Isomer-Dependent Complexation of Malononitrile by Dicyclohexano-18-crown-6

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The X-ray crystal and molecular structure of molononitrile complexes with cis-syn-cis and cis-anti-cis isomers of dicyclohexano-18-crown-6 (1 and 2, respectively) are reported. The complexes exhibit 1:1 (1) and 2:1 (2) malononitrile:crown ether ratios and are the first example of isomer-dependent, neutral molecule complexation by crown ethers. Molecular mechanics calculations are performed on the complexes by using parameter sets that have been developed for describing these intermolecular interactions. Very good agreement is observed between calculated and observed structures and binding enthalpies. A rationale for the observed isomer-dependent complexation is presented.

Interest in neutral-molecule complexation by crown ethers arises from the potential these systems have for modeling biochemically important host–guest binding interactions[1] and their practical utility in chromatography, separations, molecular transport, and catalysis.[2] From a theoretical perspective, interest in this area is particularly keen[3] since crown ether complexes are also of a suitable size for computational investigation via molecular and quantum mechanical methods. As part of a systematic study of specificity in neutral molecule complexation, we have recently obtained the X-ray crystal and molecular structure of the *cis-syn-cis-* and *cis-anti-cis-*dicyclohexano-18-crown-6 (Figure 1) complexes with malononitrile (1 and 2, respectively). These complexes exhibit 1:1 (1) and 2:1 (2) malononitrile:crown ether ratios and are the first example of isomer-dependent, neutral molecule complexation by crown ethers. As such, 1 and 2 offer a unique opportunity to investigate how subtle differences in the binding site environment alters the selectivity of guest binding. In the present work we address the problem of isomer-dependent complexation of malononitrile by employing a hybrid of experimental and computational investigative techniques.

Experimental Section

Dicyclohexano-18-crown-6 was purchased as a mixture of isomers from Aldrich Chemical Company and was separated into the cis-syn-cis and cis-anti-cis isomeric forms (**3** and **4**, respectively) by using previously reported procedures.[4] Crystals of 1 and 2 suitable for X-ray crystallography were obtained by slow evaporation of diethyl ether solutions of the crowns and excess (2.5:1) malononitrile.[5] All analyses were consistent with proposed stuctures. For 1 ($C_{23}H_{38}N_2O_6$): mp 115–119 °C; ^{1}H NMR ($CDCl_3$) δ 4.6 (s, 2, $(CN)_2CH_2$), 3.4–3.8 (m, 20, OCH), 1.2–1.9 (m, 16, CCH_2C). For **2** ($C_{26}H_{40}N_4O_6$): mp 110–113 °C; ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 4, $(CN)_2CH_2$), 3.5–3.7 (m, 20, OCH), 1.2–2.1 (m, 16, CCH_2C).

Table I. Calculated Binding Energies for 1:1 and 2:1 Complexation of *cis-syn-cis-* and *cis-anti-cis-*Dicyclohexano-18-crown-6 with Malononitrile[a]

parameter set[b]	ΔE_1[c,d]	ΔE_2[e]
cis-syn-cis-Dicyclohexano-18-crown-6		
original	7.4	10.4
PEOE1	9.1	9.1
PEOE2	8.5	8.9
MULL1	8.5	8.7
MULL2	8.5	8.7
cis-anti-cis-Dicyclohexano-18-crown-6		
original	8.4	12.1
PEOE1	8.8	12.4
PEOE2	7.9	11.8
MULL1	8.4	11.4
MULL2	8.4	11.4

[a] In kcal/mol. Reported as the negative of calculated binding energies. [b] See ref 3 for a description of the parameter sets. [c] ΔE_1 for 1:1 (malononitrile:crown) complexation. Calculated from E(CM) – E(C) – E(M), where E(CM) = steric energy of complex, E(C) = steric energy of dicyclohexano-18-crown-6, and E(M) = steric energy of malononitrile. [d] Malononitrile is proximal to the syn cyclohexyl groups. [e] ΔE_2 for 2:1 (malonitrile:crown) complexation. Calculated from E(MCM) – E(CM) – E(M), where E(MCM) = steric energy of the 2:1 complex. See footnote *c* for a difinition of E(CM) and E(M).

