Organic Ligand-Receptor Interactions between Cucurbituril and Alkylammonium Ions†,[1]

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Abstract: Experimental binding energies for 24 substituted ammonium ion ligands for the synthetic receptor cucurbituril are adjusted for ligand solvation and then are factored by regression analysis into contributions from various fragments of the ligands in their inclusion complexes. This allows quantitative estimation of noncovalent forces occurring in the interaction of ligand with receptor. It is concluded that the center of cucurbituril constitutes a lipophilic region but that the entrances to the interior (ammonium ion binding site) are countervailingly lipophobic. Enhanced dispersion forces involving the thioether functional group may exist in the receptor complexes of such ligands, but they make no extra contribution to the hydrophobic effect generally. The specificity of cucurbituril as a molecular receptor is explained in terms of ion-dipole attractions and shape complementarity with ligands.

The phenomenon of noncovalent bonding is a topic of major significance to investigators of interactions between biological molecules. The weak intrinsic affinities between nonpolar moieties in aqueous solution are thought to be responsible for the aggregation of lipids, and in many instances for the binding of enzyme substrates, inhibitors, hormones, antigens, etc. to their receptor sites. These noncovalent forces involving small molecules are sufficiently weak that as a practical matter they can only be studied when their effects are cumulative. In this regard the recent availability of synthetic molecular ligand-receptor systems introduces major opportunities for systematic chemical investigation of this important, but ill-understood topic.

Cucurbituril (Figure 1) is a novel nonadecacyclic cage compound of hexagonal symmetry, which is readily assembled by acid-catalyzed condensations between urea, glyoxal, and formaldehyde [$2H_2NCONH_2 + CHOCHO \rightarrow C_4H_6N_4O_2$ (glycoluril), $6C_4H_6N_4O_2 + 12CH_2O \rightarrow C_{24}H_{36}N_{24}O_{12}$ (cucurbituril)].[2] It has a relatively rigid structure, with a hollow core of several angstroms diameter, which is accessible from the exterior. Recently we have shown that the interior of this molecule comprises a hydrophobic region, into which small hydrocarbon moieties tend to be attracted from aqueous solution.[3,4] Cucurbituril has also been shown to be an effective catalyst for a specific cycloaddition.[5] This article focuses upon the noncovalent binding properties of cucurbituril as a receptor for aliphatic residues. By systematic variation of ligand structure we attempt to elucidate quantitatively which features of a resident ligand species are responsible for stability and selectivity within complexes of cucurbituril.

A unique aspect of cucurbituril as a molecular receptor is its structural rigidity. Because of its polycyclic nature, it cannot easily conform itself to the shape of incorporated small molecules. This leads to exceptional specificity in complexation and thereby provides an opportunity to probe systematically the factors involved in noncovalent binding. We have previously suggested a model for the structure of alkylammonium ion ligand-receptor complexes of cucurbituril. It is summarized in Figure 2 for the *n*-pentylammonium ion adduct. This picture emerges from comparisons of the specificities of a large number of ligands for cucurbituril, expressed as K_d values, plus NMR and other data for the complexes.[4] There are two general features that are readily identified as contributing to stability of these adducts. The cumulative effect of six carbonyl dipoles focused at each portal of the hollow cage structure (Figure 1) creates a cation binding site to which an ammonium ion may coordinate, with ion-dipole interactions facilitated by bipodal hydrogen bonding. This type of coordination is demonstrated to be a major contributor to the association by the generally much tighter binding of alkanediamines, specifically $H_2N(CH_2)_5NH_2$ and $H_2N(CH_2)_6NH_2$, in comparison with *n*-alkanemonoamines (i.e., 2-3 orders of magnitude in binding constant in acidic solution). Secondly, should an alkyl group attached to the ammonium ion be of a proper size, it enters the interior of cucurbituril, displacing solvent water molecules from within the receptor and from the solvation sheath of the ligand, thereby contributing a hydrophobic effect to the stability of the complexes. It is with the latter feature that this paper is chiefly concerned.

