The role of the counteranion in the cation-π interaction

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Chemical double mutant cycles have been used to quantify cation-π interactions in chloroform as a function of the nature of the counteranion. The cation-π interaction is −2.5 ± 0.4 kJ mol⁻¹ and independent of the anion, even though the overall stability of the complexes varies by an order of magnitude due to competition of the anion for alternative binding sites.

Any intermolecular interaction involving an ionic species necessarily involves a contribution from the counterion, since the anion and cation always come together. A particularly large counterion effect has been observed in the complexation of cations by aromatic hosts in organic solvents,[1–3] and a number of different explanations have been proposed:

• Ion pairing between the anion and cation competes with the receptor binding interaction.[2,4] This is consistent with an empirical correlation found between the electrostatic potential on the surface of the anion, the binding constant and the solubility of the salt.[5]

• The anion changes the conformation or electronic properties of the receptor.[6,7]

• The anion interacts directly with both the receptor and the cation in the complex.[8]

The anion is intrinsic to the system in these experiments, and so it is impossible to distinguish multiple equilibria involving the three components from an effect of the anion on the properties of the cation-π interaction itself. Indeed the complexity of most molecular recognition processes makes it difficult to dissect and quantify the contribution of any individual factor. One solution is the double mutant experiment that we have been using to quantify functional group interactions in synthetic supramolecular systems.[9] Recently, we used this approach to study substituent effects on the cation-π interaction.[10] In the course of these experiments, it became clear that the anion played an important role in determining the stability of the complexes. In this paper, we report a quantitative study of these effects that sheds some light on the role of the anion in the systems discussed above.

The double mutant cycle experiment for quantification of the interaction of the edge of a pyridinium cation with the face of an aromatic ring is illustrated in Fig. 1. The difference between the stabilities of complexes A and B ($\Delta G_A - \Delta G_B$) measures the cation-π interaction together with secondary interactions. However, these secondary effects can be quantified by the difference $\Delta G_C - \Delta G_D$, and so it is possible to dissect out the thermodynamic contribution of the interaction of the pyridinium cation with the aromatic ring from all of the other interactions involved in complex A. The effect of the anion on the cation-π interaction can therefore be directly quantified by performing this experiment with various anions.

Compounds **2–6** required for the double mutant cycles were prepared as described previously (Fig. 2).[9,10]† Compound **1** was prepared by precipitation from a mixture of **3** and ammonium tetraphenylborate in methanol–water. ¹H NMR dilution experiments of the pyridinium salts **1–3** revealed the presence of three species: discrete ions, ion pairs, and dimers of ion pairs (Fig. 3).[10,11] Table 1 shows the association constants

and complexation-induced changes in chemical shift (CIS) for the formation of these complexes. The CIS values indicate that the major site of interaction in the ion pair is on the pyridinium unit as might be expected (only protons **a**, **b** and **c** are significantly perturbed). The positive CIS value for **c** associated
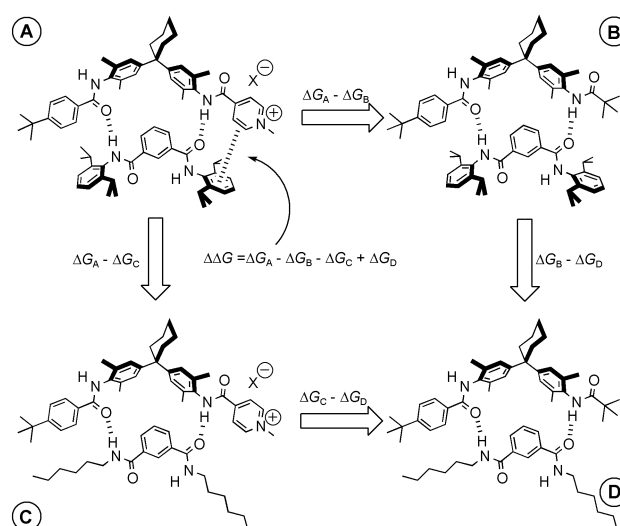

Fig. 1 Chemical double-mutant cycle for determining the magnitude of the cation-π interaction in complex A. X = BPh₄, PF₆ or I.
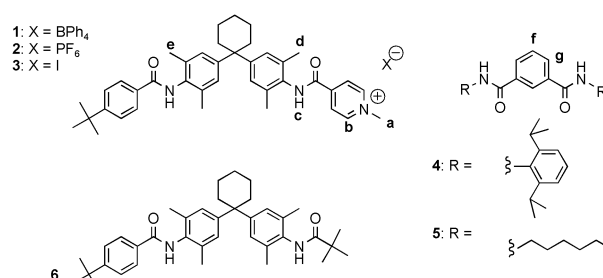