Crystals of 1 are orthorhombic, space group P_{abc}; a = 11.975 (4) Å, b = 18.205 (5) Å, c = 23.383 (7) Å, V = 5097.1 (27) Å^3, Z = 8, D (calcd) = 1.13 g cm^{-3}, R_f = 6.38%, R_{wf} = 6.93%, GOF = 1.274. Crystals of **2** are triclinic, space group $P1$: a = 8.409 (2) Å, b = 8.640 (2) Å, c = 10.177 (3) Å, α = 80.11 (2)°, β = 81.55 (2)°, γ = 76.76 (2)°, V = 704.6 (3) Å^3, Z = 1, D(calcd) = 1.19 g cm^{-3}, R_f = 4.97%, R_{wf} = 6.06%, GOF = 1.215. Structures were solved by direct methods using the SHELXTL package. All non-hydrogen atoms were refined with anisotropic temperature factors; all hydrogen atoms were found and refined isotropically. All bonding parameters are normal and there are no close intercomplex contacts. Views of the X-ray molecular structures of 1 and **2** are shown in Figure 2.

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[3] Anderson, W. P.; Urban, J. J.; Damewood, J. R., Jr. *J. Comput. Chem.*, in press.

[4] Izatt, R. M.; Haymore, B. L.; Bradshaw, J. S.; Christensen, J. J. *Inorg. Chem.* **1975**, *14*, 3132.

[5] A complex formed between a mixture of **3** and **4** and malononitrile has been reported. el Basyony, A.; Klimes, J.; Knöchel, A.; Oehler, J.; Rudolph, G. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1976**, *31B*, 119Z.

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Table II. Selected Calculated Structural Features of 1:1 and 2:1 Complexes of *cis-syn-cis-* and *cis-anti-cis-*Dicyclohexano-18-crown-6 with Malononitrile[a]

parameter set[d]	P-Dist[b]	Tilt Angle[c]	Twist 1[c]	Twist 2[c]
	cis-syn-cis-Dicyclohexano-18-crown-6			
	1:1 Malononitrile Complex			
	(1.701)	(176.6)	(9.8)	
original	2.039	147.9	4.0	
PEOE1	1.712	151.3	7.5	
PEOE2	1.732	151.1	7.6	
MULL1	1.811	157.4	5.1	
MULL2	1.810	158.1	4.7	
	2:1 Malononitrile Complex[e]			
original	1.883 2.341	150.7 175.3	6.5 1.7	149.4
PEOE1	1.827 2.237	148.2 174.5	7.9 2.6	152.1
PEOE2	1.833 2.337	148.1 174.5	7.9 2.5	150.9
MULL1	1.931 2.377	153.1 174.8	7.3 2.1	150.3
MULL2	1.940 2.378	153.4 174.8	7.4 2.1	150.9
	cis-anti-cis-Dicyclohexano-18-crown-6			
	1:1 Malononitrile Complex			
original	2.014	155.7	13.5	
PEOE1	1.972	150.7	17.2	
PEOE2	1.996	150.6	16.8	
MULL1	2.062	159.7	10.7	
MULL2	2.062	160.3	10.4	
	2:1 Malononitrile Complex			
	(2.078)	(174.6)	(22.2)	(180.0)
original	2.089[f]	156.7[f]	11.5	180.0
PEOE1	2.078[f]	153.5[f]	13.6	180.0
PEOE2	2.086[f]	153.3[f]	13.5	180.0
MULL1	2.123[f]	158.9[f]	10.3	180.0
MULL2	2.125[f]	159.1[f]	10.2	180.0

[a] Experimental values are in parentheses. [b] In Angstrom units. See ref 19 for a definition of P-Dist. [c] In degrees. See ref 20 for a definition of the Tilt and Twist angles. [d] See ref 3 for a description of the parameter sets. [e] The upper value of the structural feature corresponds to the malononitrile which is proximal to the syn cyclohexyl groups, the lower value corresponds to the malononitrile which is distal to the syn cyclohexyl groups. [f] Reported as the average of symmetry-related structural features.