† This paper is respectfully dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

Results

The pattern of *specificity* by cucurbituril for binding of substituted ammonium ions has previously been described qualitatively.[4] Among *n*-alkylammonium ions, the butyl substituent provides the most stable adduct with affinity toward cucurbituril diminishing monotonically for homologues. The interior of cucurbituril is large enough to accommodate certain *branched* alkyl substituents; a single additional methyl group on the *n*-alkyl chain is allowed generally, and cycloalkyl rings C_3 through C_5 are incorporated. For purposes of systematic analysis, we have compiled a set of data for an appropriate series of alkylammonium ions, plus certain thioether analogues, for which quantitative measurements of affinity for cucurbituril exist.[4] As previously described, binding data has been obtained chiefly by NMR competition experiments, in which a pair of slowly exchanging substituted ammonium ions (in excess) are allowed to compete for a limited amount of cucurbituril in HCO_2H-D_2O solution. Because the aliphatic portions of a ligand bound within the interior of the receptor experience an upfield shift of NMR signal relative to their counterparts free in solution, it is generally a simple matter to obtain relative binding constants for a pair of ligands by integration of the appropriate signals. By establishing proper relays, a scale of affinities of ligands for cucurbituril may be created with this and related techniques described elsewhere.[4] Pertinent relative formation constants are assembled in Table I (first column). Our purpose in this article is to provide a suitable analysis of this information, which will yield a quantitative evaluation of factors contributing to the stability of the ligand-receptor complexes of cucurbituril.

As our standard conditions for measurement of equilibrium binding constants (as well as for kinetic studies), we have previously adopted for practical reasons a solvent composed of a 1:1 (v/v) mixture of water and 88% formic acid at 40 °C. In this medium cucurbituril has reasonable solubility (10% solutions may easily be obtained). Furthermore, this mixture apparently retains

(1) Taken from the Ph.D. Thesis of N.-Y. Shih, University of Illinois at Chicago, 1981; *Diss. Abstr. Int. B* **1982**, *42*, 4071.
(2) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.
(3) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618.
(4) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.
(5) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619.

0002-7863/88/1510-4706$01.50/0

Table I. Noncovalent Binding Data for Ligand–Receptor Complexes of Cucurbituril

ligand	K_f[a] (relative)	area,[b] 10^9 cm^2/mol	volume,[b] cm^3/mol	log γ[c]	$-\Delta G$,[d] kcal/mol
1. NH_3	0.25			4.02[e]	0.0
2. CH_3NH_2	0.25	3.86	24.21	3.53	−0.70
3. $CH_3CH_2NH_2$	0.3	5.21	34.44	3.45	−0.70
4. $CH_3(CH_2)_2NH_2$	37.6	6.56	44.67	3.30	2.09
5. $CH_3(CH_2)_3NH_2$	307.	7.91	54.90	3.15	3.18
6. $CH_3(CH_2)_4NH_2$	74.	9.26	65.13	3.00	2.08
7. $CH_3(CH_2)_5NH_2$	7.0	10.61	75.36	2.85	0.40
8. $CH_3(CH_2)_6NH_2$	0.3	11.96	85.59	2.70	−1.76
9. $(CH_3)_2CHCH_2NH_2$	67.	7.90	54.89	3.07	2.12
10. $(CH_3)_2CH(CH_2)_2NH_2$	109.	9.25	60.12	2.92	2.21
11. $(CH_3)_2CH(CH_2)_3NH_2$	13.	10.60	75.35	2.77	0.67
12. $CH_3CH_2CH(CH_3)CH_2NH_2$	6.0	9.25	65.12	2.92	0.40
13. $CH_3CH_2CH(CH_3)(CH_2)_2NH_2$	3.5	10.60	75.35	2.77	−0.15
14. c-$(CH_2)_2CHCH_2NH_2$	45.	6.36	48.01	4.01	3.22
15. c-$(CH_2)_3CHCH_2NH_2$	1130.	7.71	58.24	3.86	5.01
16. c-$(CH_2)_4CHCH_2NH_2$	1040.	9.06	68.47	3.71	4.74
17. c-$(CH_2)_2CHNH_2$	1.2	5.01	37.78	4.16	1.17
18. c-$(CH_2)_3CHNH_2$	9.2	6.36	48.01	4.01	2.23
19. c-$(CH_2)_4CHNH_2$	19.5	7.71	58.24	3.86	2.48
20. $CH_3S(CH_2)_2NH_2$	52.		55.47	5.78	5.84
21. $CH_3CH_2S(CH_2)_2NH_2$	105.		65.70	5.76	6.25
22. $CH_3S(CH_2)_3NH_2$	27.		65.70	5.63	5.22
23. $CH_3CH_2S(CH_2)_3NH_2$	2.3		75.39	5.61	3.66
24. c-$(CH_2S)_2CHCH_2NH_2$	1810.		68.47	9.23	12.99

