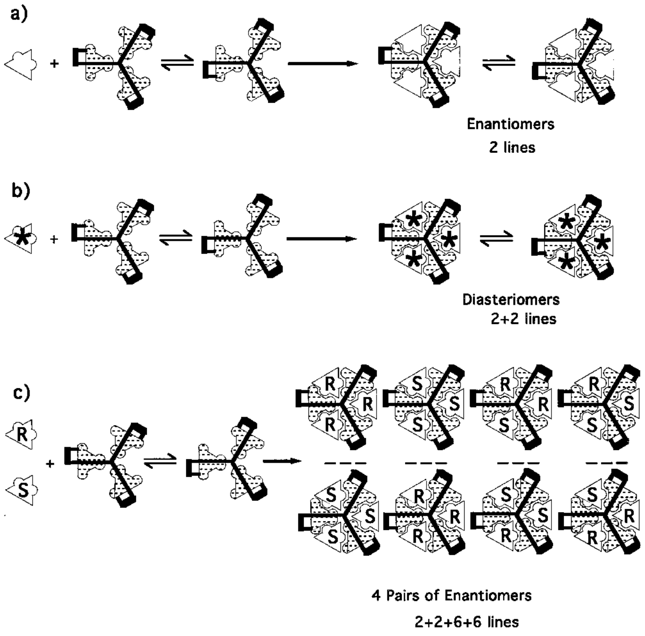
S0022-3263(96)01546-0 CCC: $14.00

Scheme 2. Effect of the Choice of Solvent[a]



[a] (a) Mixing achiral CA with hub(M)$_3$ results in the formation of C_3 aggregates that give two imide lines. C_1 aggregates (not shown) give six imide lines. (b) If the CA is optically-active, diastereomers result. Instead of two lines in the imide region we expect—and observe—two pairs of two lines. C_1 aggregates (not shown) exist as a pair of diastereomers, and we see two pairs of six lines. (c) If a racemic CA is used, four pairs of enantiomers are obtained for the C_3 isomer. Those containing exclusively (*R*)- or (*S*)-CA will give two lines. Those containing equimolar mixtures of (*R*)- and (*S*)-CA have six unique environments for the CA and can give up to six lines each. The C_1 aggregates exist as eight enantiomeric pairs of diastereomers.

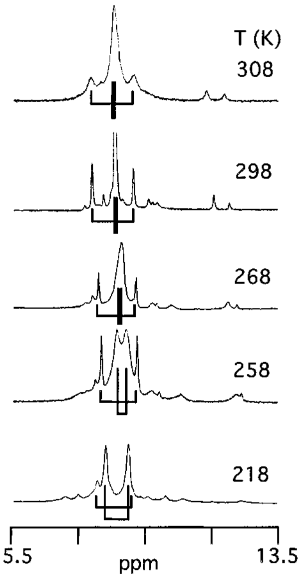


Figure 1. ^{1}H NMR of hub(M)$_3$·3CA, where CA = (*R*)- or (S)-(naphthylethyl)isocyanuric acid. The variable temperature spectra show two C_3 diastereomers clearly (bold lines). Only some of the lines corresponding to the C_1 diastereomers are seen.

scaffold has been used to resolve enantiomers of a monomethine dye.[12] Self-assembling systems that adopt[13–16] helical symmetry have also been reported.

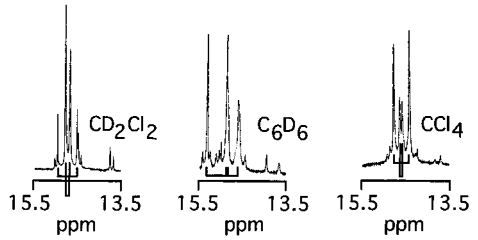


Figure 2. ^{1}H NMR spectra of aggregates of hub(M)$_3$·3CA. The imide region of **1-R** in a variety of solvents is shown. The spectra were obtained at 298 K. The major and minor C_3 diastereomers are discernible and indicated with brackets.

