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Highly Strong Complexation of Carboxylates with 1-Alkylpyridinium Receptors in Polar Solvents

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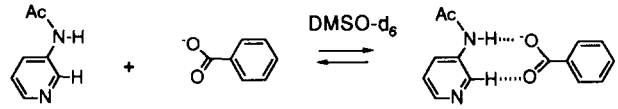
Abstract: Mono- and bispyridinium salts are shown to bind strongly with carboxylates in polar media through multiple hydrogen bonds and additional electrostatic interactions. The association constants of monopyridinium salt with various benzoates are in the range of 110 - 430 M^{-1} in DMSO-d_6, depending on substituents, while those between bispyridinium salts and adipate are >10^3 M^{-1} in 10% D_2O/DMSO-d_6. © 1997 Elsevier Science Ltd.

Hydrogen bonds have been widely exploited for development of synthetic receptors[1] and artificial enzymes,[2] and for design of supramolecular crystals.[3] Most of works focused on strong N-H···X and O-H···X (X = N, O) hydrogen bonds. In recent years, it has been reported that C-H···X hydrogen bonds play an important role in the stabilization of nucleobase quartet,[4] tRNA structure,[5] and many crystal structures.[6] The C-H groups adjacent to neutral or protonated nitrogen atom are often involved in hydrogen bonding in the crystal structures.[7] However, C-H···O hydrogen bonds are quite rarely incorporated into synthetic receptors as a determining force to stabilize the complexes in solution.[8] To investigate the significance of C-H···O hydrogen bonds in highly polar solvents, we initially studied the complexation between 3-(acetylamino)pyridine (**1**) and tetrabutylammonium benzoate (**2a**). ^1H NMR titration of **1** with **2** in DMSO-d_6 gave the association constant of $K_a = 16 \pm 1$ M^{-1} at 298 K.



1 **2a**

In order to increase hydrogen donor ability of CHs and NH, 3-(acetylamino)pyridine (**1**) was treated with methyl iodide to give the corresponding quaternary salt **3** in a 57% yield. When a DMSO-d_6 solution of this salt was treated with tetrabutylammonium benzoate (**2a**), large chemical shift changes were observed as shown in figure 1. It is worthwhile to note that the signals of the H_o, H_p and NH protons in **3**, all of which might be directly involved in hydrogen bonding, were significantly downfield-shifted, while other aryl proton resonances were slightly upfield-shifted (< 0.1 ppm). Especially, the large downfield shifts ($\Delta\delta_{max}$~ 0.5 ppm) of both CHs, H_o and H_p, indicate that C-H···O hydrogen bonds might participate in the stabilization of the

complex **2a**·**3**. Two plausible binding modes are shown below.[9] Since the magnitude and trend of the H_o and H_p chemical shift changes are very similar during the titration, there might be no strongly favarable mode in the complexation.

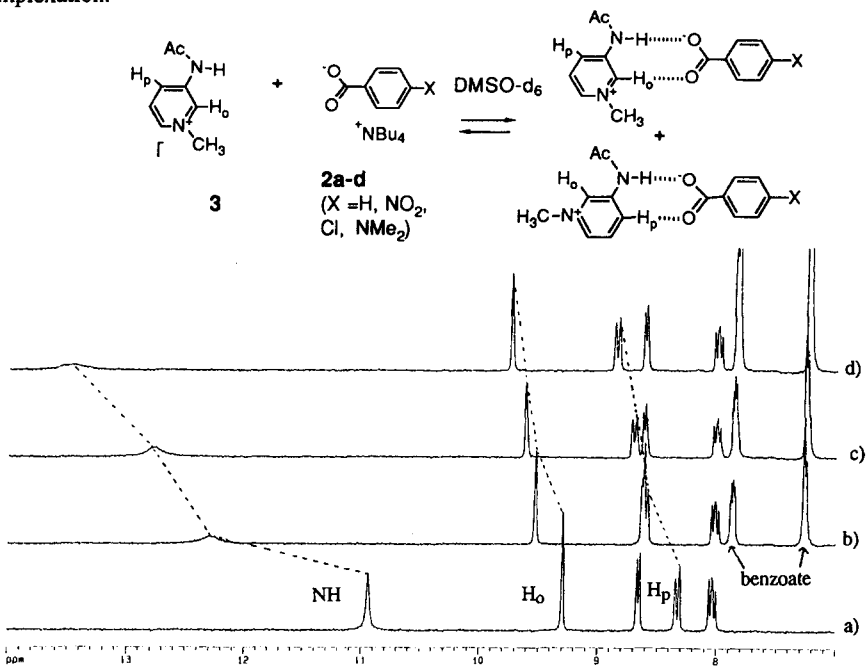


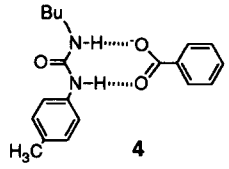
Figure 1. Partial ^1H NMR spectra of the salt **3** (10 mM in DMSO-d_6) in presence of a) 0, b) 0.5, c) 1.0, and d) 2.0 equiv. of tetrabutylammonium benzoate (**2a**).