[a] Formation constant in 1:1 (v/v) HCO_2H–H_2O, 40 °C, relative to *p*-$CH_3C_6H_4CH_2NH_2$ (1.0), for which an absolute K_d value is known (ref 4). [b] Calculated from the compilations of Bondi (ref 6). Group contributions to van der Waals surface area (10^9 cm^2/mol) and molecular volume (cm^3/mol) as follows: CH(R)$_3$ 0.57, 6.78; CH$_2$(R_2) 1.35, 10.23; CH$_3$(R) 2.12, 13.67; NH$_2$(R) 1.74, 10.54; S(R_2) -, 10.8. No allowance is made for protonation of the amino group in acidic solution, as this would provide a constant additive factor, which may be neglected for comparative purposes. [c] Calculated from the compilation of Hine and Mookerjee (ref 7). Group contributions as follows (for 25 °C): CH$_3$(X) −0.62, CH$_2$(C)$_2$ −0.15, CH(C)$_3$ +0.24, CH$_2$(C)(S), −0.02, CH$_2$(C)(N) −0.08, S(C)$_2$ +2.35, NH$_2$(C) +4.15, CH(C)$_2$(N) +0.31 (est), CH(C)(S)$_2$ +0.51 (est). [d] Values for $-\Delta G$ (kcal/mol) = 2.3(RT log K_f + RT log γ), normalized to ΔG = 0.0 for NH_3. [e] Based on NH bond contribution of 1.34 (×3) (ref 7).

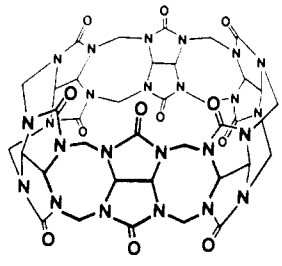

Figure 1. Cucurbituril.

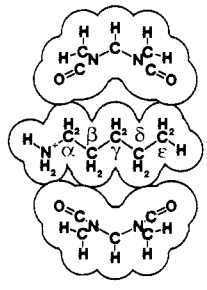

Figure 2. Conjectured cross-sectional representation of ligand–receptor complex for $C_{24}H_{36}N_{24}O_{12}$·$CH_3(CH_2)_4NH_3^+$. Outlines drawn to van der Waals radii (maximum projection for all atoms upon axial rotation of cucurbituril, with crystallographically determined interatomic distances for cucurbituril. Two N—H···O=C hydrogen bonds may form, but the third N^+—H projects incorrectly for coordination to the receptor (ref 4).

a similar lipophobicity as has pure water itself. Evidence for this assertion derives from the comparative solubility of hydrocarbons in this medium, specifically that of *cyclopentane*. A saturated aqueous (D_2O) solution of C_5H_{10} yields an ^1H NMR signal that is 40% as intense (integral) as that from free (unbound) cyclopentane in a saturated solution of our standard solvent (D_2O–HCO_2H) containing cucurbituril. (A separate NMR signal is obtained from the stoichiometric complex of C_5H_{10} within cucurbituril under these conditions.) Hence, this small difference in solubility (amounting to a free energy difference of 0.57 kcal/mol at 40 °C or 0.11 kcal/mol per CH_2 unit) indicates that our aqueous formic acid is a water-like medium. We shall rely upon this observation to justify utilizing the concepts of hydrophobicity in interpretation of our data.

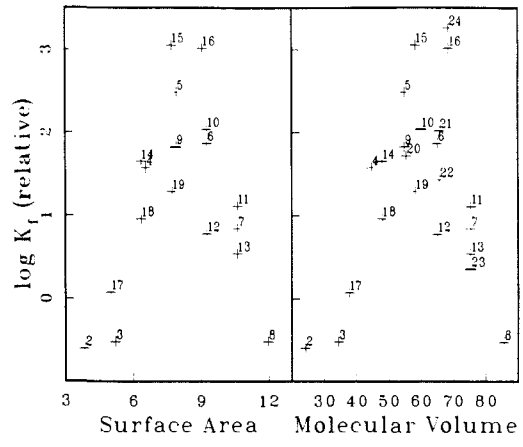

Figure 3. Plots of log K_f(relative) vs van der Waals surface area and molecular volume for ligands (10^9 cm^2/mol and cm^3/mol, respectively, ref 6). Ligand number key, Table I.

