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RECEPTORS FOR URIC ACIDS. 2. A CAUTIONARY OBSERVATION

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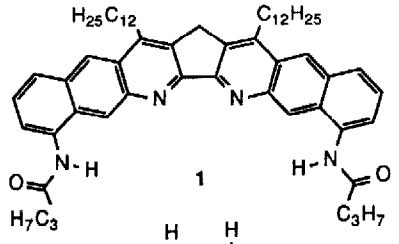
Abstract. *Receptor 4 was designed to exceed the already high affinity of 1 for 2. Synthesis of 4 and its binding with 2 are described.*

The development of receptors which recognize neutral guests and the understanding of the principles which govern such interactions are goals of current interest.[1] Recently, we reported[2] that the heptacyclic receptor **1** binds uric acid (solubilized as its tritylethyl derivative **2**) with high affinity (K_{assoc} = 1.0 x 10^6 M^{-1}) in nonpolar organic solvents. Binding is believed to occur via complex **3**.



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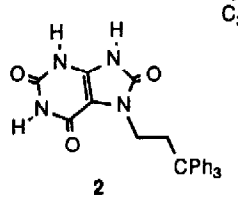

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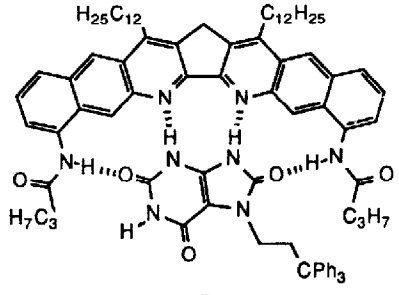
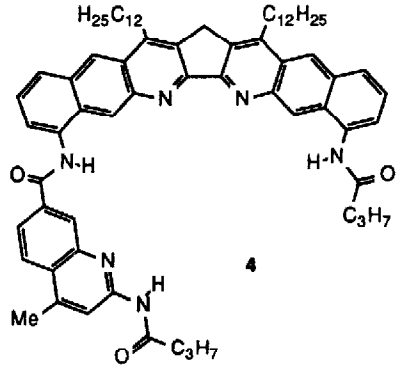


3

With the objective of examining the consequences of including within a molecule similar to **1** additional hydrogen bonding sites for the binding of **2**, we designed a new receptor, **4**. In **5**, the putative complex of **4** with **2**, the two partners would be held together by a total of six hydrogen bonds, two more than are present in **3**. Both systems (**3** and **5**) were designed using CPK models; the seemingly good "fit" in the CPK model of **3** (see ref.[2] for



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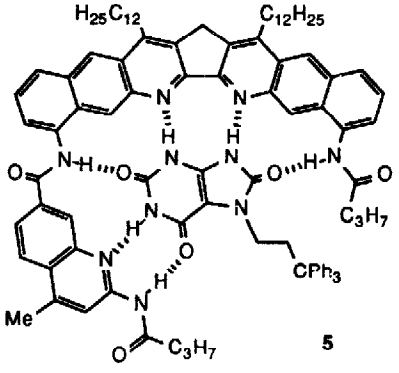
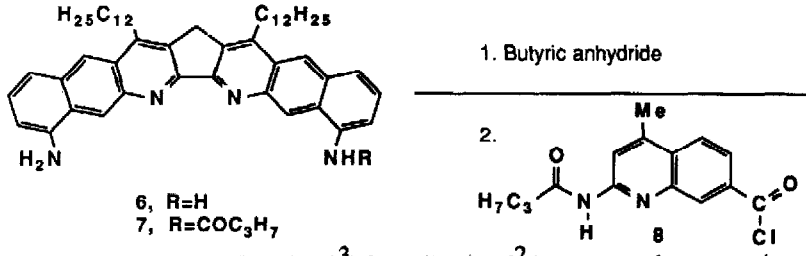


5

a photograph) and the tight binding observed between **1** and **2** engendered confidence that the apparently good fit found in a CPK model of **5** was predictive of even stronger binding between **2** and **4**. We have now prepared **4** and examined its affinity for **2**. Contrary to expectations **4** is inferior to **1** as a receptor for uric acid **2**.

