

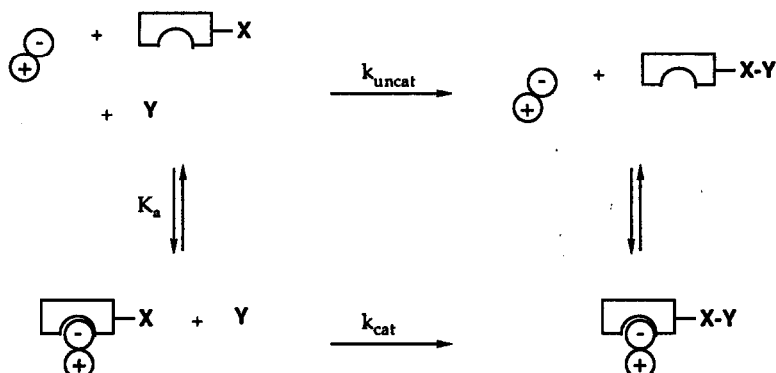
ION PAIR BINDING BY A UREA IN CHLOROFORM SOLUTION.

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Abstract. An arylurea has been found to bind very strongly to ion pairs containing sulfonates, phosphates, and carboxylates in chloroform. The data suggest that complexation is due to hydrogen bonding between the urea and the anion. Applications to the design of molecular catalysts are envisioned.

Our use of sulfonate anions to demonstrate the intramolecular salt effect has led us to examine the complexation of salts with neutral receptors.¹ This work was undertaken because the strong effects that local electric fields from ion pairs have upon organic reactions could be used in catalytic schemes if good binding sites for ion pairs were available (Scheme 1).

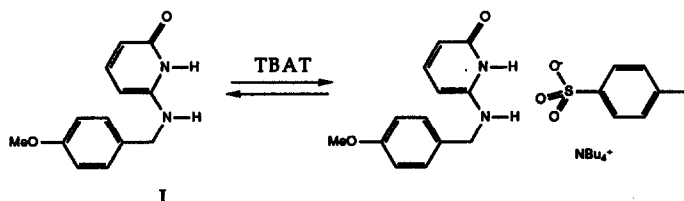
Scheme 1



Preliminary work in this laboratory has shown that a 6-alkylamino-2-pyridone I binds moderately to tetrabutylammonium tosylate (TBAT) in chloroform ($K_a = 400\text{-}800\text{ M}^{-1}$). HNMR data for this system suggest that the pyridone is forming a pair of hydrogen bonds, presumably with oxygen atoms on the sulfonate ion (Figure 1). Diethyl urea was tested and found to be a very weak binder of TBAT in CDCl_3 ($K_a = 47\text{ M}^{-1}$). In hopes of increasing the strength of sulfonate anion binding, other structural analogs which might act as more potent hydrogen bond donors were sought.

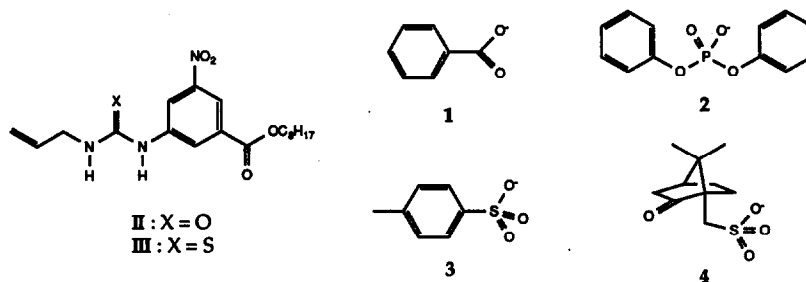
In an influential paper, Etter, et al., have shown that bis-(*m*-nitroaryl)ureas are particularly good donors for neutral acceptors.² Curran and Kuo prepared the symmetrical bis-arylthiourea analog of III and evaluated it as a host for neutral guests.^{3a} With these results in mind, receptor II was synthesized and tested for binding with several representative ion pairs in chloroform. Anions 1-4 were used as their tetrabutylammonium salts (Figure 2). Urea II was found to be an excellent host for ion pairs containing sulfonates, phosphates and carboxylates in solution. A bis-(*m*-nitroaryl)urea related to II had

Figure 1



yet higher affinities for these ion pairs, but the presence of a single *m*-nitroaryl group is sufficient for strong binding, and the absence of the other aryl group provides a site for attachment of a variety of functional groups (per Scheme 1) at the second urea nitrogen. The thiourea III, too, is a better host than II, but thioureas are more susceptible to nucleophilic and electrophilic attack and might take part in undesirable side reactions when applied in catalytic schemes.^{3b} We have therefore focused our initial investigation on the mono-(*m*-nitroaryl)urea host II.