Discussion

In assessing the importance of various contributing factors affecting the comparative affinities of ligands toward cucurbituril as exhibited in Table I, a number of criteria were tentatively considered. For example, possible correlations between formation constant and van der Waals molecular surface area and volume of the ligands (Table I, columns 2, 3) with use of the compilations of Bondi,[6] are noted in Figure 3. In these analyses a summation of increments for each fragment of the ligand (CH_3, CH_2, CH, S, NH_2), using appropriate previously tabulated values for these parameters, yields a calculation of the total size of the ligand. In the plots shown, the vertical axis is proportional to binding energy

(6) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(log K_f). To our mind such correlations do not satisfactorily explain the relative stabilities of the complexes. It may be observed that binding energy typically peaks at intermediate size of ligand (rather than for the maximum size bound) and that ligands of similar size by these criteria have disparate affinities for cucurbituril, in some cases amounting to greater than 2 orders of magnitude in formation constant. Therefore, we have sought a more sophisticated interpretation of the factors governing stability of receptor complexes.

The difficulty in applying a gross assessment of size (such as total molecular volume or surface area for bound species), is that the interior of cucurbituril has a definite *shape* and *distribution of polarity*. The requisite complementarity between receptor and its ligand depends more subtly upon the structure of the bound entity. Consequently, we have opted for an empirical treatment of our data, which would yield an indication of how various regions of the interior of cucurbituril interact with ligands.

A major complication in interpreting the disparate affinities of various ligands for cucurbituril is that the experimental K_f values that we have obtained represent differences between the *stabilization energy* of the *complexes* and the *solvation energy* of the individual components prior to association. Consequently, a large differential between the strength of complexation of any two alkylammonium ions with cucurbituril might actually reflect major differences in their solvation in the absence of the receptor, rather than any very great difference in the absolute stabilities of the complexes themselves. This is particularly so, when it is realized that ligands are effectively sequestered from solvent when ensconced within cucurbituril (Figure 2). Therefore, a systematic treatment of comparative affinities for cucurbituril must first account for solute–solvent effects in the free (unbound) ligands.

A resolution for this problem has been identified by Hine.[7] In principle, the reference state for the uncomplexed ligand should be the *dilute vapor phase*, rather than in solution, so that all intermolecular contacts are negated in the dissociated state. In such a case the relative affinities of ligands for cucurbituril would solely reflect stability of the complexes. Although such a measurement is not directly feasible in our case, data exists that allows computation of an energy term for solvation of each of our ligands. Hine and Mookerjee define the intrinsic hydrophilicity of an organic substance as log γ, where $\gamma = C_w/C_g$, in which C_w is the concentration of a substance in dilute aqueous solution at 25 °C and C_g is the concentration in the gas phase in equilibrium with the aqueous solution (both in moles/liter).[7] In order to discuss the relationship between molecular structure and the intrinsic hydrophillic character of compounds in quantitative terms, they have carried out correlations in terms of a structure-additivity scheme. That is, they collected data on the vapor pressures and solubilities of a large number of organic substances and made a regression analysis based on both a bond-contribution and a group-contribution scheme. Parameters for these schemes were determined by the method of least squares. This treatment gives a satisfactory correlation between calculated and experimental log γ values for 212 diverse substrates. By use of Hine's data, the value of log γ for each of our alkylamines can be calculated (Table I, column 4).

The appropriate log γ adjustment has been made to each experimental relative binding energy ($2.3RT \log K_f$) in order to yield a "corrected" relative binding energy, $-\Delta G$ (Table I, column 5). Some obvious additional corrections have been neglected. The heat of protonation of the ligand is ignored. Since every member of the series contains a primary amine (most are H_2NCH_2R), for which the pK values should all be similar, this would provide a constant, additive contribution, which may be disregarded for comparison of *relative* binding energies. Perhaps more worrisome is the application of a correction factor ($2.3RT \log \gamma$), which has been derived for neutral aqueous solution to data obtained in mixed solvent. However, as previously noted, the solubility of cyclopentane in our solvent medium is essentially the same as in pure H_2O. Since C_5H_{10} is typical of the alkyl portion of the amines in this study, we think that our application of log γ is appropriate. In short, experimental binding free energies in solution have been "corrected" for solvation of the alkyl moiety of the ligand (although not for the unligated receptor, which is a constant factor). The resulting numbers have then been normalized to the value for ammonia, effectively assuming in the process that all other extrinsic factors that might affect ligand binding to cucurbituril would be constant throughout the series. This should provide a pure measure of the fit of each of the ligands to the interior of cucurbituril (Table I, $-\Delta G$).

