Enolate Complexation in Acetonitrile with a Neutral Polyaza Cleft

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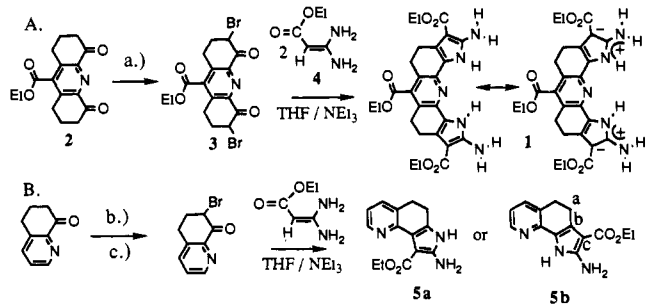
Anion complexation[1] by quaternary ammonium salts,[2] or by polyamines[3] and guanidines[4] in both high-dielectric[5] and low-dielectric solvents,[6] is a relatively well developed field in molecular recognition. Binding is attributed to electrostatics and desolvation,[7] with hydrogen bonding probably playing a secondary role. In contrast, complexation of neutral guests with neutral hosts in aprotic, low-dielectric solvents such as chloroform is typically[8] driven by hydrogen-bond formation.[9] A vast number of molecular recognition studies have relied upon strong hydrogen bonding in chloroform.[10]

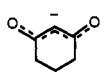
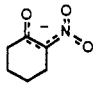
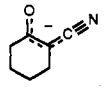
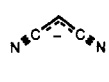
In order to complex 1,3-diketo-like enolates by a neutral synthetic receptor via hydrogen bonding in relatively high dielectric solvents such as acetonitrile,[11] we reasoned that very cooperative interactions between host and guest would be required.[12] Jorgensen[13] proposes that by placing all hydrogen-bond donors on the receptors, and all hydrogen-bond acceptors on the guest (or vice versa), maximum cooperativity in hydrogen-bonding secondary interactions would be achieved. Furthermore, enhancement of the positive character of the hydrogen-bond donors should accentuate binding. Herein, the synthesis and enolate complexation studies of a polyaza cleft **1** which fits the Jorgensen criteria and possesses large positive character on its hydrogen-bond donors are presented.

Scheme I. Syntheses of **1** and **5**



(a) Pyridinium bromide perbromide in THF at room temperature for 12 h. (b) Me_3SiCl/NEt_3 in THF for 3 h. (c) NBS in THF at −30 °C for 15 min.

Table I. Binding Constants between **1** and **5b** with 15-Crown-5 Sodium Salts in Acetonitrile[a]

	guest			
host				
5b	1.1×10^2	67	–[b,c]	–[b]
1	7.1×10^3	2.3×10^3	3.5×10^3[c]	3.9×10^2

[a] Typical error values are 10%. Percent saturation varied between 57% for the lowest binding constant and 95% for the largest binding constant. [b] Could not be determined due to small chemical shift changes. [c] Error estimated at 30% due to ^1H NMR peak broadening.

Cleft **1** possesses preorganized and convergent hydrogen-bond donors complementary to divergent 1,3-diketo-like enolates. Similar crescent-moon-shaped polyaza clefts have been shown previously to complex neutral guests such as urea[14] or uric acid[15] in chloroform. The synthesis of **1**[16] starts with the known compound **2**,[17] followed by bromination with pyridinium bromide perbromide[18] in acetic acid to form **3**. Alkylation with ethyl 3,3-diamino-2-propenoate[19] (**4**) (Scheme IA) yields **1** in 58% yield from **2**. To confirm the structure of **1**, the regiochemistry of alkylation of **3** with α-bromo ketones needed to be checked. Model system **5**[20a] was synthesized similarly to **1** (Scheme IB). No

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(16) **1**: ^1H NMR ($CDCl_3$, 300 MHz) δ 11.6 ppm (s, 2 H), 5.7 (s, 4 H), 4.4 (q, 2 H), 4.2 (q, 4 H), 3.0 (t, 4 H), 2.8 (t, 4 H), 1.4 (t, 3 H), 1.3 (t, 6 H); high-resolution MS, *m/e* (100 eV, CI) 507 (M^+, 100); *m/e* calcd for $C_{26}H_{29}N_5O_6$ 507.211 784, measured 507.213 362.

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(20) (a) **5**: ^1H NMR ($CDCl_3$, 300 MHz) δ 12.1 (br s, 1 H), 8.3 (d, 1 H), 7.3 (d, 1 H), 6.8 (t, 1 H), 5.4 (s, 2 H), 4.2 (q, 2 H), 2.9 (m, 4 H), 1.3 (t, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 166.4, 149.3, 147.0, 144.2, 134.8, 129.0, 125.4, 119.6, 118.7, 93.4, 58.9, 28.4, 21.1, 14.5. (b) The structural ambiguity between **5a** and **5b** was found by examining the ^{13}C–^{13}C correlated spectra. Resonance a at 21.5 ppm correlated to b at 123.5 ppm, which correlated to c at 93.4 ppm. The high-field resonance of c supports a resonance similar to that shown for **1**. Thus structure **5b** is assigned.

