Anion Recognition by Tripodal Receptors Derived from Cholic Acid

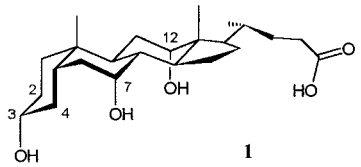
Anthony P. Davis,* Justin J. Perry, and Robert P. Williams

Department of Chemistry, Trinity College Dublin 2, Ireland

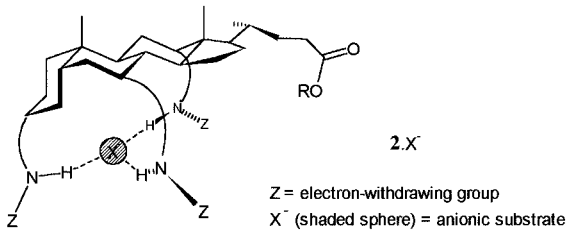
Received August 26, 1996

In recent years, the recognition of anions has become an intensively-studied area of supramolecular chemistry.[1] However, there are still quite few anionophores which parallel the classical cation receptors (e.g., crown ethers and cryptands) in being electrically neutral, lipophilic, and essentially organic in nature.[2] Anion receptors which fulfill these criteria usually rely on the cooperative action of neutral H-bond donor groups.[2c−r] For strong and selective binding, these groups should be comparatively acidic, preorganized to complement the target anion and minimize intramolecular hydrogen bonding, and embedded in lipophilic structures which maintain solubility in nonpolar media. We have previously illustrated the potential of cholic acid (**1**) in anionophore construction, through its elaboration into a "cryptand" able to bind halide anions using a well-dispersed but convergent 3D array of H-bond donor functionality.[2r,3] We now present an alternative, more "tunable", strategy which has yielded a receptor with exceptional affinity for chloride anion in a nonpolar organic solvent.

The new receptors are based on a podand-type architecture, shown schematically as **2**. Anion recognition is achieved through (at least) three NH-containing groups attached to the steroid through positions 3, 7, and 12. Options which we have explored thus far are (a) carbamates -OCONHR, which may be introduced by treatment of the hydroxyls in **1** with isocyanates and (b) amides -NHX (X = COR or SO_2R), for which steroidal OH → NH_2 conversions are required. Unlike the earlier cryptand, receptors **2** may not fully surround their substrates. However, this disadvantage is countered by the versatility of the system, including the potential for tuning NH acidity to optimize H-bond donor properties.[4]



1

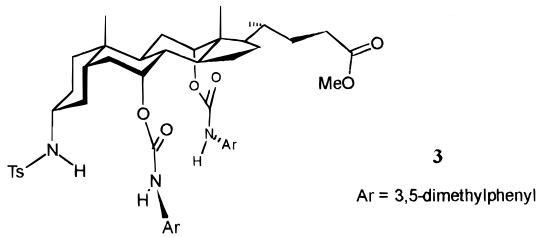


2.X^-

Z = electron-withdrawing group

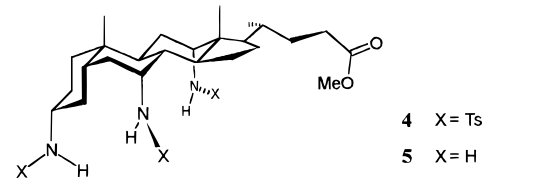
X^- (shaded sphere) = anionic substrate

In this paper, we focus on two versions of **2**, the bis-carbamoyl sulfonamide **3** and the tris-sulfonamide **4**. Both feature TsNH groups as H-bond donor units, chosen for their chemical stability and relatively high acidity.[2e,f] Receptor **3** was synthesized *via* methyl 3α-azido-7α,12α-bis(formyloxy)cholanoate, which could be accessed from **1** using our previously-described double-inversion procedure.[3h] Receptor **4** was prepared by sulfonylation of methyl 3α,7α,12α-triaminocholanoate (**5**), an "azaequivalent" of methyl cholate.[5] Molecular modeling[6] on **4** highlighted a particular advantage of the 7α- and 12α-sulfonamido groups. Their axial disposition restricts rotation about the steroidal C−N bond, such that the N−H bonds are forced to point inward, preorganized for anion recognition (eq 1). Intramolecular hydrogen bonding between these groups is clearly impossible, while the 3α-NHTs group (although free to rotate) can form, at best, very weak interactions with either.[7]



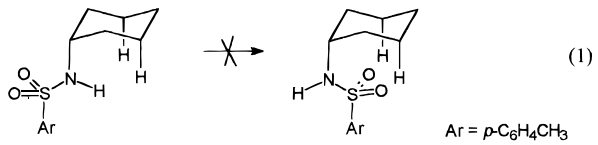
3

Ar = 3,5-dimethylphenyl



4 X = Ts

5 X = H



(1)

Ar = p-$C_6H_4CH_3$

(1) Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457.