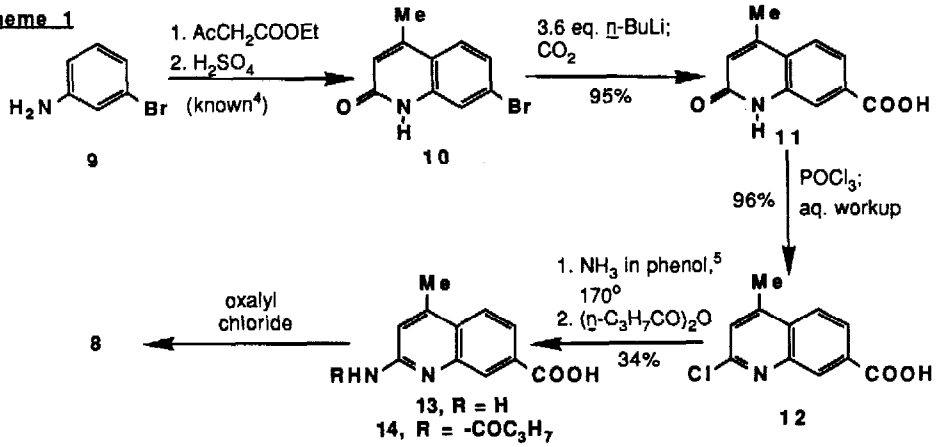


(Eq. 1)

6, R=H
7, R=COC_3H_7

Receptor **4** was prepared (Equation 1[3]) from diamine **6**[2] in two steps by conversion of **6** to the mono-butyramide **7** and acylation of **7** with acid chloride **8**. Acid chloride **8** was synthesized[3] from **10** as shown in Scheme 1; not surprisingly, **8** is somewhat unstable and must be used immediately upon preparation.

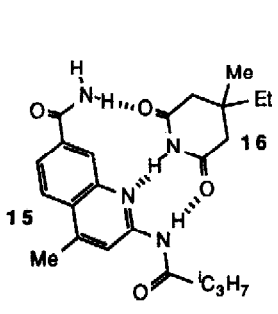
Scheme 1

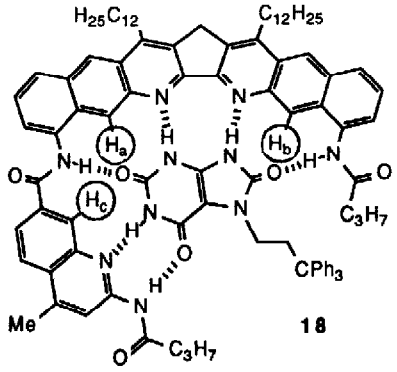


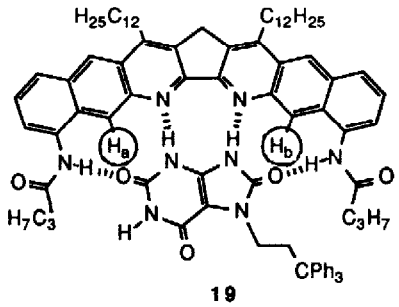
The binding of **2**[6] with **4** was measured (UV) in 1:1 CH_2Cl_2/toluene[2b] under conditions identical to those[2] used for determining the binding of **1** with **2** (a control experiment with **1** and **2** reproduced the previously reported binding constant). The K_{assoc} for **2** and **4** is 1.1 x 10^4 M^{-1}; the affinity of **4** for **2** is thus a factor of ninety less than that of **1** for **2**.

The finding that **4** is inferior to **1** as a receptor for **2** was unanticipated. Unfortunately, the very limited solubility of **2**, **4** and **2·4** in those nonpolar organic solvents which do not interfere with hydrogen bonding precluded the use of ^1H NMR to determine what is "wrong" in the **2·4** complex. With the objective of probing the matter in greater detail we prepared **15** and examined its binding with **16** as a model for that proposed for the southwest portion of **5**. The strength of the binding interaction between **16** and **15** [K_{assoc} = 1.9 x 10^2 M^{-1} in $CDCl_3$] is consistent[7] with the existence of three hydrogen bonds, and changes[10] in the δ's of the protons in **15** and **16** upon binding accord with the assignment of **17** as the structure of the **15·16** complex. Thus, while the subunits **1** and **15** behave as expected individually, the whole (**4**) is apparently less than the sum of its parts.

