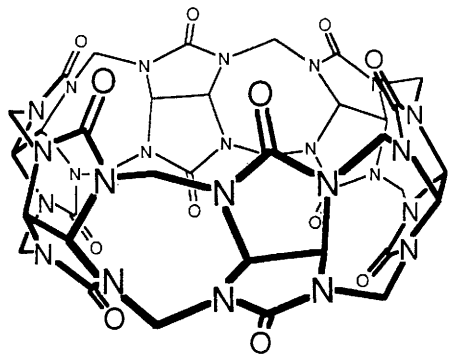
A Cucurbituril-based Molecular Switch

William L. Mock* and John Pierpont

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60680-4348, USA

Upon encapsulating the ligand $PhNH(CH_2)_6NH(CH_2)_4NH_2$, the nonadecacyclic molecular receptor cucurbituril ($C_{36}H_{36}N_{24}O_{12}$) exhibits a bimodal binding pattern contingent upon pH.

Engineering of devices on the organic molecular scale is an objective which is being brought within practical range by recent advances in noncovalent recognition phenomena. Perhaps the simplest component for such ultimate reduction in machine size is a 'molecular switch,' a ligand–receptor system which has the capability to exist in more than one state, contingent upon some controlling element.[1] The ready availability and exquisite selectivity of the receptor cucurbituril **1** invites exploitation in this direction. Cucurbituril is a novel nonadecacyclic cage compound which is synthesized by acid-catalysed condensations between urea, glyoxal, and formaldehyde (equations 1 and 2). It has a relatively rigid structure and a hollow core of several Ångstroms diameter, which is accessible from the exterior. The encapsulation of alkylammonium ions within **1** has been extensively investigated.[2] The essential interactions yielding firm complexation



1

$PhNH(CH_2)_6NH(CH_2)_4NH_2$

2

are an ion–dipole attraction providing H-bond coordination of cationic ligand RNH_3^+ to the collection of appropriately polarized carbonyl (ureide) groups surrounding each occulus of **1**, and a hydrophobic effect associated with liberation of solvent species consequent on insertion of an alkyl substituent into the interior of **1**.[3] The most firmly bound ligands for cucurbituril are protonated alkanediamines, for which the ion–dipole affinity may be doubled when each sextet of urea residues in **1** has been saturated with a cationic RNH_3^+ group. It has previously been found that hexane-1,6-diamine is optimal in this regard; the interatomic distance between nitrogen atoms for its extended conformation apparently registers advantageously with the oxygen–oxygen distance (6 Å) axially spanning the cavity of **1**.[2] Relevant to this article is the observation that the formation constant for complexation of $NH_3^+(CH_2)_6NH_3^+$ with **1** (K_f = 2.8 × 10^6 dm^3 mol^{-1}) exceeds that for the shorter guest $NH_3^+(CH_2)_4NH_3^+$ (K_f = 2.7 × 10^5 dm^3 mol^{-1}) by a significant amount.

$$2H_2NCONH_2 + CHOCHO \rightarrow \underset{\text{(glycouril)}}{C_4H_6N_4O_2} \quad (1)$$

$$6C_4H_6N_4O_2 + 12CH_2O \rightarrow \underset{\text{(cucurbituril)}}{C_{36}H_{36}N_{24}O_{12}} \quad (2)$$

Triamine ligand $PhNH(CH_2)_6NH(CH_2)_4NH_2$ **2** has been specifically designed and prepared so as to be capable of binding in two distinct ways to **1**. The important feature of **2** is that the pair of nitrogen atoms not connected directly to a benzene ring ought to be 10^6-fold more basic than the one which is. The anilinium nitrogen of **2** shows a typical pK_a value of 4.69 (±0.03) in buffered aqueous solution by spectrophotomeric titration. However, in the presence of one mole-equivalent of **1**, this pK_a increases to 6.73 (±0.02). Such behaviour was quite predictable, and its physical cause is revealed by NMR examination of the stoichiometric **1·2** complex. As may be seen in Fig. 1, in acidic solution a distinct family of signals from the alkyl portions of **2** is displayed in D_2O, including a unique resonance at δ 0.4. The latter is attributed to the methylene groups in the middle of the hexyl chain, residing in the especially shielding environment at the centre of **1**.[2] As the solution is neutralized, the set of NMR signals characteristic of coordination to the hexyl portion of **2** is systematically diminished, ultimately to be replaced by a new family, which must be attributed to ligation to the butyl

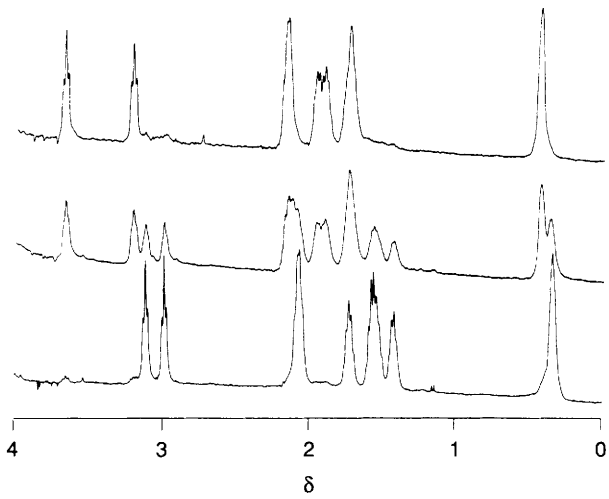


Fig. 1 Aliphatic region of ^1H 400 MHz NMR spectra of stoichiometric complex **1·2** in D_2O acidic solution (top), alkaline solution (bottom), and at a pD of *ca.* 6.7 (middle). Split signals arise from methylene units of **2** external to the cavity of **1**; encapsulation shields protons and broadens resonances

