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A Cyclohexane Spacer for Phosphate Receptors

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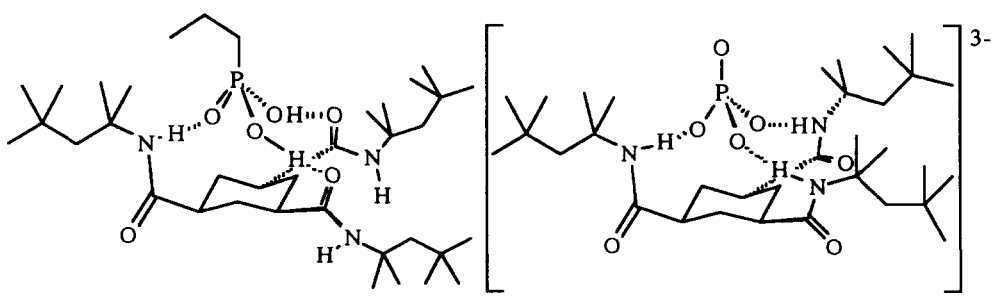
Abstract: *A cyclohexane tricarboxylic acid is shown to be a good spacer for phosphate guests. The combination of 8-aminochromenone-2-carboxamide groups with the cyclohexane spacer leads to a versatile receptor which sets six hydrogen bonds with either phosphonic acids or phosphates. Large association constants are obtained for this receptor in DMSO and methanol when tetraalkylammonium phosphates are used as guests.*

The search for phosphate receptors is of current interest due to their many possible applications, in biological systems[1], as sensors and in the development of artificial hydrolases[2], because of the similarities between phosphates and ester hydrolysis transition states.

Most phosphate receptors are based on ammonium compounds, either macrocyclic[3] or of the cleft type[4]. Neutral compounds such as ureas and thioureas have also been shown to complex phosphates[5]; however, only two hydrogen bonds are present in these weak complexes and it therefore seems attractive to make use of triangular-shaped spacers to prepare receptors able to form more hydrogen bonds with a tetrahedral phosphate. CPK models show that 1,3,5-cyclohexane tricarboxylic acid can be a reasonable base for this kind of receptors[6].

Due to the high chloroform-insolubility of cyclohexane tricarboxylic acid, the first receptor we studied was the triamide **1**[7] (figure 1), readily prepared from the acid chloride and 1,1,3,3-tetramethylbutylamine.