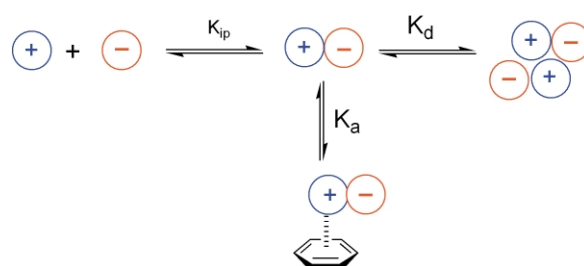**Fig. 2** Compounds **1–6** used in the double mutant cycles. The proton labelling scheme is shown.

Fig. 3 The ion pair (K_{ip}), dimerisation (K_d) and complexation (K_a) equilibria. Anion–cation H-bonding interactions compete with intermolecular binding, and the effects are strongly anion dependent.

Table 1 Ion pair (K_{ip}) and dimerisation (K_d) constants (mM^{-1}) and limiting changes in chemical shifts ($\Delta\delta$, ppm) in $CDCl_3$ at 300 K

	K_{ip}/mM^{-1}	K_d/mM^{-1}	$\Delta\delta_{ip}$/ppm			$\Delta\delta_d$/ppm		
			a	b	c	a	b	c
1	600 ± 40	0.98 ± 0.03	-1.7	-1.4	-1.6	-1.0	-1.8	0.6
2	700 ± 50	0.76 ± 0.09	-1.3	-1.4	-0.4	0.3	0.2	0.5
3	1900 ± 100	0.14 ± 0.02	-1.7	nd	1.0	0.5	nd	-0.4

with ion pairing in the iodide salt is indicative of H-bonding in this system (Fig. 3). The ion pair dimerisation constants are three orders of magnitude lower than the ion pairing constants. In addition, there is a clear correlation between the ion pairing and ion pair dimerisation constants: the more strongly the anion and cation interact (K_{ip}), the weaker the dimerisation interaction (K_d). This suggests that the anion must be displaced to some extent in order to form the dimer.

To probe the location of the anion in these complexes, NOE difference experiments were carried out on compound **1** at different concentrations (Table 2).[12] NOEs between the tetraphenylborate protons and the cation provide evidence for displacement of the anion on dimerisation. In the ion pair, the anion sits close to **a**, but in the dimer, the relative magnitudes of the NOEs between the anion protons and **b**, **d** and **e** increase significantly. This clearly demonstrates a change in the distribution of sites occupied by the anion.

Table 2 Magnitudes of anion–cation NOEs observed for the salt **1** in the ion pair (**1**), the dimer (**1·1**), and the complexes formed with **4** (**1·4**) and **5** (**1·5**)[a]

	a^a	b	d	e
1	1.0	0.5	0.2	0.2
1·1	1.0	1.0	0.6	0.5
1·4	1.0	2.1	0.7	0.0
1·5	1.0	nd	0.7	0.0

[a] The experimental values were extrapolated to the fully bound states using the binding constants in Tables 1 and 3. The values for proton **a** were used to normalise the data. nd: not determined

For the double mutant cycle experiments, ^1H NMR titrations were carried out at mM concentrations. Under these conditions, the ion pair is fully associated but dimerised only to a small extent. The titration data were fitted to a 1:1 complexation model that allowed for dimerisation but ignored possible dissociation of the ion pair.[10] Thus the binding constants and CIS values quoted in Table 3 are for the complexes formed between **4** and **5** and the ion pairs (Fig. 3). The binding constants depend strongly on the nature of the anion: the tetraphenylborate complexes are an order of magnitude more stable than the iodide complexes. The anion effects are similar in the complexes formed with **4** and **5** (Table 2) as well as for dimerisation of the ion pairs (Table 1). Competition of the anion for H-bonding interaction sites is the most likely explanation, and the anion–cation NOEs observed for the **1·4** and **1·5**

Table 3 Association constants (K_a, M^{-1}), limiting complexation-induced changes in chemical shift ($\Delta\delta$, ppm) in $CDCl_3$ at 300 K