In order to process the revised data in as unprejudiced a manner as possible, we adopt as our fundamental variable for correlating structure with binding affinity the intramolecular *distance* of an alkyl fragment of a bound ligand from its ammonium ion. The rationale for this approach is that the binding site for the RNH_3^+ moiety is established and is presumeably invariant (for the most part); i.e., the ammonium ion coordinates with the carbonyl dipoles of cucurbituril as depicted in Figure 2. We then inquire as to the *contributions* of hydrocarbon (or thioether) fragments in the α, β, γ, etc. positions, as also notated in Figure 2, to the stability of the ligand–receptor complexes. In order to do this most efficiently, we simply count hydrogen atoms at each of these positions. Since the hydrogens represent regions of contact with the receptor, they provide an elementary index of potential interaction with the interior of cucurbituril. No distinction is made between primary (CH_3), secondary (CH_2), or tertiary (CH) hydrogens in our analysis; i.e., a methylene group is assumed to be twice as consequential as a methine moiety. In the case of branched or cyclic alkyl substituents, the number for a particular type of hydrogen is incremented accordingly.

The purpose of this breakdown is to be able to perform a *regression analysis* upon the ΔG values and thereby to identify how the *location* of each individual ligand–CH fragment influences stability of the receptor complexes. For each substrate in Table I, an equation may be written that relates ΔG with a number of structural parameters: $\Delta G_t = n_1\Delta G_{\alpha H} + n_2\Delta G_{\beta H} + n_3\Delta G_{\gamma H} + \ldots + \Delta G_0$. In this scheme the relative binding energy is factored into contributions from each individual CH group (times the number of such groups present), plus a residual (ΔG_0) involving the ammonium ion and any other constant factor across the series. As an example, for no. 21 in Table I the relationship might be ΔG_t (= −6.25) = $2\Delta G_{\alpha H} + 2\Delta G_{\beta H} + 0\Delta G_{\gamma H} + 2\Delta G_{\delta H} + 3\Delta G_{\epsilon H} + 1\Delta G_{\gamma S} + \Delta G_0$. A similar equation may be drawn for every other substrate, and then an appropriate set of values for the parameters ($\Delta G_{\alpha H}$, $\Delta G_{\beta H}$, etc.) is established by a simultaneous least-squares fit of the matrix of equations to the data set of ΔG_t values represented in Table I.

In order to get meaningful results from such an approach, it is necessary to restrict the number of disposable parameters to a minimum. Preliminary multiparameter fitting[1] indicated that certain individual CH-fragment contributions could be combined for purposes of simplification. It appeared that hydrogens in the γ and δ positions (Figure 2) were the major hydrocarbon contributors to stabilization of the complexes and that their contributions were comparable. Accordingly, these parameters were united. Conversely, hydrogens in the α or the ϵ and $\epsilon+$ positions (i.e., immediately next to or more than four atoms removed from the nitrogen, as in *n*-pentyl- through *n*-heptylamine) made an *unfavorable* contribution to ligand–receptor interactions. These too were combined into a single parameter. The influence of hydrogens in the β position (Figure 2) appeared to be nearly neutral, and these were therefore ignored in our final fit. Sulfur atoms (thioether linkages in the γ or δ positions) made a strong positive contribution, and they were assigned to a separate parameter. We were ultimately able to secure an adequate fit of binding energies for all 24 substrates in Table I to a four parameter equation, which is given in Table II along with the resulting values for the binding coefficients.

With reference to the model of Figure 2, a picture may be drawn embodying the factors contributing to ligand–receptor stabilization. It generally appears that hydrocarbon fragments that reside in a narrow zone near the center of the cavity of cucurbituril provide

(7) Hine, J.; Mookerjee, P. K. *J. Org. Chem.* **1975**, *40*, 292.

