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Binding Multiple Phosphodiesters With a Polyazacleft

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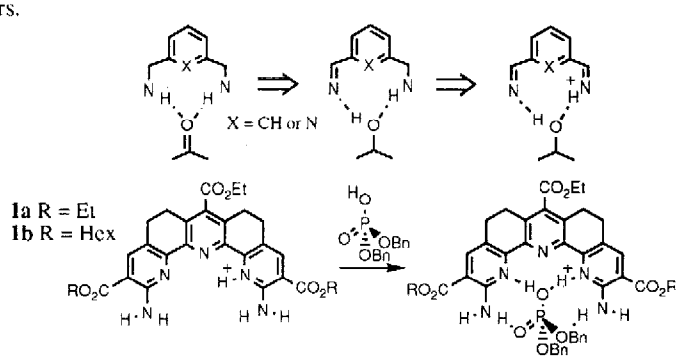
Abstract: Polyazaclefts designed to bind a phosphoric acid ester with either four or two hydrogen bonds were both found to bind multiple phosphoric acid esters in chloroform.

The design of receptors that recognize and bind common organic functional groups is a current goal in molecular recognition.[1] Rigid preorganized polyazaclefts with convergent hydrogen bond donors and acceptors have been found to complex the planar guests urea[2] and uric acid,[3] while slightly more flexible polyazaclefts have been developed for the binding of barbituate derivatives.[4] These receptors possess a common structural motif; NH groups are spatially preorganized, by attachment to meta substituted benzenes, to be complementary to the divergent nature of carbonyl oxygen lone pairs. By replacing one of these hydrogen bond donors on the host with a hydrogen bond acceptor, one creats a receptor complementary for alcohols (Scheme 1). In addition, a hydrogen bond acceptor on the host could be switched to a hydrogen bond donor by prior protonation with an acid. The incorporation of other hydrogen bond donors or acceptors into the receptor could then lead to the recognition of organic functional groups which possess alcohol subgroups such as carboxylic acids and phosphoric acid esters.



Scheme 1: Design of an alcohol receptor as an extension of a ketone receptor. Incorporation of the concept into a phosphodiester receptor.

Compound **1**[5] forms a cavity with three convergent hydrogen bond donors and one hydrogen bond acceptor in a spatial arrangement to form four hydrogen bonds to a phosphodiester. The shape of the cleft and preorganization of the hydrogen bonding contacts are evident from the crystal structure of the monopicric acid salt of **1a** (Figure 1).[6] A water was found in the cavity with an OH bound in the manner postulated for an OH of an alcohol or a bound phosphodiester. In solution, the cleft undoubtedly exists in a twisted d,l form and a puckered meso form.[7]

When the ^{31}P NMR spectra of a constant concentration of dibenzyl phosphate in chloroform was followed with incremental increases in the concentration of **1b** picrate, the curve shown in Figure 2 was

generated. Figure 3 displays the ^{1}H NMR titration curve generated when dibenzylphosphate was incrementally added to a constant concentration of **1b** picrate. The shape of these two titration curves indicate multiple equilibria with the possible binding of two or more phosphodiesters. In order to delineate the stoichiometry between receptor and phosphodiester, the simpler analog **2**[5] was studied thoroughly.

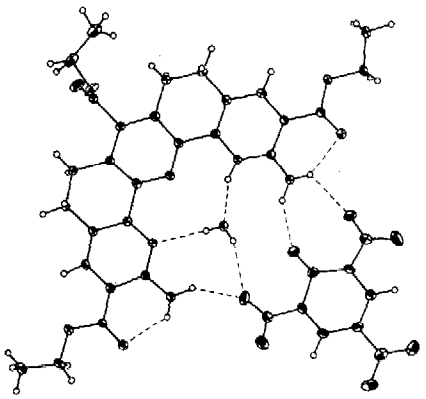


Figure 1: X-ray crystal structure of the monopicric acid salt of **1a**. A water of crystallization is bound in the cavity.

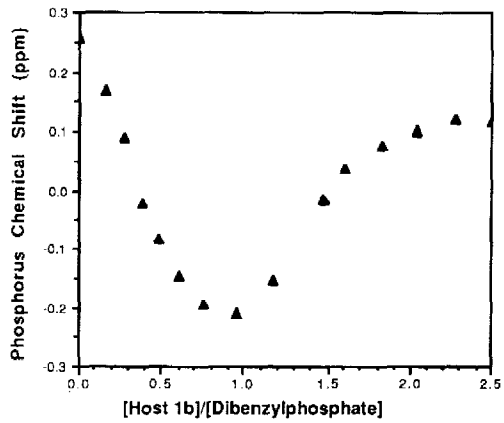


Figure 2: Experimental points determined by following the ^{31}P NMR spectra of dibenzyl phosphate with incremental increases in host **1b** concentration. Concentration of dibenyzl phosphate was 0.018 M