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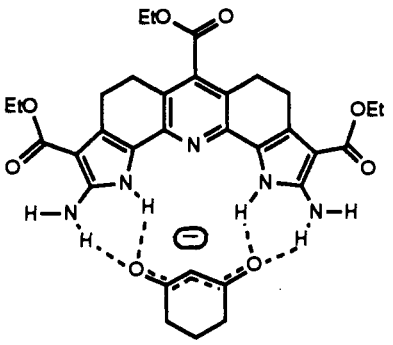
obvious ^1H or ^{13}C NMR resonances could distinguish **5a** from **5b**. Thus, a ^{13}C–^{13}C correlated NMR spectrum[21] was run on **5**, and tracing carbons a, b, and c yields the regiochemistry as shown for **5b**.[20b]

When 15-crown-5 sodium enolates of 1,3-diketone functionalities are incrementally titrated into a solution of 1.0×10^{-3} M **1** and 2.0×10^{-3} M **5b** in acetonitrile-d_3, the NH and NH_2 ^1H NMR resonances shift to lower field, typically over a range of 1.5 and 0.7 ppm, respectively. The binding constants calculated with the typical binding algorithm[22] are shown in Table I. Compound **1** binds each anion significantly better than **5b**, reflecting the cooperativity between the two symmetric halves of **1**. The successful complexation reflects several interactions. The first is a lack of strong hydrogen bonding between the solvent and the enolates. The second is completely cooperative hydrogen bonding between relatively acidic NH and NH_2 groups and the basic enolate oxygens. As Whitlock discussed,[23] the more basic the hydrogen-bond acceptor, the stronger the complexation. However, we found that the correlation between basicity and binding strength does not hold when the hydrogen-bond acceptors are of different structure. Of the anions studied, malononitrile anion is the most basic,[24] but has the lowest binding constant. This is probably due to fewer hydrogen bonding contacts with **1**, or possibly increased association with the 15-crown-5 sodium. However, the fact that the enolate is relatively "naked"[25] and has little ability to coordinate to the counter sodium ion in a 15-crown-5 undoubtedly enhances complexation with **1**. Studies to confirm these effects are underway.

The proposed complexation geometry of 1,3-cyclohexanedionate with **1** is shown below.[26]



Of the enolates tested, this one binds the strongest to **1**. This is likely due to the rigid structure of the enolate, which diverges the keto oxygens in an optimum manner to complement the convergence of the host hydrogen-bond donors of **1**. In contrast, the enolates of 2,4-pentanedione and 2-acetylcyclohexanone were found not to bind, due to increased conformational freedom over the other guests, and the preferred anti conformation of oxygens.[27]

Enolization catalysts[28] and enolate-binding synthetic hosts such as **1** have the potential for controlling the regiochemistry, stereochemistry, and kinetic reactivity of reactions involving enolates. Studies using **1** as a catalyst and the enolates discussed as transition-state analogues are in progress.

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Gradient-Enhanced HMQC and HSQC Spectroscopy. Applications to ^{15}N-Labeled Mnt Repressor

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The availability of high-quality shielded gradients for high-resolution NMR has provided new approaches to attain coherence selection[1] and water suppression.[2] Gradient techniques hold promise particularly for heteronuclear ^1H detected experiments (e.g., HMQC[3] and HSQC[4]), where coherence of protons not bound to the heteronucleus is usually canceled by subtraction in consecutive scans. Gradient techniques can select for the desired coherence-transfer pathway in a single scan, while dephasing signals arising from other pathways. Thus, an inherent frequency-independent solvent suppression is attained when sufficient gradient strength is available. Compared to presaturation, there is the advantage that the time for magnetization transfer from saturated water to exchangeble protons is very short, allowing efficient detection of, for instance, amides in proteins.

We present the gradient-enhanced HMQC[1g-i] and a novel gradient-enhanced HSQC experiment and apply them to ^{15}N-labeled Mnt repressor (1–76) (dimer, M_w = 17 500) in ^1H_2O solution. Spectra are obtained with inherent ^1H_2O suppression in only 150 s, illustrating for the first time that these techniques are feasible for studying exchangeable protons in biomolecules.

The ratio of gyromagnetic ratios (γ_{1H}/γ_{15N} = 9.88) determines the phase acquired during t_1 and t_2 and thus the relative gradient strengths necessary to attain proper rephasing of the required coherence. In the gradient-enhanced HMQC experiment (Figure

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§ General Electric NMR.

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