Computational Section

Calculations were performed on 1 and 2 and their uncomplexed crowns (3 and 4) by employing the molecular mechanics[6] method and the program MM2.[7,8] The five parameter sets (Original, PEOE1, PEOE2, MULL1, MULL2) developed previously[3,9] for use in describing neutral-molecule complexes of crown ethers were employed in this study. The bond moments of the C–H bonds in the cyclohexyl portion of the molecule were maintained at their original MM2 values (0.0) for these calculations. Complexation energies for 1:1 complexes (ΔE_1) were obtained by subtracting the molecular mechanics strain energies of malononitrile and the appropriate isomer of dicyclohexano-18-crown-6 from the total strain energy of the complex.[10] Complexation energies for 2:1 complexes (ΔE_2) were obtained by subtracting the molecular mechanics strain energy of malononitrile and appropriate 1:1 complex of dicyclohexano-18-crown-6 from the total strain energy of the 2:1 complex. In the case of 1–4, X-ray crystal structures were used as geometric input. For the 1:1 malononitrile complex of 4, one of the symmetry-related malononitrile molecules from the 2:1 complex was removed.[11] For the 2:1 complex of 3, the second malononitrile molecule was positioned so as to be centrosymmetrically related to the first in the input structure.[11] All geometries for hosts, guests, and complexes were completely optimized. Binding energies obtained by these calculations are reported in Table I.[10] Selected calculated bonding parameters are reported in Table II. Views of calculated structures for 1 and 2 (MULL1) are shown in Figure 3.

Figure 1. *cis-syn-cis*-Dicyclohexano-18-crown-6 (left) and *cis-anti-cis*-dicyclohexano-18-crown-6 (right).

Crystal Structures

The cis-syn-cis isomer of dicyclohexano-18-crown-6 (3) forms a 1:1 complex with malononitrile (1). In this structure, malononitrile is on the side of the crown ring that is proximal to the syn cyclohexyl groups (proximal complex) and the complex adopts a structure of approximate C_s symmetry. The approximate symmetry plane, which is clearly visible by inspection of Figure 2, is perpendicular to the mean plane of the crown ring, contains oxygen atoms O2 and O5, and is nearly coincident with the heavy atoms of malononitrile. In this configuration, crown-ring oxygen atoms O2 and O5 are eclipsed by the C–N bonds of malononitrile (C23–N2 and C22–N1, respectively). One of the nitrile moieties in 1 (C23–N2) is flanked by two cyclohexyl methylene groups ($C6H_2$ and $C19H_2$). The steric influence of these flanking methylene groups may be important in determining the conformation of malononitrile adopted in this complex (see below). All of the bonding parameters for 1 are within normal bonding ranges.

The conformation observed for the uncomplexed cis-syn-cis dicyclohexano-18-crown-6 (3) is of approximate C_2 symmetry.[12] Complexation of 3 with the neutral molecule malononitrile is therefore able to affect the same conformational change (i.e., C_2 to C_s) observed previously for ionic complexes of 3.[13f]

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(7) Allinger, N. L.; et al. *QCPE* **1981**, *13*, 359.

(8) For examples of previous computational studies of crown ethers, see: (a) Yamabe, T.; Hori, K.; Akagi, K.; Fukui, K. *Tetrahedron* **1979**, *35*, 1065. (b) Bovill, M. J.; Chadwick, D. J.; Sutherland, I. O.; Watkin, D. *Chem. Soc., Perkin Trans. 2* **1980**, 1529. (c) Truter, M. R. *Metal Ligand Interactions in Organic Chemistry and Biochemistry*; Proceedings of the 9th Jerusalem Symposium on Quantum Chemistry and Biochemistry; Pullman, B., Goldblum, N., Eds.; 1976; Part 1, p 317. (d) Bartsch, R. A.; Carsky, P. *J. Org. Chem.* **1980**, *45*, 4782. (e) Leszczynski, J.; Nowek, A.; Wojciechowski, W. *J. Mol. Struct.* **1981**, *85*, 211. (f) Wipff, G.; Weiner, P.; Kollman, P. *J. Am. Chem. Soc.* **1982**, *104*, 3249. (g) Perrin, R.; Decoret, C.; Bertholon, G.; Lamartine, R. *Nouv. J. Chim.* **1983**, *7*, 263. (h) Hori, K.; Yamada, H.; Yamabe, T. *Tetrahedron* **1983**, *39*, 67. (i) Weiner, P. K.; Profeta, S., Jr.; Wipff, G.; Havel, T.; Kuntz, T.; Langridge, R.; Kollman, P. *Tetrahedron* **1983**, *39*, 1113. (j) Dobler, M. *Chimia* **1984**, *38*, 415. See also: Kollman, P. A.; Wipff, G.; Singh, U. C. *J. Am. Chem. Soc.* **1985**, *107*, 2212. (k) Ranghino, G.; Romano, S.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1985**, *107*, 7873. (l) Lindsten, G.; Wennerström, O.; Isaksson, R. *J. Org. Chem.* **1987**, *52*, 547.