Table II. Coefficients Fitting $-\Delta G$ Values to Regression Equation[a]

$$\Delta G_i = n_1\Delta G_{\alpha H,\epsilon H,\epsilon+H} + n_2\Delta G_{\gamma H,\delta H} + n_3\Delta G_{\gamma S,\delta S} + \Delta G_0$$

$\Delta G_{\alpha H,\epsilon H,\epsilon+H}$	0.38 ± 0.11 kcal/mol
$\Delta G_{\gamma H,\delta H}$	−0.38 ± 0.12 kcal/mol
$\Delta G_{\gamma S,\delta S}$	−5.3 ± 0.5 kcal/mol
ΔG_0	−1.2 ± 0.6 kcal/mol

[a] Derivation of equation in text; n_1, n_2, n_3 take integer values 0–9 according to number of hydrogens (or S atoms) in positions α, β, γ, etc. with respect to nitrogen (see Figure 2). Tolerances listed are standard errors from least-squares analysis.

beneficial noncovalent binding amounting to ca. −0.76 kcal/mol per CH_2 group (2 × 0.38, because of two hydrogens). Wolfenden has independently estimated from appropriate thermodynamic data for volatile *n*-alkanes that the transformation of a methylene unit from the vapor state to a hydrocarbon liquid is exergonic by $\Delta G = -0.82 \pm 0.19$ kcal/mol.[8] Hence it is a reasonable conclusion that the central interior of cucurbituril is typically "hydrocarbon-like", since our $-\Delta G$ values are also referenced to the vapor state. In contrast, forcing a CH fragment to reside in the vicinity of one of the oxygen atoms of cucurbituril apparently has a *destabilizing* effect, which is coincidentally of similar absolute magnitude. The polarized regions surrounding the carbonyl groups of the receptor (adjacent to and opposite from the ammonium ion binding site, Figure 2) reject hydrocarbons. It is the concurrent interactions of these juxtaposed regions of the receptor that are responsible for the exceptional selectivities that cucurbituril exhibits toward hydrocarbon-containing ligands. This point will be elaborated upon subsequently. Placing a sulfur atom within the interior of cucurbituril appears to result in an even greater stabilization ($\Delta G = -5.3$ kcal/mol per S). This will receive detailed consideration also. The value of ΔG_0 has no significance; the experimental ΔG values have been normalized to that of ammonia, and this number merely expresses a deviation of that ligand from the mean of the ammonium portion of the other ligands. Since all of our substrates have but a single ammonium ion, no independent estimate of the contribution of that moiety to the stability of the complexes may be ascertained. In principle, a value for $\Delta G_{NH_3^+}$ could be acquired by the incorporation of several alkanediamines into our data set. However, a second ammonium ion in fact has a disproportionate effect, and it cannot be meaningfully placed on the same scale as the hydrocarbon fragment increments here considered (at least not with reference to the vapor phase). For what it may be worth, 1,5-pentanediamine [K_f (relative) = 7500] binds more tightly than *n*-pentylamine by −2.8 kcal/mol (uncorrected ΔG). This may be a reasonable estimate for the attractive contribution to binding by six carbonyl dipoles interacting with one ammonium ion (over and above the stabilization provided by aqueous formic acid).

The quality of the fit of our data to the equation in Table II is depicted graphically in Figure 4. The diagonal represents the regression line for a least-squares minimization of residuals. The standard errors for the CH coefficients in Table II are approximately 30%; this is about as good as can be expected from the data[4] and from the uncertainties in the log γ adjustments.[7]

It might be noted from Figure 2 that the favorable hydrocarbon binding region appears to be "off-center". It would seem by symmetry that the δ position ought to be similar to the β position, which we find to make a neutral contribution to stabilization of the complexes (i.e., the "crossover point" between positive and negative effect). However, this is probably an artifact of the model embodied in Figure 2, which shows the ligand in its most extended conformation. In actuality, the dimensions of the interior of cucurbituril should allow smaller substrates (e.g., *n*-butylammonium ion, no. 5) to adopt *gauche* conformations in which a CH fragment in the δ position experiences an environment more similar to that of the γ position. Indeed, this must hold true for certain branched-hydrocarbon ligands (e.g., isopentylammonium ion, no. 10). A detailed inspection of models of individual cucurbituril–ligand complexes can explain some of the more egregious deviations from the regression line in Figure 4, but that is unnecessary for the purposes of this article.

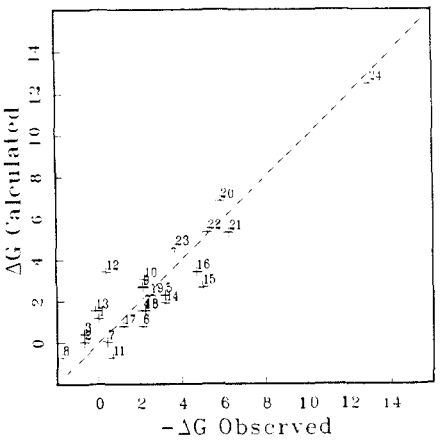

Figure 4. Plot of calculated $-\Delta G$ values, according to equation of Table II, vs experimental $-\Delta G$ values, Table I. Diagonal is regression line.