(2) (a) Worm, K.; Schmidtchen, F. P.; Schier, A.; Schäfer, A.; Hesse, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 327. (b) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4069. (c) Pascal, R. A., Jr.; Spergel, J.; Engen, D. V. *Tetrahedron Lett.* **1986**, *27*, 4099. (d) Farnham, W. B.; Roe, D. C.; Dixon, D. A.; Calabrese, J. C.; Harlow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7707. (e) Valiyaveettil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900. (f) Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, *58*, 7602. (g) Scheerder, J.; Fochi, M.; Engbersen, J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815. (h) Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448. (i) Beer, P. D.; Gale, P. A.; Husek, D. *Tetrahedron Lett.* **1995**, *36*, 767. (j) Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255. (k) Fan, E.; Arman, S. A. V.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369. (l) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085. (m) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072. (n) Hamann, B. C.; Branda, N. R.; Rebek, J., Jr. *Tetrahedron Lett.* **1993**, *34*, 6837. (o) Ishida, H.; Suga, M.; Donowaki, K.; Ohkubo, K. *J. Org. Chem.* **1995**, *60*, 5374. (p) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483. (q) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140. (r) Davis, A. P.; Gilmer, J. F.; Perry, J. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1312. (s) Hughes, M. P.; Shang, M. Y.; Smith, B. D. *J. Org. Chem.* **1996**, *61*, 4510.

(3) Further applications of cholic acid and the other bile acids in supramolecular chemistry are discussed: (a) Davis, A. P. *Chem. Soc. Rev.* **1993**, *22*, 243 (and references cited therein). (b) Bonar-Law, R. P.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1995**, *117*, 259. (c) Hsieh, H.-P.; Muller, J. G.; Burrows, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 12077. (d) Cheng, Y. A.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 1813. (e) Janout, V.; Lanier, M.; Regen, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1573. (f) Maitra, U.; D'Souza, L. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2793. (g) Venkatasan, P.; Cheng, Y.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6955. (h) Davis, A. P.; Walsh, J. J. *J. Chem. Soc., Chem. Commun.* **1996**, 449. (i) Davis, A. P.; Menzer, S.; Walsh, J. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1996**, 453.

(4) The cryptand relied on hydroxyl groups abetted by simple annular amides. Individually these groups show modest affinities for species such as halide anions. See: reference 2r. (a) Coterón, J. M.; Hacket, F.; Schneider, H. J. *J. Org. Chem.* **1996**, *61*, 1429.

(5) The synthesis and properties of this promising scaffold unit and "facial amphiphile" will be discussed separately.

(6) MacroModel V4.0, employing Amber* and MM2* force-fields with $CHCl_3$ solvation. See: 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.

(7) Distances for S=*O*···*H*−N of *ca.* 3 Å under MM2*/$CHCl_3$.

S0002-7863(96)02993-9 CCC: $14.00

Table 1. Association Constants (K_a, M^{-1}) of **3** and **4** with Tetrabutylammonium Salts in $CDCl_3$[a]

anion	complex with **3**	complex with **4**
F^-	15400(±1500)	*b*
Cl^-	7200(±660)	92000(±28000)[c]
Br^-	7200(±760)	9200(±700)
I^-	930(±70)	525(±45)
TsO^-	865(±120)	950(±80)

[a] Bu_4N^+ salts were added to receptors (1−10 mM) in $CDCl_3$ which had been partially dried and deacidified over K_2CO_3. Salts and receptors were dried under vacuum for at least 3 h before solution preparation. The titrations were performed at 298 K. Binding constants K_a were calculated using an iterative nonlinear least-squares curve-fitting program. Figures in parentheses represent standard deviations of the binding constant values calculated from each point on the curve. Although the NH signals generally moved further than any others, they were broad and, in many cases, hard to follow. The sharper signals due to Ar−H or 19-CH_3 gave more accurate data and were therefore used in the analyses. Dilution studies on **3** and **4** indicated that self-association was insignificant at the concentrations used for the binding studies. [b] Not determined. [c] The concentration of **4** was 1.2 mM. This binding constant is near the upper limit accessible through NMR titration and is therefore relatively uncertain. A second titration with [**4**] = 1.5 mM gave K_a = 140 000(±76 000) M^{-1}. The high affinity for Cl^- was confirmed by a competition experiment in which $Bu_4N^+Cl^-$ was added to **4** in the presence of $Bu_4N^+Br^-$ (7 equiv). Although quantitative analysis was hampered by limited movements of the observable NMR signals, the data implied a selectivity consistent with the figures in this table.

The three NH protons can be positioned to form H-bonds of *ca.* 2.5 Å to a centrally-located substrate atom. Although the bis-carbamate **3** is less preorganized than **4**, its opportunities for intramolecular H-bonding are limited to S═*O*···*H*—N interactions (*ca.* 2 Å). Assuming an unstrained, planar conformation for the carbamate groups, it can form a slightly larger binding pocket with potential N*H*···substrate distances of *ca.* 2.7 Å.