(9) (9) For a detailed description of the parameter sets see ref 3.

(10) For convenience, throughout the remainder of this paper we will refer to binding energies or enthalpies as their negatives.

(11) For a description of this technique, see ref 3. Since a complete conformational analysis was not performed on the complex, these 2:1 binding energies for 3 must be considered lower limits to ΔE_2. We note that this qualification does not alter the conclusions presented in this work.

(12) Dalley, N. K.; Smith, J. S.; Larson, S. B.; Christensen, J. J.; Izatt, R. M. *J. Chem. Soc., Chem. Commun.* **1975**, 43.

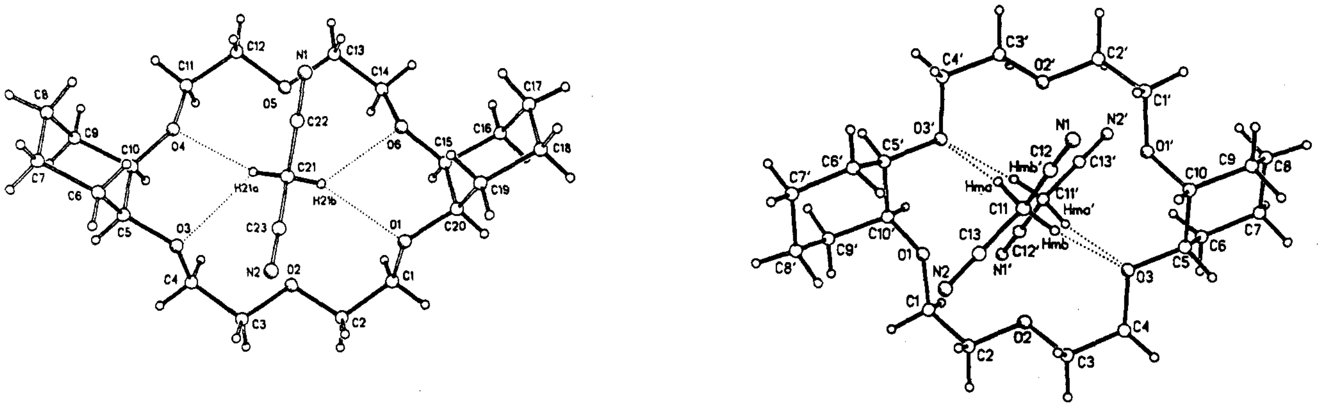

Figure 2. Views of the X-ray crystal structures of **1** (left) and **2** (right). Views are approximately perpendicular to the mean plane of the crown ring.

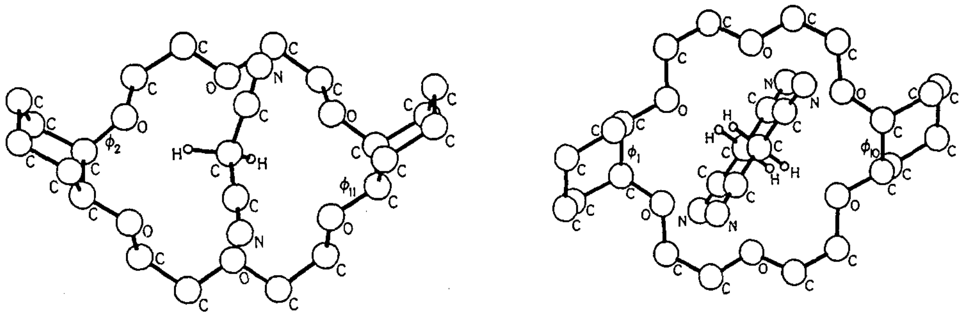

Figure 3. Views of the calculated (MULL1[21]) structures of **1** (left) and **2** (right). Views are approximately perpendicular to the mean plane of the crown ring. Torsion angle descriptors (required for supplementary material) are indicated on each isomer.

