New "Cholapod" Anionophores; High-Affinity Halide Receptors Derived from Cholic Acid

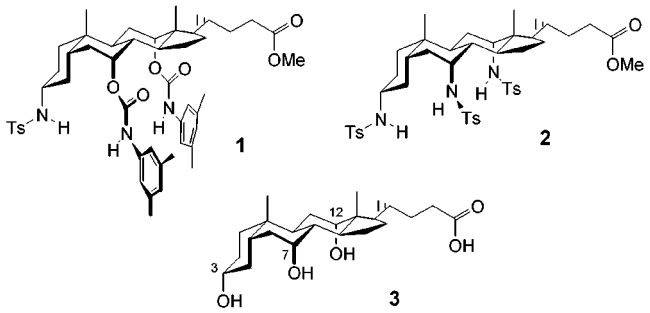
Alan J. Ayling,[†] M. Nieves Pérez-Payán,[‡] and Anthony P. Davis*,[†]

School of Chemistry, University of Bristol Cantock's Close, Bristol BS8 1TS, UK
Department of Chemistry, Trinity College Dublin 2, Ireland

Received August 8, 2001

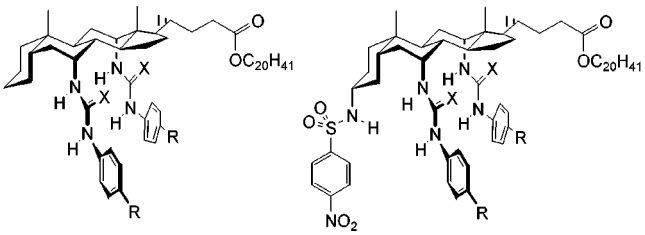
The study of anion recognition is one of the more active areas of supramolecular chemistry.[1] An important subset of anion receptors are designed to operate in organic solvents through H-bond donation by electroneutral functional groups.[2] These neutral, organic hosts may be seen as the anion-binding counterparts of the classical cation-binding crown ethers, cryptands, and spherands. However, in terms of affinity, the anionophores have yet to match the cationophores. While association constants $\geq 10^{10}$ M^{-1} are not uncommon for cryptands and spherands,[3] reported binding constants to neutral organic anionophores rarely exceed 10^5 M^{-1}.[4]

Recently, we described the synthesis and binding properties of the steroid-based tripodal receptors **1** and **2**, both derived from cholic acid **3**.[5] The steroidal framework preorganizes the H-bond



donor groups, largely prevents intramolecular hydrogen bonding, and promotes solubility in nonpolar media. **1** and **2** were found to bind tetrabutylammonium chloride with $K_a = 7200$ and 92 000 M^{-1} in $CDCl_3$ respectively. These initial "cholapods"[6] had clear potential for improvement; further H-bond donors could be added, and stronger (more acidic) donor groups could be used. We have now incorporated such changes and report a new series of cholapods which show exceptional affinities for chloride and bromide anions.

The new receptors **4**−**10** feature the following developments: (i) the introduction of urea/thiourea groups in positions 7 and 12 of the steroid, raising the number of H-bond donors to 4 (for **4**−**7**) and 5 (for **8**−**10**); (ii) the use of electron-withdrawing substituents to raise donor power; and (iii) the C_{20} side chains, which increase solubility and lipophilicity. The urea/thiourea groups are axially disposed which, as noted previously for **2**,[5] aids preorganization by restricting rotation about the C(7/12)−N bonds. The favored planar, all-*anti*-urea conformation transmits this effect, so that all four (thio)urea N−H groups are positioned for anion binding. Equally, intramolecular H-bonding is suppressed. Modeling[7] indicates that no such interactions are possible for **4**−**7**. In **8**−**10** the sulfonamide oxygens can make hydrogen bonds to the NHAr groups, but these involve distortion of ureas from planarity and are probably intrinsically weak.[8]



4 R = H, X = O
5 R = CF_3, X = O
6 R = NO_2, X = O
7 R = NO_2, X = S

8 R = CF_3, X = O
9 R = NO_2, X = O
10 R = NO_2, X = S

Receptors **4**−**10** were synthesized from **3** via protected aminosteroids **11** and **12**,[9] as described in the Supporting Information. Despite their arrays of polar functionality, all were freely soluble in $CHCl_3$. The ^1H NMR spectra of **4** and **5** in $CDCl_3$ were well-resolved, while those of **6**−**10** were broadened. However, all receptors gave well-resolved spectra after addition of excess bromide or chloride (as tetraethylammonium or tetraphenylphosphonium salts). In a titration of **5** with $Et_4N^+Cl^-$, the NH resonances broadened initially then sharpened after addition of 1 equiv, having moved downfield by 1.6−2.1 ppm. Although the signals could not be followed accurately, their motions appeared to be roughly linear with $[Et_4N^+Cl^-]$. Additional halide (up to 10 equiv) produced little further change ($\Delta\delta < 0.09$ ppm, no evidence of saturation). In titrations of **9** and **10** with the same substrate, spectra again sharpened at 1 equiv with minor changes thereafter.