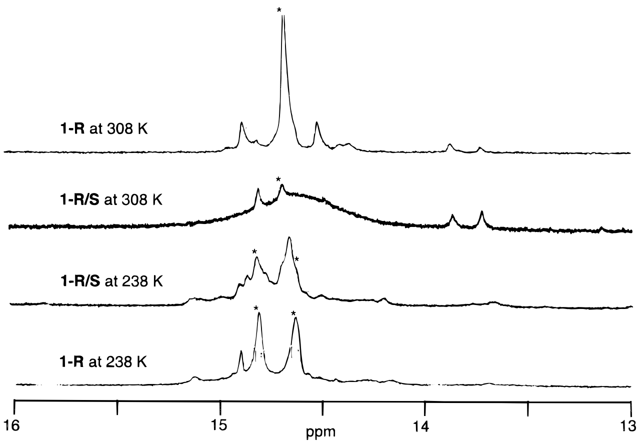


Figure 3. Complicated spectrum resulting from mixing hub(M)$_3$ with equimolar portions of (*R*)- and (*S*)-(naphthylethyl)isocyanuric acid. For details of the available isomers, see Scheme 2. Lines that may belong to the symmetric (*RRR* or *SSS*) C_3 diastereomers are indicated with an asterisk. This assignment is based on the chemical shift of these peaks and is tentative.

Mixing hub(M)$_3$ with racemic (naphthylethyl)isocyanuric acid results conceptually in a number of different isomers (Scheme 1). The ^{1}H NMR spectra of this aggregate are shown in Figure 3. These spectra show a greater number of lines at all temperatures. Most of these lines are broader than the lines of **1-P** (or **1-M**).[17] We expect four pairs of enantiomers for the C_3 diastereomers and eight pairs for the C_1 diastereomers. That is, 56 lines (2 lines × 4 C_3 isomers + 6 lines × 8 C_1 isomers) are possible. On the basis of the relative simplicity of the ^{1}H NMR spectra, we believe that most of the isomers exist in low concentrations.

Table 1 summarizes the optical rotations and α_D obtained for these aggregates. We observe a slight "amplification" of optical rotation of solutions for **1-P** (or **1-M**) compared with an equivalent amount of CA in the absence of hub(M)$_3$. This amplification is not as dramatic as that seen by Katz *et al.* in self-aggregating helicenes.[18]

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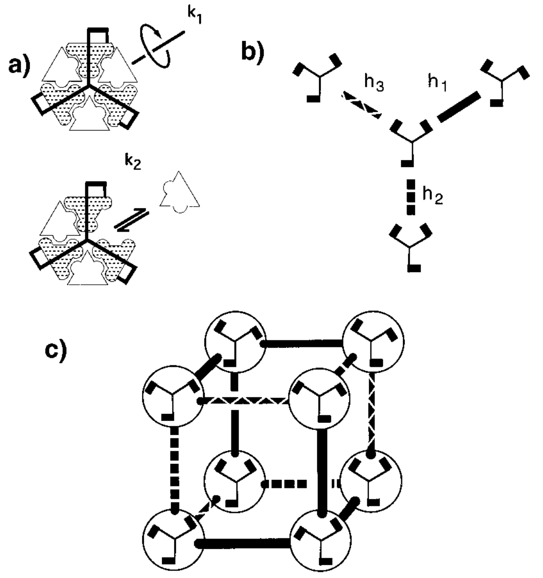
(17) It is unclear whether the sharp lines in the spectrum correspond to the C_3 diastereomers of **1-P** (or **1-M**): the slight difference in chemical shift makes their assignment difficult.

Table 1. Optical Rotations[a]

component	rotation (deg)	α^{25}_D
(R)-CA	1.1	5.6 (c = 5)
(S)-CA	−1.1	−5.6 (c = 5)
hub(M)$_3$·3((R)-CA)	1.7	0.6 (c = 17.3)
hub(M)$_3$·3((S)-CA)	−1.6	−0.6 (c = 17.3)
hub(M)$_3$·$^3/_2$((R)-CA)·$^3/_2$((S)-CA)	0.02 (0)	0 (c = 17.3)

[a] The optical rotations of a series of solutions with 5 mg of (R/S)-CA (CA = (naphthylethyl)isocyanuric acid) dissolved in 1 mL of CHCl$_3$; c is concentration in mg/mL.

Scheme 3. Exchange Processes in These Aggregates[a]



[a] The ^{1}H NMR spectra give details of the relative rates of different exchange processes occurring in these aggregates. (a) We envision exchange of CA between equivalent sites leading to the averaging of the two imide lines to a single coalesced peak to occur by k_1 or k_2. These processes occur faster than those described in b. (b) We envision the equilibration of the C_3 and C_1 isomers of these aggregates to occur by flipping of spokes shown by h$_1$, h$_2$, and h$_3$. The patterns of these processes correspond to the equilibration scheme shown in c. (c) We summarize the interconversion of enantiomers (if the CA is achiral or diastereomers if the CA is optically-active) as occurring through isomers that can be diagrammed as a cube. Enantiomeric pairs are shown on distant corners. That is, the enantiomeric C_3 hubs are shown in the upper-left rear and lower-right front corners.