Figure 2



The HNMR chemical shift data for the N-H resonances of II alone and in the presence of one equivalent each salt are shown in Table I. All concentrations are 2.0 mM. The large downfield shifts ($\Delta\delta$) observed upon addition of salt imply that hydrogen bonded complexes are being formed. (N-H)_a and (N-H)_b represent the aryl- and alkylurea N-H signals, respectively.

Table I. HNMR data for 2.0 mM solutions of II alone and in the presence of one equivalent of various salts. Chemical shifts are in ppm in deuteriochloroform at 298K.

salt	$\delta(\text{N-H})_a$	$\delta(\text{N-H})_b$	$\Delta\delta(\text{N-H})_a$	$\Delta\delta(\text{N-H})_b$
none	6.62	4.77	-	-
1	11.61	8.57	4.99	3.80
2	10.07	6.88	3.45	2.11
3	9.27	6.89	2.65	2.12
4	9.45	7.11	2.83	2.34

Though large NMR signal changes were observed, accurate association constants were better determined using UV/vis spectrophotometry. Concentrations required for UV/vis analysis were lower than for NMR analysis and resulted in an increased accuracy due to the increased range of saturation observed.⁴ Titration of a chloroform solution of II with salts 1-4 gave a series of absorption spectra containing two distinct isosbestic points in the region between 280 and 460 nm (none of the salts absorb

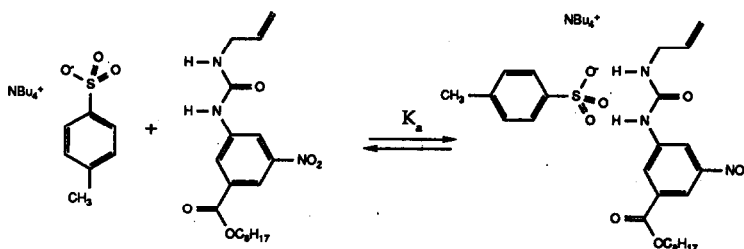
significantly in this region). Solutions containing 100 μM host and from 25 to 500 μM salt were used. The observed extinction coefficients at a fixed wavelength as a function of added salt concentration were used to quantify binding. The results of these experiments are shown in Table II.⁵

Table II. Results from binding experiments with host II in chloroform at 298K.⁵

guest	K_a (M^{-1})	$-\Delta G$ (kcal/mol)	λ_{max} complex (nm)
none	-	-	(338)
1	$2.7 \pm 0.8 \times 10^4$	6.0	361
2	$9.0 \pm 2.0 \times 10^3$	5.4	351
3	$6.1 \pm 1.2 \times 10^3$	5.2	350
4	$6.9 \pm 1.4 \times 10^3$	5.2	353

Complexation of ion pairs by neutral molecules which are not conjugate acids or bases of the relevant anion or cation has been termed heteroconjugation by Kolthoff and Chantooni.⁶ Numerous examples of this phenomenon have been reported and complexation has often been attributed to hydrogen bonding interactions.⁷ Our data indicate that this is the situation in the present case. We believe that the complexes which are formed consist of contact ion pairs bonded to the urea moiety via hydrogen bonds to the anion.⁸

Figure 3



Alternate explanations for the observed binding have been considered. In none of the experiments were charge transfer absorption bands observed. The similar binding constants obtained for tetrabutylammonium tosylate and camphorsulfonate discredit the notion that π -stacking is contributing to binding. Proton transfer seems extremely unlikely due to the large difference in pK_a between even the most basic anion used and an arylurea.⁹ We also discount the notion that this is a (relatively) non-specific "bulk dielectric" effect. Such effects cause continuous shifts in the absorption maxima and not distinct isosbestic points as were observed here.¹⁰

This strong binding of salt dipoles will be tested for the reversible activation of functional groups in reactions which are subject to electrostatic catalysis, as depicted in Scheme 1.¹¹ In situations where $k_{\text{cat}}/k_{\text{uncat}}$ is large, the nature of the salt can be used to control the microenvironment in which the reaction occurs. Such control can be exploited to increase the enantio-, diastereo- and regioselectivity of chemical transformations.

Acknowledgments: P.J.S. thanks the Department of Education for a graduate fellowship. This work was supported by funds from the University of Pittsburgh and the Sloan Foundation. We are grateful to Professor Dennis Curran and Mr. Lung-Huang Kuo for discussions and a sample of the bis-(*m*-nitroaryl)thiourea.

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- (8) Addition of II to solutions of TBAT in chloroform causes small increases in conductivity, indicating that host binding increases dissociation of ion pairs. Recent results show that II binds to the zwitterion 4-tributylammonium-1-butananesulfonate ($K_a = 8.5 \times 10^3 \text{ M}^{-1}$) just as effectively as it binds to ion pairs 1-4.
- (9) The $\text{p}K_a$ of benzoic acid in water is 4.17.^{12a} The equilibrium $\text{p}K_a$ of *N,N'*-diphenylurea in DMSO is 19.5 and that of *N,N'*-diphenylthiourea in DMSO is 13.5.^{12b}
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