Molecular Recognition: Consideration of Individual Hydrogen-Bonding Interactions†

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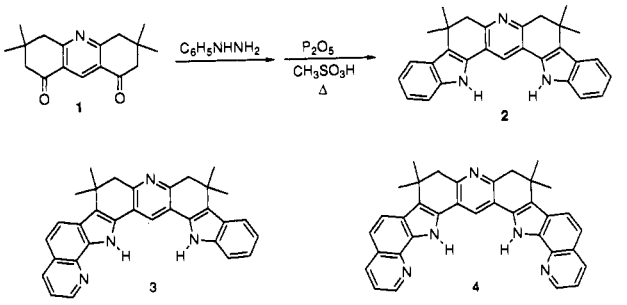
Received April 9, 1993

The recognition and subsequent complementary binding between a receptor and a substrate molecule is the first step in many vital supramolecular processes. Considerable effort has recently been directed toward the design of synthetic receptors which utilize hydrogen-bonding interactions for molecular recognition in a specific, predictable, and useful fashion.[2] One substrate for such systems is the urea molecule, which can form as many as six H-bonds.[3] In a previous study we demonstrated that the pyrido[3,2-*g*]indole subunit can be particularly effective in binding urea, and a host molecule containing two of these subunits was found to form a stable complex with imidazolidone.[4]

Our synthetic approach to these urea binders is sufficiently flexible to allow the systematic design of analogous hosts in which one or two of the binding sites has been eliminated. The appropriate selection of these modified hosts and urea or amide guests can then permit a more careful evaluation of the relative importance of the individual H-bonds involved in complex formation.

The hosts **2**–**4** were synthesized from the tetramethyloctahydroacridinedione **1**[5] by utilizing well-established Fischer indole methodology.[6,7] The bis-phenylhydrazone of **1** could be cyclized to **2** in 77% yield by heating with P_2O_5 in methanesulfonic acid. Treatment of **1** with 8-hydrazinoquinoline (8-QH)[4] provided both the corresponding mono- and bis-hydrazones. Fischer cyclization of the mixture provided host **4**[4] and a monoketone which could be further elaborated to **3** through its phenylhydrazone.



Cyclization of the quinoline hydrazone of 1-tetralone (**5**) provided a pyrido[3,2-*g*]indole in which some oxidation of the ethano bridge had occurred. Treatment of this material with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the fully aromatized species **6**.

Association studies were conducted by titrating $CDCl_3$ solutions of the hosts with incremental amounts of the guests shown in Chart I and monitoring the downfield shift of the C–H resonance nearest the indole NH on the interior of the host cavity. Analysis of the data according to the method of Wilcox[8] provided the association constants reported in Table I. Possible guest aggregation prompted us to measure this value where possible and to make appropriate corrections. Self-association for barbital[9] gave a K_a of 9.0 M^{-1}, and imidazolidone and butyrolactam[10] both gave K_a values of 3.0 M^{-1}. These values all agreed well with previously reported ones. For *n*-butylurea and dimethylurea, self-association was too weak to measure (<1–2 M^{-1}). The hosts did not evidence any self-association; however, a small dilution correction was applied to the data.

Chart I. Structures of Guest Molecules

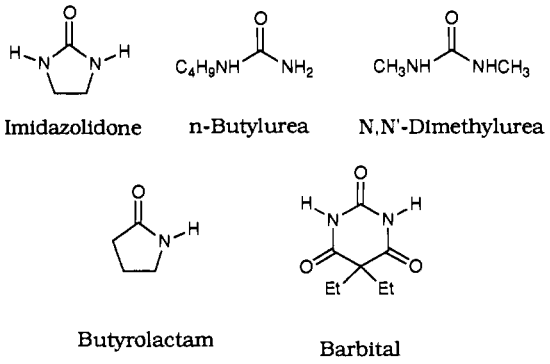


Table I. Association Constants (K_a, M^{-1} at 18 °C) for Host–Guest Complexation in $CDCl_3$[a]

	host			
guest	**4**	**3**	**2**	**6**
imidazolidone	8300 (5.2)	130 (2.8)	41 (2.1)	17 (1.6)
n-butylurea	1200 (4.1)	260 (3.2)	38 (2.1)	15 (1.6)
N,N'-dimethylurea	117 (2.8)	124 (2.8)	20 (1.7)	9 (1.3)
butyrolactam	165 (3.0)	144 (2.9)	43 (2.2)	9 (1.3)
barbital	39 200 (6.1)	406 (3.5)	*b*	95 (2.6)

[a] Estimated errors are ±20% for K_a values < 200 and ±10% for all others. Imidazolidone, butyrolactam, and barbital were corrected for dimerization of the guest, and thus values for host **4** differ slightly from those reported earlier.[4] Number in parentheses is the corresponding ΔG for binding in kcal/mol. [b] Too small to measure.

† Dedicated to the memory of Professor Paul G. Gassman.

(1) Visiting scholar from the Institut für Organische Chemie der TU Braunschweig, FRG, 1991.