Complex	K_a^a	$\Delta\delta$/ppm			
		a	b	f	g
1·4	740 ± 150	-1.4	-1.2	-1.4	-0.3
1·5	140 ± 20	-1.1	-1.2	-0.6	-0.3
2·4	105 ± 11	0.9	0.5	-1.9	-0.4
2·5	22 ± 1	0.5	0.4	-1.1	-0.2
3·4	66 ± 8	1.2	0.3	-1.2	-0.3
3·5	16 ± 2	1.4	0.5	-1.2	-0.3
6·4	43 ± 1	—	—	-1.6	-0.4
6·5	14 ± 2	—	—	-0.7	-0.2

complexes (Table 2) clearly show that there is a change in the location of the anion on complexation, as observed for dimerisation of these salts.

The pattern of CIS values in the core of the complex (signals **f** and **g** in Table 3) is similar for all of the systems studied.[9] NOEs observed in ROESY experiments confirm that the three-dimensional structure of the core of the complexes is unaffected by the chemical mutations. The results can therefore be used to construct the double mutant cycles shown in Figure 1. The pyridinium-π interactions for the tetraphenylborate, hexafluorophosphate and iodide salts are -2.7 ± 0.7 kJ mol^{-1}, -2.5 ± 0.6 kJ mol^{-1} and -2.2 ± 0.7 kJ mol^{-1} respectively (strictly speaking, these are ion pair-π interactions). Although the binding constants for the complexes depend strongly on the anion, the double mutant cycles show that the cation-π interaction energy is almost constant at 2.5 ± 0.4 kJ mol^{-1}. Thus the anion effect on the stabilities of the complexes is not due to differences in the cation-π interaction energy but is caused by the anion competing for some of the other binding sites in the complex.

These experiments demonstrate that the significant anion effects that are observed in cation recognition can be explained simply based on the multiple equilibria that are present and competition for interaction sites between the anion and cation. The anion has almost no effect on the intrinsic properties of the cation-π interaction.

Notes and references

† All new compounds gave satisfactory spectroscopic data.

1 G. De Iasi and B. Masci, *Tetrahedron Lett.*, 1993, **41**, 6635–6638.
2 A. Arduini, W. M. McGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Uguzzoli and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1996, 839–846.
3 R. Arnecke, V. Böhmer, R. Cacciapaglia, A. Dalla Cort and L. Mandolini, *Tetrahedron*, 1997, **13**, 4901–4908.
4 V. Böhmer, A. Dalla Cort and L. Mandolini, *J. Org. Chem.*, 2001, **66**, 1900–1902.
5 S. Bartoli and S. Roelens, *J. Am. Chem. Soc.*, 1999, **121**, 11908–11909; S. Bartoli and S. Roelens, *J. Am. Chem. Soc.*, 2002, **124**, 8307–8315.
6 K.-S. Jeong, K.-M. Hahn and Y. L. Cho, *Tetrahedron Lett.*, 1998, **39**, 3779–3782.
7 A. Arduini, G. Giorgi, A. Pochini, A. Secchi and F. Uguzzoli, *J. Org. Chem.*, 2001, **25**, 8302–8308; A. Arduini, A. Pochini and A. Secchi, *Eur. J. Org. Chem.*, 2000, 2325–2334.
8 S. Kubik and R. Goddard, *J. Org. Chem.*, 1999, **64**, 9475–9486; S. Kubik, *J. Am. Chem. Soc.*, 1999, **121**, 5846–5855.
9 H. Adams, F. J. Carver, C. A. Hunter, J. C. Morales and E. M. Seward, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1542–1544; F. J. Carver, C. A. Hunter, D. J. Livingstone, J. F. McCabe and E. M. Seward, *Chem. Eur. J.*, 2002, **13**, 2846–2859; G. Chessari, C. A. Hunter, C. M. R. Low, M. J. Packer, J. G. Vinter and C. Zonta, *Chem. Eur. J.*, 2002, **13**, 2860–2867.
10 C. A. Hunter, C. M. R. Low, C. Rotger, J. G. Vinter and C. Zonta, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 4873–4876.
11 Ions corresponding to the dimer, $[M_2X]^+$, were found in the mass spectra of all of the salts **1–3** and **4–6**.
12 C. Hofstetter and T. C. Pochapsky, *Magn. Reson. Chem.*, 2000, **38**, 90–94.