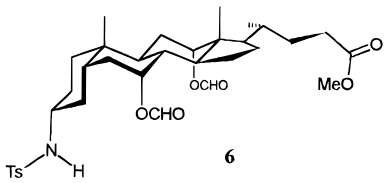
The addition of tetrabutylammonium salts of inorganic anions to **4** and **5** in $CDCl_3$ caused changes in the receptor ^1H NMR spectra, indicative of anion binding (*vide infra*). All signal movements, where examined, were consistent with 1:1 complex formation. Analysis of the data gave the binding constants listed in Table 1. Among the halides, receptor **3** showed the expected preference for fluoride and modest binding of iodide but did not discriminate between bromide and the more basic chloride.[8] In contrast, receptor **4** exhibited good selectivity for chloride vs bromide, binding the former with remarkable affinity.[9] The tripodal anion tosylate was bound by both receptors with moderate efficiency. Control experiments established that the generally high binding constants were due to cooperative action of the three H-bond donor groups in each receptor. For example, sulfonamide **6** and bis-carbamate **7** bound bromide under the same conditions with K_a = 40(±1) and 17(±3) M^{-1}, respectively. Comparison of **4** with the flexible tris-sulfonamide **8**, previously studied by Reinhoudt and co-workers,[2e] highlighted the importance of preorganization. Under our standard conditions, **8** was found to bind chloride and bromide with K_a values of just 4400(±470) and 420(±17) M^{-1}, respectively.

The complexation-induced chemical shifts could be used to infer quite detailed pictures of the binding geometries. As expected, substantial downfield movements of the N*H* signals were observed in all experiments. However, the degrees of movement varied considerably, as illustrated for the TsN*H* signals in Table 2. For the binding of halides to **4**, the figures

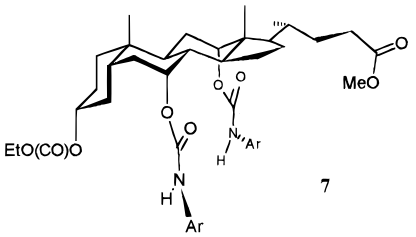
Table 2. Chemical Shift Changes (ppm) for TsN*H* Signals in **3** and **4** Induced by Anion Recognition[a]

anion	**3** (3α-N*H*)	**4** (3α-N*H*)	**4** (7α-N*H*)	**4** (12α-N*H*)
Cl^-	2.37	0.6	2.3	1.55
Br^-	1.95	0.35	1.7	1.0
TsO^-	2.16	2.0	1.45	0.85

[a] Extrapolated to 100% saturation. Assignments are from HH-COSY.

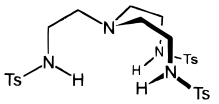


6



7

Ar = 3,5-dimethylphenyl



8

suggest short contacts to the 7α- and 12α-NH groups accompanied by weaker interactions with the 3α-NH. The inability of the latter to participate fully in complex formation may be due to the spacing between the NH groups, or perhaps to steric interference from the 2α and 4α hydrogens.[10] Either way, the problem appears to be circumvented by the larger, pyramidal tosylate anion. Downfield motions of steroidal α-*H* signals were discernible in many cases, implying close contact between the anions and the underside of the steroid nucleus.[11] The 4α-*H* signal was especially susceptible, moving through 0.8 and 0.5 ppm, when either chloride or bromide was added to **3** and **4**, respectively. Additional motions of up to ±0.5 ppm for aromatic CH signals and 0.15 ppm for the steroidal 19-CH_3 were ascribed to conformational alterations in the side chains and were often useful for determining the binding constants (see Table 1).

In conclusion, our studies on **3** and **4** have shown that steroid-based tripodal anionophores can display exceptional potency, with selectivities which are nicely sensitive to variations in receptor structure. The preorganization inherent in our strategy should facilitate the rational design of further examples with improved and/or complementary anion recognition properties.

Acknowledgment. Financial support was provided by Bayer (Ireland) (scholarship to R.P.W.), Materials Ireland, BioResearch Ireland, and Forbairt (the Irish science and technology agency). We are grateful to Peter Ashton (University of Birmingham) for mass spectra, to Shay Broderick for the studies on **8** and the competition experiment on **4**, and to Freedom Chemical Diamalt GmbH for generous gifts of cholic acid.

Supporting Information Available: Synthetic procedures and characterization for **3** and **4** and sample binding curves (9 pages). See any current masthead page for ordering and Internet access instructions.

JA9629930

(8) Evidence from a range of studies suggests that in nonpolar solvents the halide anions will tend to associate with H-bond donors according to their basicity (i.e., in the order $F^- > Cl^- > Br^- > I^-$. For example, see: refs 4a, 2g, 2i, 2q, and 2r. For **3**, the lack of Cl^-/Br^- selectivity probably implies a particular complementarity to bromide.

(9) The complex between **4** and chloride was also detectable by negative-ion FAB MS.

(10) These two axial hydrogens form a "steric ridge", which separates the 3α- from the 7/12α-NH groups and may impede H-bond formation by the three groups to a spherical anion.

(11) Similar effects are documented in refs 2d and 2r.