Tris(2-aminoethyl)amine, a Suitable Spacer for Phosphate and Sulfate Receptors

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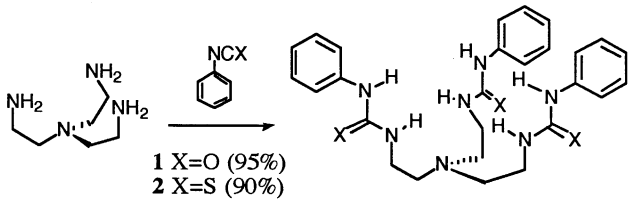
(Received May 2, 1995)

Tris(2-aminoethyl)amine and cis-1,3,5-tris(aminomethyl) cyclohexane have been checked as spacers for phosphate receptors. Ureas are better binding arms than thioureas for these spacers while the combination of this first functional group with chromenone fragments permits further increases in the phosphate and sulfate association constants.

Current interest in phosphate receptors[1] lies in their many possible applications in biological systems,[2] analytics or as artificial transacylases.[3]

Ureas have been shown to complex phosphates.[4] These aggregates are weak due to the presence of only two hydrogen bonds. A suitable spacer able to combine several urea units should allow the preparation of stronger complexes. Study of CPK models shows that despite its flexibility the commercially available tris(2-aminoethyl)amine is adequate for this task.[5]

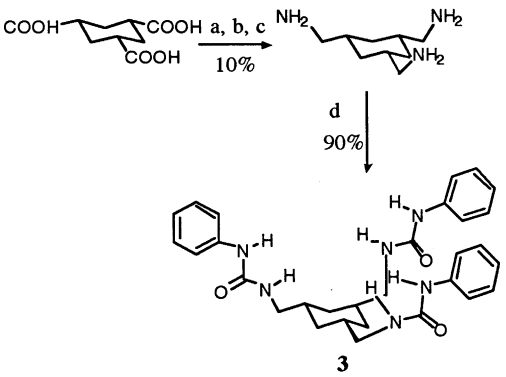
In order to study the possibilities of this polyamine as a spacer for phosphate receptors, compound **1** was prepared. The three urea groups of this receptor should be able to set up six linear hydrogen bonds with a phosphate. The preparation of compound **1** (m.p. 184-186°C) is straightforward, reacting tris(2-aminoethyl) amine with phenyl isocyanate (scheme 1).



Scheme 1. Synthesis of receptors **1** and **2**.

Receptor self-association was studied making use of dilution experiments in DMSO-d_6 in the range 10^{-2}-10^{-3} M which fully includes the concentrations used for titration experiments. Under these conditions only the NH protons were slightly shifted (< 0.01 ppm), showing that if receptor **1** aggregates in this strongly competitive solvent the association must be very poor, allowing a direct measurement of the guest association constants[6].

A first association experiment[7] was carried out with tris(tetramethylammonium) phosphate in DMSO-d_6, obtaining a K_{ass} value of $1.1x10^4$ M^{-1}. This high association constant makes tris(2-aminoethyl)amine a very promising spacer, although a more rigid spacer could provide higher association constants. Because the cyclohexane spacer reduces the rotational degrees of freedom and because CPK models show that it leaves a similar



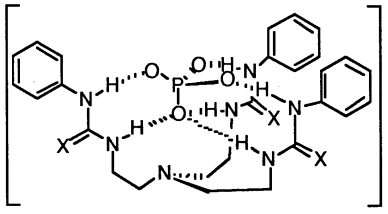
a) $SOCl_2$, b) NH_3aq, c) $LiAlH_4$, d) Phenyl isocyanate

Scheme 2. Synthesis of receptor **3**.

geometry in the complex, receptor **3** (m p 242-244°C) was prepared by reacting cis-1,3,5-tris(aminomethyl)cyclohexane[8] with phenyl isocyanate. However, in this case the association constant with the foregoing phosphate shows a value of only $1.1x10^3$ M^{-1}. CPK models indicate that probably the cyclohexane spacer provides a cavity which is slightly too large for the phosphate, therefore, it was discarded.

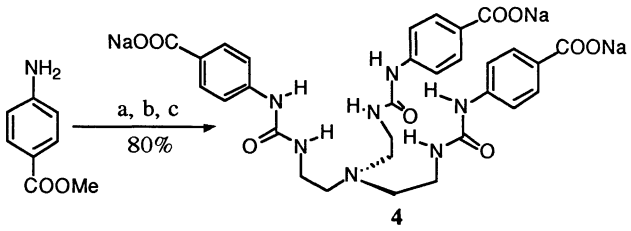
Thioureas are more acidic than oxyureas and have therefore been used in hydrogen bonding complexes.[9] The reaction of phenyl isothiocyanate and tris(2-aminoethyl)amine readily afforded receptor **2** (m p 94-98°C). This compound is a weaker phosphate binder than receptor **1** in DMSO-d_6, showing a K_{ass}= $1.6x10^3$ M^{-1}. As a possibility, intramolecular hydrogen bonds can be stronger due to the higher acidity of thiourea in receptor **2** than in receptor **1**. In other thiourea-based receptors it has been also observed that they are not always better than the oxyureas.[10]

The above association processes in DMSO seem to be slow at room temperature, so gentle heating is needed for achieving reproducibility in the proton shifts. This drawback disappears in methanol; in this solvent receptor **1** does not show significant self-association and a K_{ass}= $1.2x10^4$ M^{-1} with the phosphate. No heating is needed either in water, where a receptor **4** (m p



X	K_{ass}DMSO
O	$1.1x10^4$ M^{-1}
S	$1.6x10^3$ M^{-1}

Figure 1. Proposed complex of receptors **1** and **2** with phosphates and their association constants in DMSO-d_6.