The above NMR data supported complex formation with predominantly 1:1 stoichiometry and receptor NH groups acting as H-bond donors. However, this technique was clearly unsuitable for determining binding constants in $CDCl_3$. While measurements might have been possible in more polar solvents, $CHCl_3$ provides a better model for certain media of interest, for example, biological

[†] University of Bristol.
[‡] Trinity College Dublin.

(1) Bianchi, A.; Bowman-James, K.; Garcia-España, E. *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 487.

(2) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1. Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443.

(3) *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Molecular recognition: receptors for cationic guests; Pergamon: Oxford, 1996; Vol. 1.

(4) For neutral organic anionophores exhibiting high affinities, see for example: (a) Bühlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron* **1997**, *53*, 1647. (b) Andrievsky, A.; Ahuis, F.; Sessler, J. L.; Vögtle, F.; Gudat, D.; Moini, M. *J. Am. Chem. Soc.* **1998**, *120*, 9712. (c) Nissink, J. W. M.; Boerrigter, H.; Verboom, W.; Reinhoudt, D. N.; van der Maas, J. H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2623. (d) Jagessar, R. C.; Shang, M. Y.; Scheidt, W. R.; Burns, D. H. *J. Am. Chem. Soc.* **1998**, *120*, 11684. (e) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675. (f) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475. (g) Anzenbacher, P.; Jursikova, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350. (h) Choi, K. H.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456.

(5) Davis, A. P.; Perry, J. J.; Williams, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 1793.

(6) We propose to use this term for podand structures based on bile acid scaffolds. For other cholapods, see: Davis, A. P.; Lawless, L. J. *Chem. Commun.* **1999**, 9. De Muynck, H.; Madder, A.; Farcy, N.; De Clercq, P. J.; Pérez-Payán, M. N.; Öhberg, L. M.; Davis, A. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 145. Boyce, R.; Li, G.; Nestler, H. P.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 7955. Venkatasan, P.; Cheng, Y.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6955. Li, C. H.; Budge, L. P.; Driscoll, C. D.; Willardson, B. M.; Allman, G. W.; Savage, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 931. Potluri, V. K.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 7764.

(7) MacroModel 7.0, Amber* force field, GBSA solvation ($CHCl_3$): Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(8) Gennari, C.; Gude, M.; Potenza, D.; Piarulli, U. *Chem. Eur. J.* **1998**, *4*, 1924.

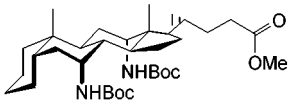
(9) Davis, A. P.; Pérez-Payán, M. N. *Synlett* **1999**, 991.

10.1021/ja016796z CCC: $20.00
Published on Web 11/17/2001

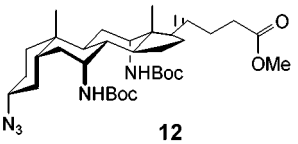
Table 1. Extraction Data, Derived Association Constants, and Binding Free Energies of Receptors **4**−**10** to $Et_4N^+Cl^-$ and $Et_4N^+Br^-$ in Water-Saturated $CHCl_3$[a]

	$Et_4N^+Cl^-$				$Et_4N^+Br^-$			
receptor	$[substrate]_{aq}$ (M)	equivalents extracted[b]	K_a (M^{-1})[c]	$-\Delta G°$ (kJ mol^{-1})	$[substrate]_{aq}$ (M)	equivalents extracted[b]	K_a (M^{-1})[c]	$-\Delta G°$ (kJ mol^{-1})
4	0.07	0.50	1.62×10^7	−41.84	0.03	0.66	9.79×10^6	−40.57
5	0.02	0.59	2.83×10^8	−49.05	0.005	0.50	1.84×10^8	−47.97
6	0.019	0.69	4.77×10^8	−50.37	0.006	0.64	2.26×10^8	−48.48
7	0.01	0.57	1.05×10^9	−52.36	0.004	0.53	3.24×10^8	−49.39
8	0.005	0.59	4.58×10^9	−56.07	0.0016	0.59	2.63×10^9	−54.67
9	0.001	0.45	6.60×10^{10}	−62.79	0.0006	0.56	1.68×10^{10}	−59.34
10	0.001	0.56	1.03×10^{11}	−63.92	0.0005	0.57	2.59×10^{10}	−60.44

[a] Receptor (0.6 mM) in $CHCl_3$ was equilibrated with aqueous substrate at 30 °C. After separation and evaporation, extracts were analyzed by NMR integration ($CH_3CH_2N^+$ vs receptor protons). For further details see Supporting Information. [b] [complex]/[receptor] in organic phase. Aqueous substrate concentrations were chosen such that this figure lay between 0.4 and 0.7. [c] Calculated according to the method of Cram et al.[10] Experimental errors estimated as ≤15%.