For the cis-anti-cis isomer of dicyclohexano-18-crown-6 (**4**), a 2:1 complex is formed with malononitrile (**2**) (Figure 2). This complex is of C_i symmetry, and symmetry-related malononitrile molecules reside above and below the mean plane of the crown ring. The observed crown-ring conformation for **2** is similar to that observed for other complexes of **4**.[13b,f,o] Unlike in **1**, the flanking methylene groups in **2** ($C6H_2$, $C6'H_2$) are found on opposite sides of the mean crown-ring plane. The malononitrile moieties are staggered with respect to the crown-ring oxygens and projections of the C–N bonds bisect two of the crown ring C–C bonds (C1–C2 and C1′–C2′).

The staggered configuration observed for **2** is also observed in the X-ray crystal structure of the 2:1 malononitrile:8-crown-6 complex.[15] This centrosymmetric, 18-crown-6 complex lacks the steric interactions with flanking methylene groups found in **1** and **2** since no cyclohexyl groups are present in the molecule. It therefore seems reasonable that the eclipsed malononitrile conformation observed in **1** is due, in part, to the steric constraints imposed by the *pair* of flanking methylene groups. Such steric interactions in **1** must be relatively weak, however, since the average distance between C6, C19, and C23 is 4.375 Å. In **2**, the molecule is less sterically encumbered, having only one flanking methylene per malononitrile (C6′(6)–C13(13′) distance, 3.808 Å), and the complex adopts the staggered structure.

In **1** and **2** the methylene hydrogens of the malononitrile are positioned to allow for hydrogen bonding[16] with crown-ring oxygens. In **1** there are four close C–H···O contacts (average C21···O distance, 3.334 Å) that result in a pair of hydrogen bonds between O3, O4, and H21a, and O1, O6, and H21b. In **2**, close C–H···O contacts (average C11(11′)···O3′(O3) distance, 3.406 Å) result in hydrogen bonds between Hmb, Hma′, and O3 and Hma, Hmb′, and O3′. While the relative strengths of these two types of hydrogen bonds is unknown,[17] C–H···O hydrogen bonding[18]

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[13] X-ray structures of complexes with two isomers of dicyclohexano-18-crown-6 (**3** and **4**) have been reported: (a) Dalley, N. K.; Smith, D. E.; Izatt, R. M.; Christensen, J. J. *J. Chem. Soc., Chem. Commun.* **1972**, 90. (b) Mercer, M.; Truter, M. R. *J. Chem. Soc., Dalton Trans.* **1973**, 2215. (c) Harman, M. E.; Hart, F. A.; Hursthouse, M. B.; Moss, G. P.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1976**, 396. (d) de Villardi, G. C.; Charpin, P.; Costes, R.-M.; Folcher, G.; Plurien, P.; Rigny, P.; de Rango, C. *J. Chem. Soc., Chem. Commun.* **1978**, 90. (e) Hughes, D. L.; Truter, M. R. *J. Chem. Soc., Chem. Commun.* **1982**, 727; (f) *Acta Crystallogr., Sect B* **1983**, *B39*, 329. (g) Simonov, Yu. A.; Krasnova, N. F.; Dvorkin, A. A.; Yakshin, V. V.; Aashkin, V. M.; Laskorin, B. N. *Dokl. Akad. Nauk SSSR* **1983**, *272*, 1129. (h) Yuguo, F.; Cheng, S.; Fengshan, W.; Zhongsheng, J.; Yaun, G.; Jiazan, N. *Fenzi Kexue Yu Huaxue Yanjiu* **1984**, *4*, 371. (i) Dalley, N. K.; Sypherd, D.; George, R. D. *J. Heterocycl. Chem.* **1984**, *21*, 497. (j) Dvorkin, A. A.; Krasnova, N. F.; Simonov, Yu. A.; Abashkin, V. M.; Yakshin, V. V.; Malinovskii, T. I. *Kristallografiya* **1984**, *29*, 471. (k) Krasnova, N. F.; Simonov, Yu. A.; Bel'skii, V. K.; Abashkin, V. M.; Yakshin, V. V.; Malinovskii, T. I.; Laskorin, B. N. *Dokl. Akad. Nauk SSSR* **1984**, *276*, 607. (l) Navaza, A.; Villain, F.; Charpin, P. *Polyhedron* **1984**, *3*, 143. (m) Krasnova, N. F.; Simonov, Yu. A.; Dvorkin, A. A.; Korshunov, M. B.; Yakshin, V. V.; Malinovskii, T. I. *Izv. Akad. Nauk Mold. SSR, Ser. Fiz.-Tekh. Mat. Nauk* **1984**, *63*, 668. (n) Krasnova, N. F.; Dvorkin, A. A.; Siminov, Yu. A.; Abashkin, V. M.; Yakshin, V. V. *Kristallografiya* **1985**, *30*, 86. (o) Fraser, M. E.; Fortier, S.; Rodrigue, A.; Bovenkamp, J. W. *Can. J. Chem.* **1985**, *64*, 816. Some of these structures were obtained from a search of the 1986 Cambridge Crystallographic Database (CCD).[14] See also: Bunchanan, G. W.; Bourque, K.; Bovenkamp, J. W.; Rodrigue, A. *Can. J. Chem.* **1985**, *63*, 2747. Buchanan, G. W.; Ripmeester, J. A.; Bovenkamp, J. W.; Rodrigue, A. *Tetrahedron Lett.* **1986**, *27*, 2239 and references therein.