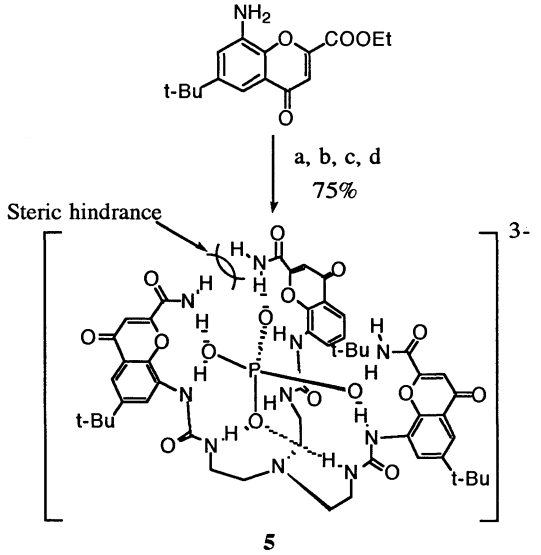
4

a) $COCl_2$, b) tris(2-aminoethyl)amine, c) NaOH

Scheme 3. Synthesis of receptor **4**.

>300°C, scheme 3) associates weakly with the phosphate (K_{ass}= $1.0x10^2$ M^{-1}). This low value is not surprising taking into account that the complex has six negative charges.

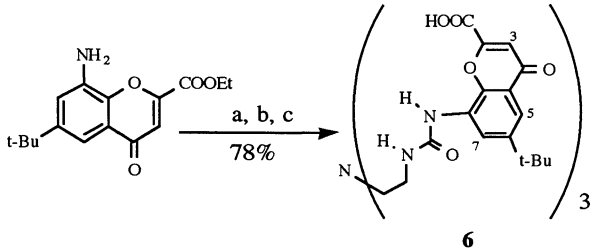
Chromane skeletons have shown to be adequate structures to associate neutral[11] and negatively charged oxygens.[12] Accordingly, they could be included in the tris(2-aminoethyl)amine spacer in order to set up nine hydrogen bonds. However, a receptor **5** (m.p. 228°C dec.), which could be promising, shows, in agreement with CPK models, steric hindrance among the three *syn* hydrogens of the amide groups of the chromenone skeleton in the complex, and it therefore



5

a) NH_3, b) $COCl_2$, c) tris(2-aminoethyl)amine, d) tris(tetramethylammonium) phosphate

Scheme 4. Synthesis of receptor **5** and its proposed complex with phosphates.



6

a) $COCl_2$, b) tris(2-aminoethyl)amine, c) NaOH

Scheme 5. Synthesis of receptor **7**.

associates tris(tetramethylammonium) phosphate in methanol-d_4 with a K_{ass} value of $6.0x10^4$ M^{-1}, only five times better than receptor **1**.

The absence of a second hydrogen in a carboxylic acid group could reduce the steric hindrance in a receptor such as **6** in which carboxylic acids substitute the carboxamide groups. Therefore, receptor **6** (Scheme 5) was prepared. The high basicity of the amine group of receptor **6**, however, suggests a zwitterionic structure for this compound, which is not suitable for phosphate binding. Strong acid protonation of compound **6** should provide the right hydrogen bond pattern to associate tetrahedral anions. In this case phosphates must be ruled out as guests because they compete for protonation due to their strong basicity. Sulfates are good alternatives as guests; they show the same tetrahedral geometry and a very low basicity.

Receptor **1** associates bis(tetramethylammonium)sulfate well, showing a K_{ass}= $3.0x10^3$ M^{-1}. Its hydroiodide also associates the previous sulfate in methanol-d_4. However, the titration curve does not fit the theoretical curve for a 1:1 complex, probably indicating complex equilibria in the solution. Therefore, an association constant cannot be deduced. The form of the curve indicates that if the expected complex is formed it is probably weak. By contrast, perchlorate of receptor **6** (m.p. 240°C dec.) titration shows a fast saturation, and therefore the complex seems to be strong. A K_{ass}=$3.5x10^4$ M^{-1} can be deduced from proton H_7 shifts (Scheme 5) but this value is however not reliable since proton H_3 shifts upfield at the beginning of the titration, changing to downfield after 0.15 equivalents and hence indicating again the presence of complex equilibria in the solution.

We thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant PB 92-0286) for its support of this work. Two of us (C. R. and M. L. M.) also thank the MEC for a fellowship.

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