A number of thioethers (no. 20–24) were deliberately incorporated into this study in order to compare the noncovalent bonding contribution of a sulfur atom with that of a methylene residue. Partly, the stimulus for this was an article by Fersht and Dingwall,[9] indicating a specific interaction between small sulfur-containing substrates and the enzymes that operate upon them. In particular, these authors have shown that cysteinyl and methionyl-tRNA synthetases of bacterial origin reject substrate analogues containing a methylene (CH_2) group in place of sulfur (S) with a discrimination factor suggesting that a "sulfur atom contributes about 5 kcal/mol to binding" and that this value includes an increment of approximately 3 kcal/mol over a correspondingly placed methylene moiety. The latter differential was attributed to the *polarizability* of the sulfur atom, which results in a lesser dispersion energy in aqueous medium (where the S is surrounded by nonpolarizable oxygen atoms) than in an enzyme–substrate complex, in which an environment may be provided for S by more polarizable hydrocarbon residues, specifically, where an "enzyme has evolved to close-pack its atoms around a group on the substrate".[9] In support of this hypothesis, a semiempirical calculation was carried out, in which estimates of the relevant dispersion energies were obtained.[10] The results were alleged to be in excellent agreement with the experimental data. Consequently, we entertained a reasonable expectation that a similar phenomenon would materialize in the thioether–ligand complexes of cucurbituril.

Inspection of Table II reveals apparent confirmation; the group contribution of a thioether in the γ or δ positions is indeed −5 kcal/mol, and this exceeds the corresponding contribution of a methylene fragment by more than 4 kcal/mol. We think it plausible to attribute this difference to dispersion forces, as suggested by Fersht.[9,10] However, closer inspection of our data yields a conclusion at variance with that of Fersht and Dingwall in regard to the overall *biochemical* significance of this phenomenon. If instead of the $-\Delta G$ values one consults the K_f measurements (which are the primary data), it may be seen that the thioether–ligands (no. 20–24) do not bind significantly more tightly than do their purely alkanyl–ligand counterparts (no. 5–7, 16). The apparent discrepancies in $-\Delta G$ for these two classes of ligand are in fact due to the log γ adjustment, which was applied so that our binding

(8) Wolfenden, R.; Lewis, C. A., Jr. *J. Theor. Biol.* **1976**, *59*, 231.

(9) Fersht, A. R.; Dingwall, C. *Biochemistry* **1979**, *18*, 1245, 1250.

(10) By calculations based on molecular refractivity and accepted interaction potentials, Fersht and Dingwall (ref 9) estimate that dispersion forces between S and CH_2 should be 2.5 times greater than between CH_2 and CH_2. They further observe that the dispersion energy between an individual methylene group and all of its neighbors in a solid hydrocarbon amounts to ca. 2 kcal/mol (empirical value, secured from heats of sublimation of alkanes). It follows that the dispersion energy of S in a close-packed hydrocarbon environment should be ca. 5 kcal/mol. By virtue of its derivation, this number represents a functional-group transfer equivalent from a hydrocarbon solid to the vapor phase.

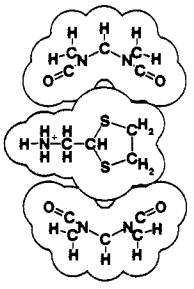

Figure 5. Conjectured cross-sectional representation of ligand–receptor complex for $C_{24}H_{36}N_{24}O_{12}$·c-$(CH_2S)_2CHCH_2NH_3^+$. Outlines as in Figure 2. Interatomic distances within ligand correspond to projections for a puckered ring filling (nearly) the cavity.

energies could be systematically referenced to the vapor state. In sum, while it appears that the thioether linkage may indeed have a higher affinity for a hydrocarbon environment than does a methylene residue, it also has a corresponding higher attraction for an aqueous environment, according to the evidence developed by Hine.[7] The calculations of Fersht and Dingwall, supposedly demonstrating the unique importance of dispersion forces in thiasubstrate binding, do not refer to transfer from aqueous medium to the enzyme surface, as does their data. In their theoretical estimation they made no allowance for the fact of preferential aqueous solvation of S relative to CH_2, $2.3RT[\log \gamma(S) - \log \gamma(CH_2)] = 3.4$ kcal/mol, which apparently is able to negate the higher stability attainable for thioether complexes, as we find to be the case. We conclude that concerning the practical enzymological aspects of *hydrophobic* binding phenomena, a thioether linkage *is* a surrogate for a methylene unit, and the two are unlikely to be distinguishable except by some specific interaction, such as enzymic metal ion coordination.[11]