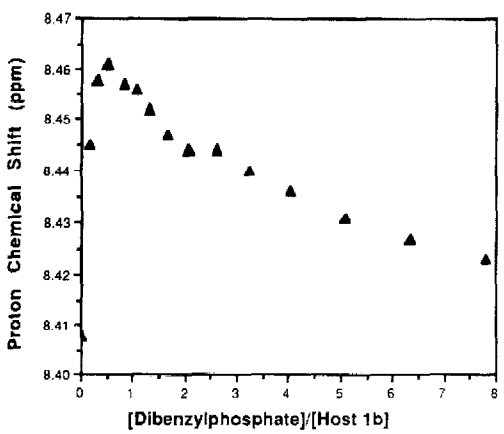


Figure 3: Experimental points determined by following the ^{1}H NMR spectra of **1b** picrate with incremental increases in dibenzylphosphate concentration. Concentration of host **1b** was 0.0081 M.

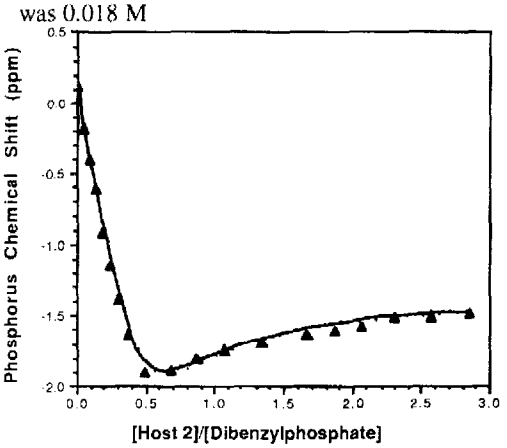


Figure 4: Experimental points and computer generated line following the ^{31}P NMR spectra of dibenzylphosphate with incremental increases in host **2** concentration. Concentration of dibenzyl-phosphate was 0.053 M.

When the ^{31}P NMR spectra of dibenzyl phosphate was followed with incremental increases in the concentration of **2** (Scheme 2), the curve shown in Figure 4 was generated. A large inflection in the ^{31}P NMR titration was found indicating multiple equilibria. Similarly, when the ^{1}H NMR spectra of a constant concentration of host **2** was followed as a function of incremental increasing concentrations of dibenzyl phosphate in chloroform, a curve which did not fit a 1 to 1 binding algorithm was generated (Figure 5).[8] However, when a binding algorithm was applied to the ^{1}H NMR titration data of Figure 5 for both a 1 to 1 and a

2 to 1 phosphate to host complex, the computer generated line shown was obtained.[9] Binding constants for the 1 to 1 complex and 2 to 1 complex of $9.0*10^2$ M^{-1} (K_1) and $1.5*10^2$ M^{-1} (K_2) were found respectively. In order to confirm the existence of 2 to 1 binding, the experimental points shown in Figure 4 were computer fit using an algorithum[10] for NMR titrations when following the spectra of the species whose stoichiometry is 2 in a 2 to 1 complex. Binding constants within 10% of those found from the ^1H NMR data of Figure 5 were extracted.

Finally, for additional evidence that a two to one complex was being formed, a Job plot[11] was performed with compound **2** and dibenzylphosphate following the ^{31}P NMR chemical shift of the phosphate. The Job plot (shown in Figure 6) shows a maximum value at approximately 0.67 mole fraction dibenzylphosphate, indicating a 1 to 2 host to dibenzyl phosphate stoichiometry.

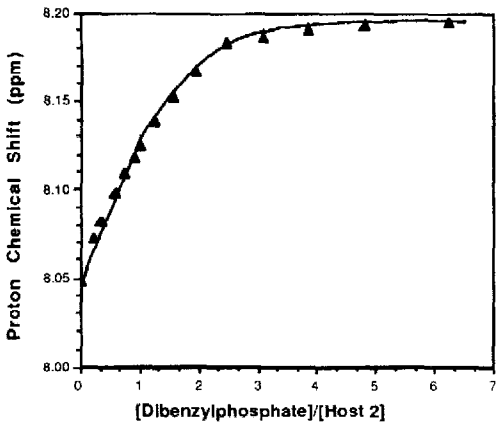


Figure 5: Experimental points and computer generated line following the ^1H NMR spectra (of the 2-aminopyridine moiety para proton) of host **2** with incremental increases in dibenzyl phosphate concentration. Concentration of host **2** was 0.014M.