[14] For leading references to the Cambridge Crystallographic Database, see: Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rogers, J. R. Watson, D. G. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2331. Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560.

[15] Kaufman, R.; Knöchel, A.; Kopf, J.; Oehler, J.; Rudolph, G. *Chem. Ber.* **1977**, *110*, 2249.

[16] We use the term hydrogen bonding to describe a close, potentially attractive C–H···O interaction. We make no implication regarding the degree of n donation (i.e., covalent bonding) between the C–H bond and oxygen.

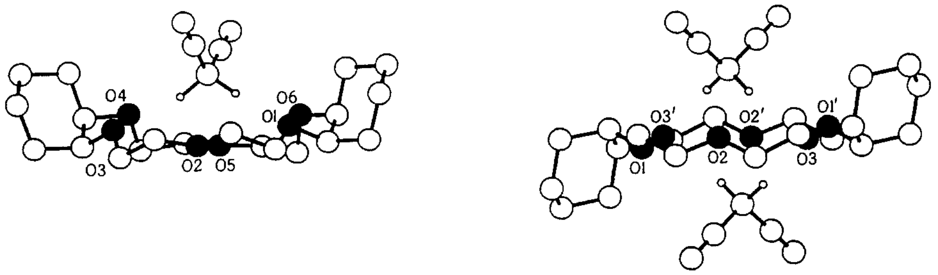

Figure 4. Views of the X-ray crystal structures of 1 (left) and 2 (right). Views are approximately along the mean plane of the crown ring. Crown-ring oxygen atoms are shaded for clarity.

has been suggested previously[1] to be of major importance in determining the efficiency of crown ether complexation of compounds that contain polar C–H bonds.

What is the origin of the observed isomer-dependent complexation of malononitrile by these two forms of dicyclohexano-18-crown-6? While qualitative arguments based on the steric requirements of the flanking methylenes can attempt to rationalize the eclipsed orientation of malononitrile in 1, simple structural arguments provide little insight into the question of why 1 forms a 1:1 and 2 a 2:1 complex. In order to address this issue and to test our qualitative steric arguments, we performed quantitative molecular mechanics calculations on 1–4.

Molecular Mechanics Calculations

We initially tested the reliability of our computational method by calculating the structures of 1–4 with the previously developed parameter sets[3] for neutral-molecule complexation (Original, PEOE1, PEOE2, MULL1, MULL2).[19] Calculated binding energies are reported in Table I and selected calculated bonding parameters are reported in Table II. Views of the calculated structures (MULLI[21]) of 1 and 2 are shown in Figure 3. As inspection of Figures 2 and 3 and Table II shows, agreement between observed and calculated structures is very good. We are thus confident that application of these theoretical techniques will provide reliable structural results.