The association constants in Table 1 were determined at 298 ± 0.5 K by ^1H NMR titration in DMSO-d_6.[10] Upon addition of small aliquots of benzoates **2a-d**, the amide NH resonance of the salt **3** were largely downfield-shifted($\Delta\delta_{max} \geq 2.5$ ppm), but became occasionally too broad to be measured accurately. The association constants were, therefore, calculated by nonlinear squares fitting method of the saturation curves, plotting H_o and H_p chemical shift change ($\Delta\delta_{max}$ 0.3-0.6 ppm) *vs* guest to host molar ratio, both of which gave the same values within 2% error.

Table 1. Association Constants (K_a ± 10%, M^{-1})of Mono- and Bispyridinium Salts with Various Carboxylates at 298 ± 0.5 K.

entry	host	guest	solvent	K_a (M^{-1})
1	**3**	**2a** (X = H)	DMSO-d[6]	300
2		**2b** (X = NO_2)	"	110
3		**2c** (X = Cl)	"	205
4		**2d** (X = NMe_2)	"	430
5	**6**	adipate	10% D_2O/DMSO-d_6	2170
6	**7**	"	"	1790
7	**8**	"	"	3090

The association constant (K_a = 300 M^{-1}) of the salt **3** with benzoate **2a** is much higher than that (K_a = 16 M^{-1}) of 3-(aceylamino)pyridine (**1**). This remarkable increase in K_a may result in part from the increased hydrogen donor ability of the CHs and NH in **3** and an additional electrostatic interaction between two opposite charges. It should be also mentioned that the complex **2a·3** is more stable than complex **4** (K_a = 150 M^{-1} in DMSO-d_6).[11]



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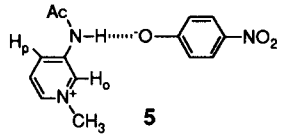

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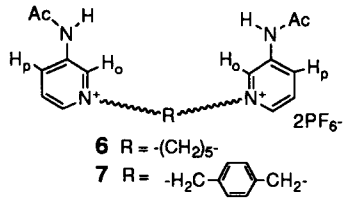
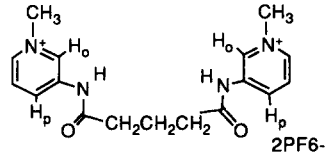
As shown in Table 1, the magnitude of the association constants (entry 1-4) is well correlated to the hydrogen acceptor ability of various benzoates **2a-d**. That is, electron withdrawing groups (X = NO_2, Cl) decrease the association constant and electron donating group (X = NMe_2) increases it. For comparison with a system **5** having only N-H···O hydrogen bond, the salt **3** was titrated with tetrabutylammonium *p*-nitrophenolate since pK_a value (10.8) of *p*-nitrophenol is similar to that (11.0) of benzoic acid in DMSO.[12] The signals for all aryl protons in **3** were slightly upfield-shifted (≤ 0.1 ppm) upon addition of *p*-nitrophenolate, affording $K_a \leq 10$ M^{-1} in DMSO-d_6. Increased stability of the complexes **2·3** relative to the complex **5** might be attributed to additional hydrogen-bonding forces including C-H···O hydrogen bond.

Furthermore, three different bispyridinium salts **6**, **7** and **8** were prepared for binding of dicarboxylates. Reaction of 3-(acetylamino)pyridine (**1**) with 1,5-dibromopentane and *p*-bis(iodomethyl)benzene in DMF, followed by anion exchange (NH_4PF_6/H_2O) gave the bispyridinium salts **6** (55%) and **7** (32%) respectively. On the other hand, the host **8** was prepared in a 26% yield by reaction of 3-aminopyridine with glutaryl dichloride, followed by salt formation (MeI/DMF) and anion exchange (NH_4PF_6/H_2O).



6 R = -$(CH_2)_5$-

7 R = -H_2C-C$_6H_4$-CH_2-



8

The binding properties of the bispyridinium salts **6**, **7** and **8** to adipate were first examined in DMSO-d_6. Titration of these salts (1.5 mM in DMSO) with adipate·2NBu_4 caused large downfield shifts ($\Delta\delta_{max}$ > 0.5 ppm) of the H_o and H_p signals with a sharp break of saturation curves on one equivalent addition of guest, affording $K_a > 5 \times 10^5$ M^{-1}. This result indicates that two pyridinium units cooperatively bind to adipate through multiple hydrogen bonds and additional electrostatic interactions. Addition of 10% D_2O considerably reduced the association constants by strong solvation of binding partners and thus more reliable values could be measured by ^1H NMR titrations, following downfield shifts ($\Delta\delta_{max}$ 0.3-0.6 ppm) of the H_o

and H_p. All of the association constants of the bispyridinium salts **6**, **7** and **8** with adipate are $>10^3$ M^{-1}, which are much greater than that (30 ± 5 M^{-1}) of the monopyridinium salt **2** with butyrate in the same conditions (10% D_2O/DMSO-d_6 at 298± 0.5 K). The Job's plots[13] showed that maximal complexation occurred at 0.5 molar fraction of the bispyridinium receptors and adipate. These observations clearly indicate 1:1 complex formation by cooperative binding of two pyridinium binding units with adipate.

In conclusion we have demonstrated that carboxylates and pyridinium receptors form unusually stable complexes in highly polar media through multiple hydrogen bonds and additional electrostatic interaction. We are currently investigating various anion receptors by incorporation of this simple pyridinium binding unit.

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