11



12

membranes or the polymer materials used in ion-selective electrodes. We therefore decided to retain $CHCl_3$ as solvent, resorting to the classical extraction method of Cram[10] to measure the association constants. Briefly, an organic phase containing a lipophilic receptor (H) is stirred or shaken with an aqueous phase containing substrate (A^+X^-). The extraction constant $K_e = [HAX]_{org}/[H]_{org}[A^+]_{aq}[X^-]_{aq}$ is determined from the quantity of substrate extracted into the organic phase at equilibrium. The association constant can then be calculated from the equation $K_a = K_e/K_d$, where $K_d = [AX]_{org}/[A^+]_{aq}[X^-]_{aq}$, that is, the distribution constant of the substrate between the two phases in the absence of the receptor. The method is especially useful for the determination of high binding constants because the degree of complexation in the organic phase can be controlled by varying substrate concentration in the aqueous phase. Receptor saturation can therefore be avoided. We have found that $Et_4N^+Cl^-$ and $Et_4N^+Br^-$ are convenient substrates for such experiments, with K_d ($CHCl_3/H_2O$) = 1.27×10^{-5} and 2.18×10^{-4} M^{-1} respectively.[11]

Application of Cram's method to receptors **4**−**10** gave the results shown in Table 1. Note that the binding constants refer to water-saturated $CHCl_3$ and are presumably slightly smaller than the corresponding values in dry solvent. As expected, the receptors were found to be substantially more powerful than **1** and **2**. Affinities increased through the series **4**−**7**, reflecting the electron-withdrawing character of the R groups and the transition from urea to thiourea.[12] The additional nitrosulfonamide group in **8**−**10** yielded a further enhancement. All receptors were moderately selective for chloride over bromide (although bromide gave the higher extraction constants, due to its greater lipophilicity).

Especially notable are the very high affinities recorded for **9** and **10**, rising to 10^{11} M^{-1} for **10** + Cl^-. It is clearly important to consider sources of error, especially in these cases. The analysis of the extraction data assumes 1:1 substrate:receptor stoichiometry, with no complicating phenomena such as self-association. To check for interference from higher stoichiometries (and for incomplete separation of aqueous from organic phases), we performed an extraction with **10** and $[Et_4N^+Cl^-]_{aq}$ = 0.1 M (a 100-fold increase compared to the conditions in Table 1). Even at this high substrate concentration, only 1.09 equiv of $Et_4N^+Cl^-$ was detected in the organic phase. The NMR data did suggest that some of the receptors may self-associate in $CHCl_3$; however, this is likely to lead to an underestimate of K_a. Indeed, for most of these receptors the (apparent) K_a values increased slightly with receptor dilution. For example, when the concentrations of **9** and **10** were reduced by a factor of 6 to 0.1 mM, extractions of $Et_4N^+Cl^-$ implied $K_a = 1.02 \times 10^{11}$ and 1.22×10^{11} M^{-1} respectively.

In conclusion, by combining Cram's extraction methodology with the cholapod architecture, we have been able to demonstrate electroneutral anionophores which are exceptionally potent while retaining compatibility with nonpolar media. Such molecules may find use in "phase transfer" applications such as sensing and catalysis, and may also show biological activity. In future work we plan to investigate these possibilities, and to improve selectivities by further elaborating the "legs" to create more enclosed and preorganized binding sites.

Acknowledgment. We thank the European Commission (Marie Curie Fellowship to M.N.P.), the University of Bristol, and the EPSRC (GR/R04584/01) for financial support of this work.

Supporting Information Available: Synthetic schemes and details for **4**−**10**, experimental procedure, and data analysis for extraction experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org/.

JA016796Z

(10) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564.

(11) Ayling, A. J.; Broderick, S.; Clare, J. P.; Davis, A. P.; Pérez-Payán, M. N.; Lahtinen, M.; Nissinen, M. J.; Rissanen, K. Full paper in preparation.

(12) Thioureas are more acidic than ureas and have often found use in anion receptors. See: Fan, E.; Arman, S. A. V.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369; also refs 4a, 4c and 4g.