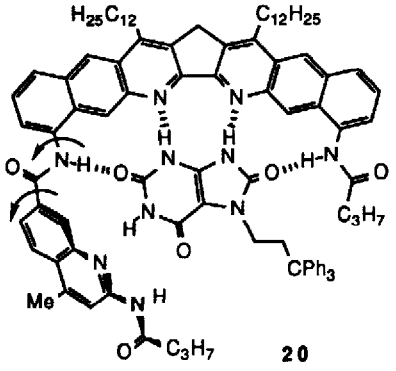
In attempting to rationalize the diminished affinity toward **2** found with **4**, we speculate that the three C-H's circled in **18** are the primary culprits. In building the CPK model of **3** the best fit was obtained by slightly "shrinking" (with a hot air gun) the two bay-region, carbon-bound hydrogens circled in **19**. Since conventional wisdom holds that CPK models are, if anything, pessimistic (for instance, models of [2.2]paracyclophane cannot

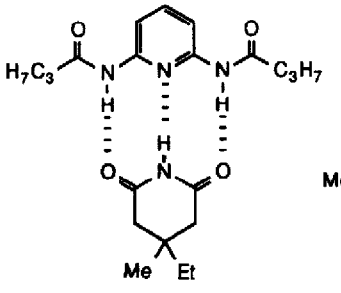


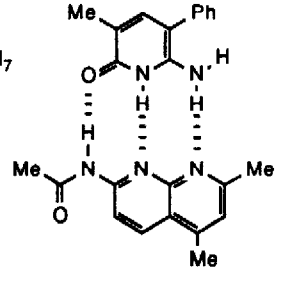




be constructed) *and since 1 was demonstrated to bind 2* with an affinity indicating the existence of four[7] hydrogen bonds, we were reassured that somewhat compressing the hydrogens was valid. The results with **4** suggest that the hydrogens are not so compressible and that, in effect, the cavity of **4** is too small. With **3**, repulsion between the two bay region hydrogens and the guest can be relieved by displacement of the guest away (down, as drawn in **19**) from the receptor. In the case of **5**, however, such a displacement would be disfavored since it would exacerbate the repulsive interaction with the C-H of the quinoline (H_c in **18**). Rotation of the quinoline away from the uric acid as in **20** would relieve that repulsive interaction, but the two new hydrogen bonding sites in the quinoline unit would then be displaced from the uric acid and incapable of providing binding interactions. Depending on which bond (e.g., C_{aryl}-C=O or NH-C_{aryl}: see arrows in **20**) rotated (to give, e.g., **20**), reduction of resonance overlap[11] and/or attenuation of one hydrogen bond interaction would account for the destabilization ($\Delta\Delta G$ = 2.7 kcal/mol) of the complex **2·4** relative to that of **2·1**.[12]





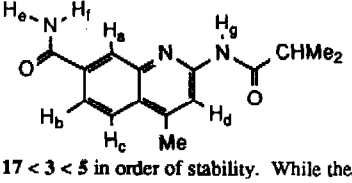


The advantages of preorganization in the design of host-guest systems are well-recognized:[14] binding of a substrate is enhanced by building into the receptor a topography inherently complementary to the substrate. The fewer degrees of freedom in the receptor which must be sacrificed upon binding, the smaller the entropic price that must be paid. While complete rigidity may characterize the ideal receptor (so long as it remains accessible to substrate), total inflexibility in the receptor requires perfect complementarity to the substrate for optimal binding. The results described herein indicate that in the design of relatively rigid receptors imprecision exacts a heavy toll. Extension of the implications of such findings to synthetic - as well as natural - enzymes, wherein both the reactant and the topographically distinct transition state must be bound (although not necessarily to equal degrees[15]) suggests that a judicious balance between preorganization and flexibility is desirable.