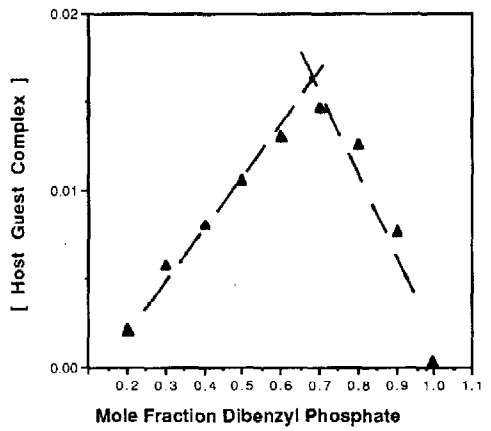
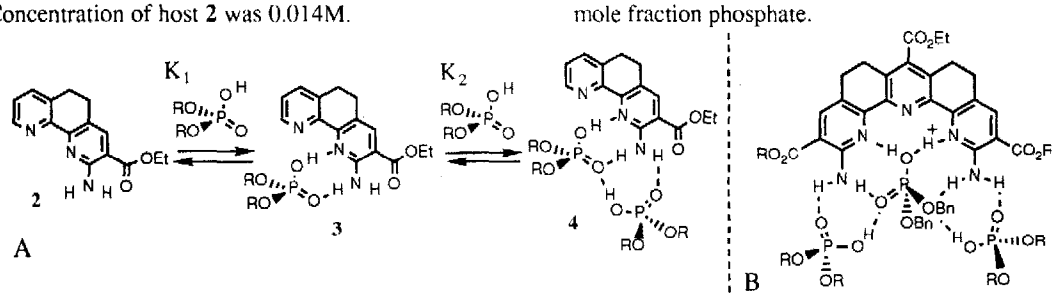


Figure 6: Job plot of **2** with dibenzylphosphate following the ^{31}P NMR. Total host and guest concentration was kept at 0.035 M. Maximum value of the graph occurs at approximately 0.67 mole fraction phosphate.



Scheme 2: A) Proposed 1 to 1 and 2 to 1 complexation geometries. Once the one to one complex is formed, a second possible complexation site is produced. B) Possible three to one complex of **1** and dibenzylphosphate.

Scheme 2A shows possible binding geometries for the 2 to 1 complex. It is proposed that once one phosphate binds in a 2 point hydrogen bonding manner (that is well precedented in other systems,[12] structure **3**), that another hydrogen bonding recognition pattern is created and a second phosphodiester associates to form structure **4**. Our proposal that the second phosphate associates on the periphery of the cleft is supported by the observation that the broad NH ^1H NMR resonances of **2** shift down field further during addition of the second eq. of phosphate than the first. This suggests that **1b** could associate three phosphodiesters, one in the cavity and two on the periphery (Scheme 2B). Thus, it is postulated that due to the highly acidic nature of phosphoric

acid esters, and their strong tendency to dimerize and oligomerize in non-polar solvents,[13] that complexes higher than one to one stoichiometry with synthetic receptors will be common. In conclusion, the high tendency of phosphoric acid esters to oligomerize should be considered in the design of receptors for lipophilic solvents.

Acknowledgements

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5. Compound **1b** was synthesized in a similar manner to **1a** as in Huang, C.Y.; Cabell, L.A.; Anslyn, E.V., *Tetrahedron Lett.*, **1990**, *31*, 7411. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.26 (m, 12H), 1.46 (t, 4H), 1.81 (t, 4H), 3.08 (m, 8H), 4.36 (t, 4H), 4.5 (q, 2H), 8.41 (s, 2H), 8.45 (bs, 4H), 8.74 (s, 2H). 13C {1H} NMR (CDCl3, 70MHz) d 13.97, 14.25, 22.48, 23.94, 24.67, 25.55, 28.37, 31.37, 62.77, 111.13, 121.8, 126.68, 127.92, 134.79, 140.87, 144.5, 145.5, 154.39, 162.14, 164.06. Anal. Calcd. for $C_{42}H_{47}N_8O_{13}$: C, 57.79; H, 5.39. Found: C, 56.12; H, 5.57. Mp 167 -168 C°
6. Crystal Data for **1**. $C_{34}H_{34}N_8O_{12}$, *M* = 778.69, triclinic, space group P$\bar{1}$ (No. 2), a = 9.3315(9), b = 13.3104(12), c = 14.6257(12)Å, a = 104.015(7), b = 96.938(7), g = 98.938(7)°, V = 1717.7(3)Å^3, Z = 2, D_c = 1.50 g cm^{-3} (173 K), F(000) = 812, m (Mo Ka) = 1.115 cm^{-1}, l = 0.7107 Å, Nicolet R3 diffractometer, 8736 reflections collected (2q range 4 - 50°) at 173 K, using a Nicolet LT-2 low-temperature device, 4271 unique reflections, R for averaging symmetry equivalent data = 0.017. The structure was solved by direct methods and refined by full-matrix least-squares using SHELXTL-*Plus* (Sheldrick, G. M. (1990). SHELXTL-*Plus* (Version 4.1)). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA. All non-H atoms were refined anisotropically. The H atoms were obtained from a DF map and refined with isotropic temperature factors. A total of 641 parameters were refined to a final R = 0.0466, wR = 0.0526 and a goodness-of-fit = 1.624 using 4271 reflections having F > 4s(F). Atomic coordinates and thermal parameters, bond lengths and angles, torsion angles, H-bonding interactions and observed and calculated structure factor amplitudes have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.
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