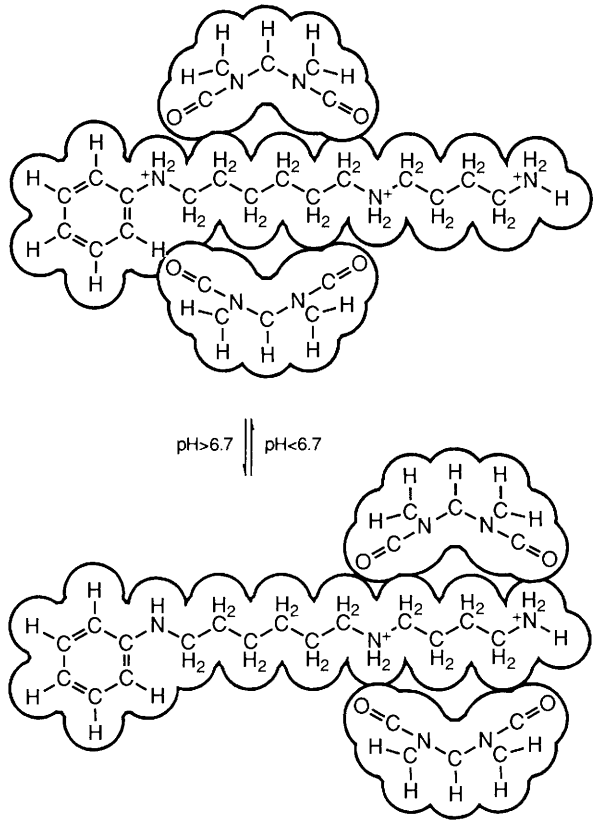


Fig. 2 Conjectured cross-sectional representations of complex **1·2** in acidic and in alkaline solution. Outlines drawn to van der Waals radii (maximum projection for all atoms upon axial rotation of **1**, crystallographically determined interatomic distances for **1**). In all probability a slight buckling of the hexyl chain actually occurs in the upper situation, better filling the cavity and bringing the ammonium ions into improved alignment with the carbonyl dipoles of **1**

portion of **2** (as evidenced by a new NMR signal at δ 0.35). At intermediate acidity, migration of **1** between these two sites is apparently slow on the NMR time scale, since separate resonances are seen for each mode. The rationalization of this behaviour is straightforward. So long as the aniline nitrogen

remains protonated, binding is favoured across the six-carbon site in **2** because of its greater complementarity to the interior dimensions of **1**, with both occuli of **1** being occupied by secondary ammonium ions. Upon deprotonation of the aniline nitrogen, the receptor translocates to the four-carbon site in **2**. While binding with a butanediammonium ion may be intrinsically less favourable, it is known to be superior to that for longer-chain alkylmonoammonium ions (n-hexylamine, $K_f = 2.3 \times 10^3$ dm^3 mol^{-1}). The evidence indicates that coordination at this subsidiary binding site is 100-fold less stable thermodynamically, since a two pH-unit bias is necessary to drive **1** to this position from its favoured location. So long as the ambient pH sustains protonation only of the nonaniline nitrogens of **2** (pK_a of >10), this species remains energetically favoured. The interpretation is pictured in Fig. 2.

In this 'switch' a hydronium ion is functioning as a control element, inducing translocation between the two ligation states, so as to maintain the ion–dipole interactions. We note that the exact pH at which the transition takes place ought to be regulable by varying the nature of substituents on the aryl ring. Tandem anchoring of modified **1** and **2** residues to suitable substrates may provide a strategy for systematically varying macroscopic dimensions of a material in response to pH.

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References

1 Previous examples: J. Rebek, Jr. and R. V. Wattley, *J. Am. Chem. Soc.*, 1980, **102**, 4853; S. Shinkai, S. Shigematsu, Y. Kusano and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3279; J. Sunamoto, K. Iwamoto, Y. Mohri and T. Kominato, *J. Am. Chem. Soc.*, 1982, **104**, 5502; S. Shinkai, K. Inuzuka, O. Miyazaki and O. Manabe, *J. Am. Chem. Soc.*, 1985, **107**, 3950; L. Echeverria, M. Delgado, V. J. Gatto, G. W. Gokel and L. Echegoyen, *J. Am. Chem. Soc.*, 1986, **108**, 6825; T. Nabeshima, T. Inaba and N. Furukawa, *Tetrahedron Lett.*, 1987, **28**, 6211; T. Nabeshima, A. Sakiyama, A. Yagyu and N. Furukawa, *Tetrahedron Lett.*, 1989, **30**, 5287; J. D. Winkler, K. Deshayes and B. Shao, *J. Am. Chem. Soc.*, 1989, **111**, 769; J. Daub, J. Salbeck, T. Knöchel, C. Fischer, H. Kunkely and K. M. Rapp, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1494; E. M. Seward, R. B. Hopkins, W. Sauerer, S.-W. Tam and F. Diederich, *J. Am. Chem. Soc.*, 1990, **112**, 1783.

2 W. L. Mock and N.-Y. Shih, *J. Org. Chem.*, 1986, **51**, 4440.

3 W. L. Mock and N.-Y. Shih, *J. Am. Chem. Soc.*, 1988, **110**, 4706.