Acknowledgements. Partial support of this work by NIH (Grant GM 39072) is gratefully acknowledged. We thank Dr. Kevin Gilbert of Serena Software[12, 13] for unstinting support and the NIH-MSU Mass Spectrometry Facility for high resolution mass spectra.[3]

References and Notes

1. For some leading references through mid 1987 on the binding of neutral guests in nonaqueous solvents see footnotes 1 and 2 in reference 2. Among more recent papers see (a) Zimmerman, S.C.; VanZyle, C.M. *J. Am. Chem. Soc.* **1987**, *109*, 7894. (b) Aoyama, Y.; Tanoka, Y.; Toi, H.; Ogoshi, H. *Ibid.* **1988**, *110*, 634. (c) Rebek, J., Jr.; Askew, B.; Ballester, P.; Costero, A. *Ibid.* **1988**, *110*, 923. (d) Kilburn, J.D.; MacKenzie, A.R.; Still, W.C. *Ibid.* **1988**, *110*, 1307. (e) Chang, S.-K.; Hamilton, A.D. *Ibid.* **1988**, *110*, 1318. (f) Pant, N.; Hamilton, A.D. *Ibid.*. **1988**, *110*, 2002. (g) Hamilton, A.D.; Pant, N. *J. Chem. Soc., Chem. Commun.* **1988**, 765. (h) Jeong, K.S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 3327. (i) Bell, T.W.; Liu, J. *Ibid.* **1988**, *110*, 3673. (j) Sheridan, R.E.; Whitlock, H.W., Jr. *Ibid.* **1988**, *110*, 4071. (k) Aoyama, Y.; Yamagishi, A.; Asagawa, M.; Toi, H.; Ogoshi, H. *Ibid.* **1988**, *110*, 4076. (l) Muehldorf, A.V.; Van Engen, D.; Warner, J.C.; Hamilton, A.D. *Ibid.* **1988**, *110*, 6561. (m) Lindsey, J.S.; Kearney, P.C.; Duff, R.J.; Tjivikua, P.T.; Rebek, J., Jr. *Ibid.* **1988**, *110*, 6575. (n) Osterberg, C.E.; Arif, A.M.; Richmond, R.G. *Ibid.* **1988**, *110*, 6903. Among recent overviews see (o) Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89. (p) Cram, D.J. *Ibid.* **1988**, *27*, 1009. (q) Diederich, F. *Ibid.* **1988**, *27*, 362.
2. (a) Kelly, T.R.; Maguire, M.P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (b) Note footnote 14a therein.
3. **Salient experimental details.** **4**: to 20 mg **14** in 2 mL dry CH_2Cl_2 under N_2 add 34 µl oxalyl chloride; 3 h at 20°C; remove volatiles in vacuo, dissolve crude **8** in 2 mL CH_2Cl_2, add to 50 mg **7** in 2 mL CH_2Cl_2; add 50 µl Et_3N; 24 h at 20°C; CH_2Cl_2/H_20 workup; PLC (97:3 $CHCl_3$/MeOH)→ 48 mg (73%) **4**. **6** →**7**: To 204 mg **6** and 100 µl Et_3N in 20 mL dry DMF under N_2 at 100° add 65 µL $(n\text{-}PrCO)_2O$; 3 h at 100°C; aq workup; flash column chromatography-silica (98:2 CH_2Cl_2/Me_2NEt)→101 mg (45%) **7**. **10**→**11**: To 10.5 g (0.044 mol) **10** in 600 mL THF at -78°C add 0.16 mol *n*-BuLi (hexane); 1 h at -78°C; add to solid CO_2→8.46 g (94.5%) **11**, mp 250°C (dec). **11**→**12**: 8.90 g **11** in 50 mL $POCl_3$; reflux 3.5 h; evap $POCl_3$; stir with H_2O→9.36 g (96.4%) **12**, mp 195°C after recryst from EtOAc/pet ether. **12**→**13**: Pass NH_3 gas through 2.00 g **12** in 10 g C_6H_5OH[5] at 170°C for 16 h; remove C_6H_5OH at ~100°/5 torr; dissolve residue in 5 mL MeOH, triturate with Et_2O→2.03 g crude **13**. **13** →**14**: 502 mg crude **13**, 0.57 mL 2,6-lutidine, and 50 mg 4-(dimethylamino)pyridine in 10 mL dry DMF; add 1.6 mL $(n\text{-}C_3H_7CO)_2O$; 