(2) For some representative examples, see: (a) Smith, J.; Ariga, K.; Anslyn, E. *J. Am. Chem. Soc.* **1993**, *115*, 362. (b) Jubian, V.; Dixon, R. P.; Hamilton, A. D. *J. Am. Chem. Soc.* **1992**, *114*, 1120. (c) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024. (d) Lehn, J.-M.; Mascal, M.; De Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 479. (e) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125. (f) Goodman, M. S.; Rose, S. D. *J. Org. Chem.* **1992**, *57*, 3268. (g) Sessler, J. L.; Magda, D.; Furuta, H. *J. Org. Chem.* **1992**, *57*, 818. (h) Sanderson, P. E. J.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314. (i) Whitesides, G. M.; Seto, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 712. (j) Cochran, J. E.; Parrott, T. J.; Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1992**, *114*, 2269. (k) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678. (l) Willner, I.; Rosengaus, J.; Biali, S. *Tetrahedron Lett.* **1992**, *33*, 3805. (m) Zimmerman, S. C.; Duerr, B. *J. Org. Chem.* **1992**, *57*, 2215.

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(7) All new host systems (**2**, **3**, and **6**) gave satisfactory spectral and C, H, and N analyses.

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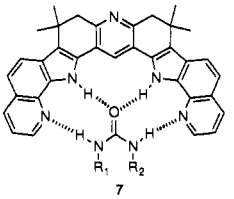
Structure **7** depicts the binding model which was developed earlier for the association of **4** with ureas.[4] Similar binding, using



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a diminishing number of H-bonds, is expected for the hosts **3**, **2**, and **6**. This premise is borne out by the decrease in K_a as we move along the series of hosts with **4** > **3** > **2** > **6**. One exception to this trend is dimethylurea, whose binding with **3** and **4** is comparable. This observation is understandable in the light of an earlier report that dimethylurea binding occurs through a *syn,anti* conformer which provides only three H-bonds.[11] In fact, this conformer fits better into the cavity of **3** than **4**, explaining the slightly higher K_a with **3**. With further regard to three-point binding, one observes that imidazolidone forms a strong complex with **4**, but with host **3** its binding is comparable to those of dimethylurea and butyrolactam since only three H-bonds are possible with host **3**. The K_a for binding of **3** with *n*-butylurea is twice as great as with imidazolidone, indicating the existence of a small *N*-alkyl retarding effect.

In general, the two-point binders **2** and **6** show fairly weak association with K_a values ranging from 9 to 95 M^{-1}. It is noteworthy that imidazolidone and butyrolactam show essentially identical binding constants with host **2** but differ by a factor of 2 with host **6**, where 2-fold symmetry would be expected to favor imidazolidone to just this extent. The ability of **2** to bind urea more strongly than **6** might be partially explained by the involvement of secondary interactions.[12] Carbonyl binding by **2** should relieve unfavorable dipole–dipole interactions, whereas binding of an amide group by **6** should result in unfavorable secondary interactions.

The fact that barbital does not show measurable binding with **2** is partly a reflection of the decreased electronegativity of the carbonyl oxygen of its urea functionality. The steric hindrance imposed by the *gem*-diethyl group on the other two carbonyls decreases their binding ability in alternative arrangements of barbital with **2**. All of this implies that the very strong binding of barbital with **4** is due mostly to the increased acidity of its amide NHs and the well-organized four-point binding array.

Hamilton and co-workers[13] and Schneider and co-workers[14] have attempted to quantify H-bonding interactions and arrived at an approximate value of 1.2 kcal/mol per H-bond. Our results indicate that the situation is somewhat more complicated, with several mitigating factors being involved. One factor is the type of H-bond (N—H···N or C=O···H) being formed and the Lewis acid/base nature of each partner in the bond. A second factor is based on entropy, where more organized systems, such as the complex of **4** with imidazolidone or barbital, show a substantial increase in binding energy upon formation of a fourth H-bond.[15] When these factors are held constant, predictable behavior occurs. If one considers the binding of host **3** with imidazolidone (130 M^{-1}) and *n*-butylurea (260 M^{-1}), the same relative enthalpy and entropy changes should be involved in binding butyrolactam (144 M^{-1}) and hexanamide, allowing us to predict a K_a of 288 M^{-1} for the latter. The measured value is 300 M^{-1}.

Acknowledgment. We are grateful to the Robert A. Welch Foundation and the National Science Foundation (CHE-8910991) for financial support of this work and to Dr. Jeff Madura, Dr. Jim Briggs, and one of the referees for helpful suggestions. The NMR spectrometer was partially funded by NSF (CHE-8616352). T.H. thanks the Cusanuswerk for financial support.

Supplementary Material Available: Details concerning the preparation and characterization of hosts **2**–**4** and **6**; tables pertaining to the dilution corrections and NMR titrations used to obtain the K_a values cited in Table I (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(15) A more quantitative evaluation of the relative importance of ΔH and ΔS on the binding energy requires determinations over a temperature range which the solubilities of our present hosts will not allow.