In order to test the validity of our steric arguments regarding the orientation of malononitrile in 1 and 2, we performed modified molecular mechanics calculations on 1. In these calculations, all force field parameters were the same as those used in the initial structural calculations except that Van der Waals parameters for the flanking methylene groups ($C6H_2$ and $C19H_2$) were set to zero. Using the X-ray crystal structure for 1 as input, calculations with these modified Van der Waals parameters yielded a new structure in which the malononitrile moiety adopts a configuration that cannot properly be described as either staggered or eclipsed. Thus, since the eclipsed structure is no longer maintained when these Van der Waals interactions are removed, our qualitative steric arguments (see above) find support in these calculations. However, since the staggered structure observed for 2 and the 2:1 malononitrile:18-crown-6 complex is not obtained from these calculations (even when a hypothetical staggered structure is used as input), other factors must also be responsible for the eclipsed configuration in 1. These additional factors are clearly revealed upon further inspection of the X-ray crystal structures. In Figure 4, side views of the X-ray crystal structures of 1 and 2 are shown, which make it immediately apparent that the configuration of the crown-ring oxygen atoms differ significantly in these two structures. In 1, there are four crown-ring oxygens atoms that project toward the malononitrile guest (O1, O3, O4, and O6). In contrast, for 2, crown-ring oxygen atoms alternate up and down around the ring perimeter, leaving two oxygens (O3 and O3′) accessible for binding malononitrile (see Figure 2). Thus, we conclude that a combination of oxygen orientation and steric interactions with the flanking methylenes are responsible for the eclipsed configuration of malononitrile observed in 1.

In order to determine the origin of the observed isomer-dependent binding ratios (1:1 and 2:1), it is necessary to investigate the energetics of malononitrile complexation. We therefore calculated the binding energies for 1:1 and 2:1 complexation of malononitrile by 3 and 4. The results of these calculations are reported in Table I. While these calculations were in progress, an experimental determination of the 1:1 complexation enthalpy between dicyclohexano-18-crown-6 and malononitrile in benzene was reported.[1j] The experimental value of 8.6 kcal/mol[1j,10] and our theoretical calculations are in excellent agreement (see Table I).

Comparison of the 1:1 and 2:1 complexation energies of malononitrile allows us to address the question of cooperativity and hence isomer-dependent binding ratios in 3 and 4. Qualitative arguments, based on the calculated and observed structures of the 1:1 complexes, predict positive cooperativity for binding a second guest to 4 ($\Delta E_2 > \Delta E_1$) and negative cooperativity for binding a second guest to 3 ($\Delta E_2 < \Delta E_1$). This reasoning follows from the observation that formation of a 1:1 complex by 4 preorganizes the host[1i] so that it is in an ideal configuration for binding the second guest. Formation of a 1:1 complex by 3, however, results in four of the available crown-ring oxygens being located on the face of the crown which is proximal to the syn cyclohexyl groups (Figure 4). These oxygen atoms are therefore unavailable for direct participation in complexation of a second guest to the distal side of the crown ring (see above). Since these qualitative cooperativity arguments suggest a greater preference for 4 forming a 2:1

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[17] Preliminary calculations at the 6-31G**//6-31G** level have provided an upper limit of 5.4 kcal/mol for the strength of these C–H···O hydrogen bonds in malononitrile. Damewood, J. R., Jr.; Kumpf, R. A., to be published. Similar calculations have shown that C–H···O hydrogen bonding is not important for the complexation of acetonitrile to 18-crown-6. Damewood, J. R., Jr. Kumpf, R. A. *J. Phys. Chem.* **1987**, *91*, 3449.

[18] For reviews of C–H···O hydrogen bonding, see: (a) Green, R. D. *Hydrogen Bonding by C–H Groups*; Wiley: New York, 1974. (b) Meot-Ner (Mautner), M. *Acc. Chem. Res.* **1984**, *17*, 186. (c) Deakyne, C. A. "Ionic Hydrogen Bonds. Part II. Theoretical Calculations" In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Ed.; VCH: Deerfield Beach, FL, Vol. II 1985; and references therein. See also: Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063. Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222.

[19] For a discussion of why five parameter sets are employed in these calculations, see ref 3.

[20] The Tilt Angle is the CT_c–X–CT_m angle. CT_c is the centroid of the crown ether oxygens, X is the methylene carbon of malononitrile, and CT_m is the centroid of the malononitrile nitrogens. P-Dist is the distance of X from the least-squares plane of the crown ether oxygens. Twist1 is the absolute value of the O–CT_c–X–N torsion angle. Twist2 is the absolute value of the CT_m–X–X′–CT_m′ torsion angle where X′ and CT_m′ refer to the second malononitrile.