40 h at 20°C; dilute with H_2O→precipitate; recryst from MeOH/H_2O→220 mg **14** (34.3% from **12**), mp > 300°C. **15**: Quench $POCl_3$ reaction of **11** with conc NH_4OH to give (46%) amide of **12**, mp 242-243°C. React that chloroamide with NH_3/phenol as in conversion of **12** to **13**; the product (amino amide, mp 264-265°C, 66%) was acylated with neat isobutyric anhydride at 75° C for 1 h (→ **15**, mp 281-282°C, 90%). All compounds gave spectra consistent with the structures assigned. Exact mass calcd for **4** ($C_{70}H_{86}N_6O_3$):1058.6720; found (FAB): 1058.6723.
4. Monti, L.; Cirelli, V. *Gazz. Chim. Ital.* **1936**, *66*, 723.
5. Hauser, C.R.; Reynolds, G.A. *J. Org. Chem.* **1950**, *15*, 1224.
6. Uric acid **2**[2] is now purified by flash column chromatography on silica gel eluting with 95:5 CH_2Cl_2/MeOH. The **2** obtained by evaporation of the eluate is virtually insoluble in 1:1 CH_2Cl_2/toluene. A sufficiently soluble form (polymorph?) of **2** was secured by dissolving the **2** from CH_2Cl_2/MeOH in THF and evaporating the THF.
7. Complexes of neutral partners bound by three hydrogen bonds generally exhibit K_{assoc}'s in the range of 10^2-10^3 M^{-1} in nonpolar organic solvents.[1,2] For instance,[2,8] the K_{assoc} of **21** is 1.2 x 10^2 M^{-1}. Occasionally, somewhat stronger binding is observed: K_{assoc} for **22**[9] = 7.5 x 10^4 M^{-1}.
8. Feibush, B.; Figueroa, A.; Charles, R.; Onan, K.D.; Feibush, P.; Karger, B.L. *J. Am. Chem. Soc.* **1986**, *108*, 3310.
9. Unpublished observations of G.J. Bridger, C. Zhao and T.R. Kelly. For related work see T.R. Kelly, C. Zhao, and G.J. Bridger, *J. Am. Chem. Soc.* **1989**, *111* in press.
10. In the absence of bemegride (**16**) the δ's for protons a-g, respectively, in a 0.01M solution of **15** in $CDCl_3$, are 8.44, 7.98, 7.91, 8.16, 6.06, 6.28 and 8.60. Upon addition of 7 equivs of **16** (which corresponds to essentially all of **15** being bound), a-g shift to 8.76, 8.08, 8.00, 8.51, 5.98, 7.40 and 10.08.



11. Rogers, M.T.; Woodbrey, J.C. *J. Phys. Chem.* **1962**, *66*, 540.
12. Molecular mechanics calculations using the MacII version of PCMODEL[13] rank **17** < **3** < **5** in order of stability. While these after-the-fact calculations are in accord with our original expectations, the basis on which the program ranks **5** as a substantially more stable complex than **3** is not clear cut since the program minimizes both **3** and **5** to complexes held together by (only) three hydrogen bonds.[7] While the relative magnitudes of the calculated (for gas phase, not solution) values of the binding energies of **3** and **5** are at variance with experiment, we have nonetheless found PCMODEL an extremely valuable tool.
13. Available from Serena Software, P.O. Box 3076, Bloomington, IN 47402.
14. Cram, D.J. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1039.
15. For a recent discussion see Kraut, J. *Science (Washington, D.C.)* **1988**, *242*, 533.

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