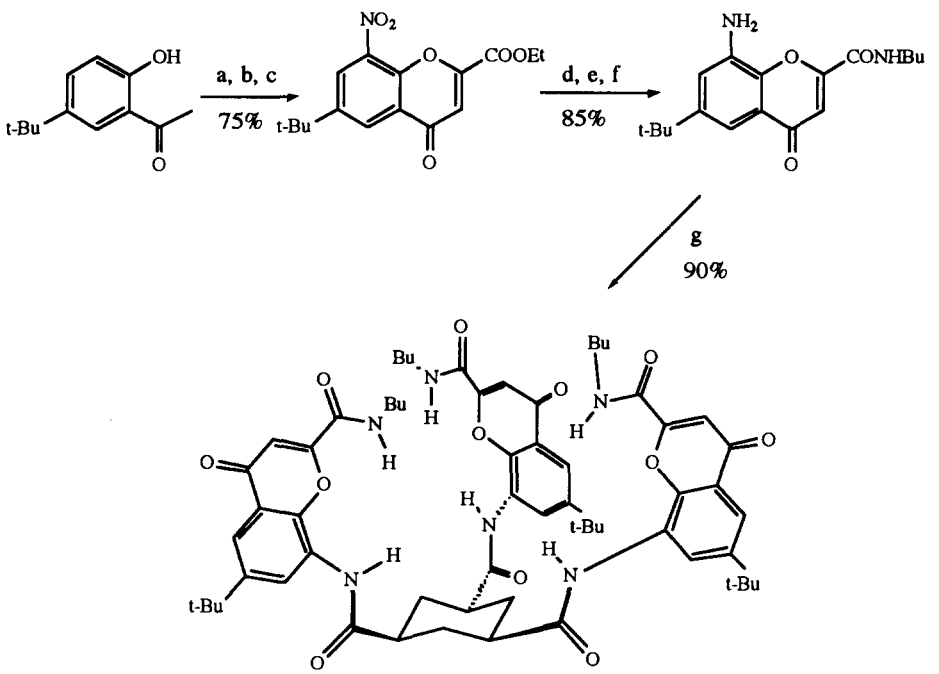
A (K_{ass} = 1.9x10^2 M^{-1})
$CDCl_3$

B (K_{ass} = 1.0x10^2 M^{-1})
$DMSOd_6$

Figure 1. Proposed complexes for receptor **1** with propyl phosphonic acid (A) or phosphates (B)

Initial experiments were carried out in chloroform with the easily available phenylphosphonic acid. This compound is only sparingly chloroform-soluble and therefore no association constant was measured with receptor **1**. However, this experiment was promising, because the chloroform-solubility of phenylphosphonic acid rapidly increases in the presence of receptor **1**. Propylphosphonic acid was chosen to measure an accurate constant[8], yielding a K_{ass}= $1.9x10^2$ M^{-1} (figure 1). The axial proton geminal to the carboxamide function was followed in the NMR titration. This proton is strongly deshielded in the complex from 2.11 to 2.65 ppm. The cyclohexane spacer seems to have the right geometry to favor binding arm cooperation, since no shifts were observed in a simple amide such as cyclohexane carboxylic acid (1,1,3,3-tetramethylbutyl)amide.

An 8-aminochromenone-2-carboxamide skeleton is very suitable to set two simultaneous hydrogen bonds with the nonbonding electron pairs of a carbonyl group; this allows one to prepare receptors for carboxylates[9] and lactones[10]. The combination of the cyclohexane spacer with chromenone fragments should allow to set six hydrogen bonds with a phosphonic or phosphoric acid. Therefore receptor **2**[11] was prepared starting from 5-t-butyl-2-hydroxyacetophenone, as shown in scheme 1.



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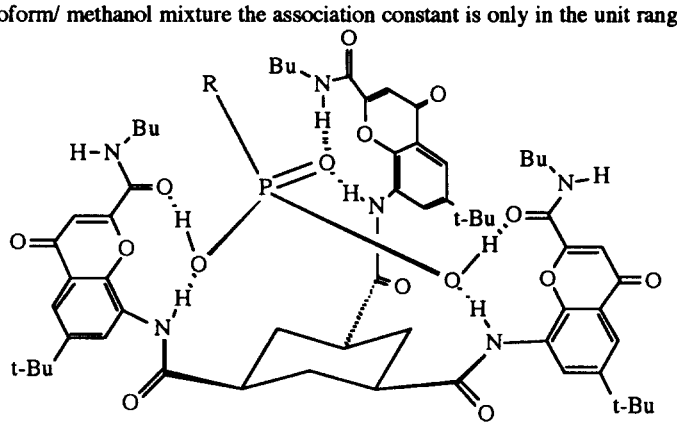
a) HNO_3, AcOH, b) Diethyl oxalate, EtONa, EtOH, c) H_2SO_4, d) $SnCl_2$, EtOH, e) $BuNH_2$, f) AcOH, g) 1,3,5-cyclohexantricarboxylic acid trichloride