A simplified model of the exchange processes available to the components of **1-M**—or any aggregate based on hub(M)$_3$·3CA—is shown in Scheme 3. From the VT spectra we hypothesize that the rates of exchange of molecules of CA between identical sites of the hub (k_{1-2}) are fast compared with interconversion of the diastereomers (h$_{1-3}$). Interestingly, the CAs of the thermodynamically preferred diastereomer undergo more rapid exchange (processes k_{1-2}) than those of the less stable isomer. That is, the minor C_3 diastereomer shows two lines—corresponding to imide protons close to and far from the *neo*-hexyl group—at temperatures (*i.e.*, 298 K) where the major C_3 diastereomer lines are coalesced due to rapid exchange.

The rates of k_{1-2} do appear to be affected by the solvent (Figure 2). In CDCl$_3$, the CAs of one diastereomer are exchanging faster than the NMR time scale. Exchange appears to be the slowest in CCl$_4$ and C$_6$D$_6$: the lines for the major diastereomer coalesce at >308 K in CD$_2$Cl$_2$, CCl$_4$, and C$_6$D$_6$ but at 268 K in CDCl$_3$. A different trend is observed for the minor diastereomer: coalescence occurs at >328 K in all solvents.

Conclusion

Establishing that **1** exists as a pair of diastereomers of **1** offers additional proof for the structure proposed for hub(M)$_3$·3CA: the hypothesized enantiomers have been resolved using optically-active molecules of CA. This aggregate serves as a model for a family of hydrogen-bonded structures based on the lattice of isocyanuric acid and melamine. Our efforts to understand both the structure of this aggregate and the imide region of the ^{1}H NMR spectrum are becoming increasingly important as these aggregates get larger and more complex showing additional lines throughout the ^{1}H NMR spectrum.

Experimental Section

^{1}H NMR Spectroscopy. Solvents for NMR spectroscopy were purchased from Aldrich Chemical and used as received. The ^{1}H NMR spectra were recorded on a Bruker AM400 NMR spectrometer.

Synthesis. Aggregates were synthesized by mixing the component molecules in CDCl$_3$ and sonicating briefly (5 s) to a homogeneous solution. The synthesis of hub(M)$_3$ has been reported.[1] The synthesis of the optically-active molecules of CA is accomplished in two steps through the biuret adduct[19] of the commerically available optically-active amines. The procedures have been detailed for achiral amines.

Biuret Adduct of Naphthylethylamine. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (br s, 1 H), 8.10 (m, 2 H), 7.94 (d, J = 4.8 Hz, 1 H), 7.84 (m, 1 H), 7.57 (m, 4 H), 6.77 (s, 2 H), 5.63 (m, 1 H), 1.52 (d, J = 4.3 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.5, 153.5, 139.9, 133.4, 130.1, 128.7, 127.4, 126.3, 125.6, 125.5, 122.9, 122.0, 44.6, 22.0. HRES-MS: calcd, [M + H]$^+$ 258.1243; obsd, 258.1238.

(Naphthylethyl)isocyanuric Acid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (br s, 2 H), 7.99 (2d, J = 4.8 Hz, 2 H), 7.85 (d, 1 H, J = 5.1 Hz), 7.78 (d, J = 4.5 Hz, 1 H), 7.53 (m, 4 H), 6.40 (q, J = 4.3 Hz, 1 H), 1.84 (d, J = 4.3 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.5, 148.5, 134.5, 133.3, 130.9, 128.9, 128.0, 126.9, 126.5, 125.4, 124.9, 122.4, 47.9, 20.7. HRES-MS: calcd, [M]$^+$ 283.0957; obsd, 283.0970.

Acknowledgment. This work was supported by the NSF (CHE 91-22331). The NMR instrumentation was supported by the NSF (CHE 88-14019) and the NIH (1 S10 RR4870). The Harvard University Mass Spectrometry Facility was supported by the NSF (CHE-90-20043) and the NIH (1 S10 RR06716-01). E.E.S. was an Eli Lilly Predoctoral Fellow (1995).

JO9615460

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(19) A variety of CAs have been prepared by this method; see ref 2 for examples.