Putting the foregoing digression aside, we should like to emphasize that the thioethers are indeed excellent ligands for cucurbituril. Dithiolanylmethylamine (no. 24) provides the strongest binding ligand containing a single ammonium ion that we have yet encountered (absolute value for $K_f = 5.9 \times 10^5$ M^{-1}). In Figure 5 we show a cross-sectional representation of its complex with cucurbituril, illustrating the snugness of fit ("close-packing" of atoms), which we believe to be responsible for its exceptional ligand properties.

In conclusion, we should like to single out the most significant aspect of noncovalent binding emerging from this investigation. The high selectivities noted for the inclusion of alkylammonium ions within cucurbituril arise from the zonal nature of the interior of cucurbituril. The very center of the molecule evidently provides a lipophilic environment, yet the vicinity of the carbonyl oxygens surrounding the portals of the cage structure are especially lipophobic (to an equal extent, energywise). Consequently there is a sharp cut-off in alkyl group affinity as molecular size (chain length) of the ligand increases. The crystal structure of cucurbituril provides a partial explanation. A water molecule is found coordinated at each portal (in ammonium ion fashion), and these are linked by hydrogen bonds to a third H_2O at the center of the cavity.[2,12] Clearly, displacement of this central water molecule by ligand hydrocarbon should be exergonic (a hydrophobic effect). However, displacement of water from the polarized region of the carbonyls evidently is countervailingly endergonic. (This is in addition to any direct interactions between ligand and receptor within the complex.) It is the close juxtaposition of hydrophobic and hydrophilic regions within cucurbituril that *doubles* the selectivity that is ordinarily obtainable in transferring hydrocarbons from aqueous to lipidlike environment. We think it highly likely that biological receptors should be able to take advantage of this phenomenon. Proteins are replete with the appropriate functionality (hydrocarbon side chains plus carboxamide dipoles). In this respect, cucurbituril is a uniquely informative biochemical model system.

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(11) Fersht, A. R.; Shindler, J. S.; Tsui, W.-C. *Biochemistry* **1980**, *19*, 5520.

(12) Freeman, W. A. *Acta Crystallogr., Sect. B: Struct. Sci.* **1984**, *B40*, 382.

Ab Initio Calculations of the Olefin Strain Energies of Some Pyramidalized Alkenes†

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Abstract: The olefin strain energies (OSEs) of four members (**10**, **1**–**3**) of a homologous series of pyramidalized, tricyclic alkenes have been computed as the difference between their hydrogenation energies and that of the bicyclic reference compound (**9**). The effects of double-bond pyramidalization on the optimized geometries and on the HOMO and LUMO orbital energies are discussed. The OSEs of cubene (**11**) and tricyclo[3.1.0.0^{2,6}]hex-1(6)-ene (**12**) have also been calculated; and, for comparison, the OSEs of bicyclo[2.2.0]hex-1(4)-ene (**13**) and bicyclo[1.1.0]but-1(3)-ene (**14**) have been computed, too. It is found that, in contrast to the series of alkenes comprised of **10** and **1**–**3**, most of the OSE in **11** and **12** is already present in their bicyclic counterparts. As a consequence of the relative ease of pyramidalizing the double bond in **13**, the OSE of cubene is predicted to be only slightly greater than that of **1**, despite the fact that the double bond in cubene is much more highly pyramidalized. It is concluded that alkenes **10** and **1**–**3** provide an ideal series of molecules in which to study the effects of double-bond pyramidalization, uncomplicated by any contribution from the OSE present in the bicyclic reference compound.

We have recently reported the synthesis[1-3] and characterization[3,4] of three members (**1**, **2**, and **4**) of a homologous series of alkenes in which a short chain of n atoms, bridging between C-3 and C-7 of bicyclo[3.3.0]oct-1(5)-ene, forces the doubly bonded carbons to pyramidalize. The chemistry that we have observed

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) Renzoni, G. E.; Yin, T.-K.; Borden, W. T. *J. Am. Chem. Soc.* **1986**, *108*, 7121.

0002-7863/88/1510-4710$01.50/0