Scheme 1: Synthesis of receptor **2**

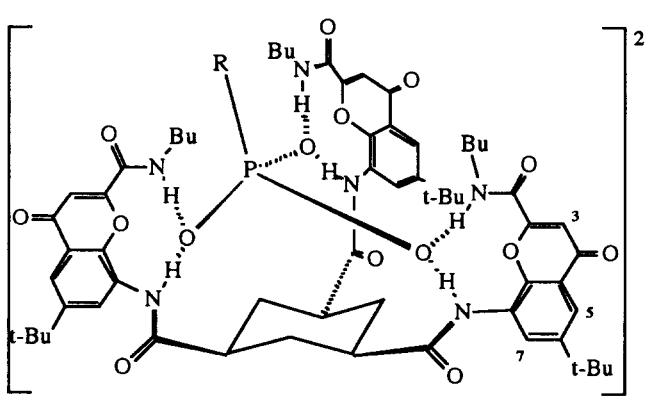
Receptor **2** is not chloroform-soluble. However, this problem was solved by adding 10% methanol. Under these conditions, receptor **2** associated both phenylphosphonic (K_{ass}= $8.0x10^2$ M^{-1}) and propylphosphonic (K_{ass}= $1.6x10^2$ M^{-1}) acids (figure 2), while no association was detected with receptor **1** due to the strong competition from methanol. Higher methanol ratios gave weaker complexes; in a 1:1 chloroform/ methanol mixture the association constant is only in the unit range.



R	$K_{ass}(M^{-1})$
Propyl	$1.6x10^2$
Phenyl	$8.0x10^2$

Figure 2: Proposed complexes for receptor **2** and phosphonic acids and their association constants in chloroform/ methanol 9:1.

The ability of amides to act either as hydrogen bond donors or acceptors should also allow receptors **1** and **2** to associate phosphates or phosphonates (figures 1 and 3). DMSO was chosen for these measurements because, as already pointed out[12], it does not compete strongly in the anion association. Under these conditions, receptor **1** essentially does not bind bis(tetrabutylammonium) phenylphosphonate and only associates the highly charged tris(tetramethylammonium) phosphate weakly (K_{ass}= $1.0x10^2$ M^{-1}). The six, close to linear, hydrogen bonds in the receptor **2** complexes afford much better results, improving the association constant with the foregoing phenylphosphonate to K_{ass}= $1.5x10^4$ M^{-1}. All the chromenone protons show significant shifts in the complex (table 1). The high charge of the phosphate leads to a K_{ass} above 10^5 M^{-1}.



R	$K_{ass}(M^{-1})$ DMSO d_6	$K_{ass}(M^{-1})$ CD_3OD
Phenyl	$1.5x10^4$	$8x10^2$
O^-	$>10^5$	$1.2x10^4$

Proton	δ Receptor	δ Complex
H_7	8.31	8.43
H_5	7.76	7.68
H_3	6.80	6.74

Figure 3: Proposed complexes for receptor **2** with phosphates or phosphonates and their association constants in DMSO and methanol

table 1: Proton shifts of receptor **2** and its complex with bis(tetrabutylammonium) phenylphosphonate extrapolated for saturation

Charged phosphate receptors, such as the guanidiniums described by Schmidtchen[13], show better association constants in methanol than in DMSO. The neutral receptor **2** follows a different behavior, showing association constants in methanol K_{ass}= $8.0x10^2$ M^{-1} for the phosphonate salt and K_{ass}= $1.2x10^4$ M^{-1} for the phosphate. Probably the lack of an electrostatic attraction means that the competition of the methanol hydrogen bonds for the phosphate would be the decisive factor in this.

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7 Receptor **1**: m. p. (Chloroform): >300°C. ^1H NMR ($CDCl_3$) δ (ppm): 2.11 (t_{broad}, 3H, J=12 Hz), 2.05 (m, 3H), 1.73 (s, 18H), 1.40 (m, 3H), 1.37 (s, 6H), 0.98 (s, 27H).

8 NMR titrations were carried out at 20°C, adding portions of a stock solution of the guest to a host solution, using software which takes into account the increasing dilution.

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11 Receptor **2**: m. p. (Methanol): 230-232°C. ^1H NMR ($DMSOd_6$) δ (ppm): 10.01 (s, 3H), 8.87 (t, 3H, J=7.2Hz) 8.31 (d, 3H, J=2.4Hz), 7.76 (d, 3H, J=2.4Hz), 6.80 (s, 3H), 3.24 (q, 6H, J=7.2Hz), 2.83 (t_{broad}, 3H, J=12Hz), 2.31 (d_{broad}, 3H, J=12Hz), 1.84 (q_{broad}, 3H, J=12Hz), 1.5-1.0 (m, 12H), 1.33 (s, 27H), 0.71 (t, 9H, J=7.2Hz).

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