[21] The structures obtained for all parameter sets are closely similar.

complex than for **3**, they are completely consistent with our experimental observations. We performed molecular mechanics calculations on this system in order to test our qualitative predictions and to place them on a more quantitative basis.

Inspection of the binding data in Table I reveals that computationally, positive cooperativity is predicted for the formation of 2:1 complexes by both **3** and **4**.[22] The 1:1 binding energies for both isomers of dicyclohexano-18-crown-6 are closely similar and range from 7.4 to 9.1 kcal/mol for **3** and 7.9 to 8.8 kcal/mol for **4**. For 2:1 complexation, the calculated positive cooperativity is greater for **4** than for **3** and 2:1 binding energies range from 11.4 to 12.4 kcal/mol and 8.7 to 10.4 kcal/mol for **4** and **3**, respectively. These quantitative results are thus in conflict with our qualitative predictions. This discrepancy is a direct result of our qualitative arguments being unable to consider the magnitude of factors like intermolecular electrostatic and Van der Waals interactions, etc., that are important in determining binding efficiency. When these factors are considered in a quantitative way by molecular mechanics calculations, positive cooperativity is predicted for both isomers.

Given the calculated positive cooperativity for both isomers of dicyclohexano-18-crown-6, why does **3** form only a 1:1 complex (**1**) in the solid state?[23] Insight into this question may be obtained from consideration of the crystalline environment of these two complexes. In **4**, cyclohexyl groups are located on both sides of the molecule and complexation with malononitrile to form the 2:1 complex results in a structure that is relatively spherical in shape and can be expected to pack efficiently into a crystal lattice (Figure 4). In the case of **3**, both cyclohexyl groups are on the same side of the molecule and formation of the proximal complex (1:1) results in a structure which should pack with similar efficiency (see Figure 4). Packing a hypothetical 2:1 complex of **3** into a crystal lattice is expected to be much less efficient than either of the above cases since regions anti to the cyclohexyl groups would, most likely, be left void in the crystal. We therefore suggest that only the 1:1 (**1**) complex of **3** is observed in the solid state due to the influence of crystal packing. Intrinsically (i.e., in isolation) an energetic preference for 2:1 complexation is expected for both **3** and **4**.[22]

Summary

A hybrid of experimental and computational techniques have been employed to investigate the isomer-dependent complexation of malononitrile by two isomers of dicyclohexano-18-crown-6 (**3** and **4**). A combination of steric interactions with flanking methylene groups in **1** and donor oxygen orientation in the complex is held responsible for the different orientations of malononitrile in **1** and **2**. Quantitative molecular mechanics calculations predict positive cooperativity for binding a second malononitrile to both isomeric forms of dicyclohexano-18-crown-6.[22] The influence of crystal packing is suggested as a reasonable explanation for the formation of only a 1:1 complex for **3** in the solid state. Isomer **4** forms the expected 2:1 complex with malononitrile.

We point out that an accurate analysis of the origins of isomer-dependent complexation in this system was only possible through a hybrid application of computational and experimental techniques. Qualitative arguments regarding the steric interaction of the flanking methylenes in **1** and cooperativity in binding malononitrile to **3** and **4** were incomplete, and would have led to inaccurate conclusions.

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Supplementary Material Available: Tables of atomic coordinates, bond distances and angles, anisotropic temperature factors, hydrogen atom coordinates, and selected calculated average bonding parameters for **1** and **2** and calculated and observed crown-ring torsion angles for **1**–**4** (13 pages); observed vs calculated structure factors for **1** and **2** (20 pages). Ordering information is given on any current masthead page.

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(22) It is important to remember, however, that since our molecular mechanics calculations do not consider factors such as entropy and solvation, which may alter binding efficiency, it is possible that positive cooperativity would be predicted for the complexes in isolation (computationally) while negative cooperativity is observed experimentally.[3]

(23) Why the 1:1 complex of **3** forms with malononitrile proximal rather than distal to the syn cyclohexyl groups (distal complex) is also of interest. Preliminary calculations indicate a 1:1 binding energy of ca. 5 kcal/mol to the distal face of **3**. However, since a complete conformational analysis was not performed on the complex, this 1:1 binding energy serves as a lower limit to complexation efficiency. We are therefore unable to conclude whether the proximal 1:1 complex is formed due to intrinsic stability differences or the influence of crystal packing (see text).