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A Systematic Evaluation of Molecular Recognition Phenomena. Part 5. Selective Binding of Tripolyphosphate and ATP to Isomeric Hexaazamacrocyclic Ligands Containing Xylylic Spacers

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Protonation constants for 3,6,9,16,19,22-hexaazatricyclo[22.2.2.2^{11,14}]triaconta-1(27),11(30),12,14(29),24(28), 25-hexaene (P2) and 3,7,11,18,22,26-hexaazatricyclo[26.2.2.2^{13,16}]tetratriaconta-1(31),13(34),14,16(33),28(32),29-hexaene (P3) and their host–guest interactions with tripolyphosphate (Tr) and ATP (At) have been determined and evaluated by ^{1}H NMR and potentiometric equilibrium methods. Ternary complexes were formed in aqueous solution as a result of hydrogen bond formation and Coulombic interactions between the host and the guest. For the case of ATP π-stacking interactions were found. Formation constants for all the species obtained are reported and compared with the isomeric 3,7,11,19,23,27-hexaazatricyclo[27.3.1.1^{13,17}]tetratriaconta-1(33),13,15,17(34),29,31-hexaene (Bn) and 3,6,9,17,20,23-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30), 25(27)-hexaene (Bd) ligands. Bonding interactions reach a maximum for H_6P2Tr^+, yielding a log K_6^R value of 12.02. The selectivity of the P3 and P2 ligands with regard to ATP and Tr substrates (S) is discussed and illustrated with global species distribution diagrams showing a strong preference for the latter over the former as a consequence of the much stronger formation constants with Tr. An analysis of the isomeric effect was also carried out by comparing the P3-S vs. Bn-S and P2-S vs. Bd-S systems. For the systems using Tr, a selectivity of more than 97% (pH 5.0) was achieved for its complexation when using the *meta* (Bd) rather than the *para* (P2) isomer, due solely to the size and shape of the receptor's cavity. In the case of the P3 and Bn ligands the selectivity toward Tr complexation decreased to 85% (pH 8.0).

INTRODUCTION

Anion recognition is an essential feature of many chemical and biological processes and currently constitutes an area of intense research [1–13]. In biology, for instance, between 70 and 75% of enzyme substrates and cofactors are anions, generally phosphate residues such as ATP and ADP or inorganic phosphates [14]. Thus it is of great importance to understand and control the different factors that govern anion recognition, and low molecular weight models constitute an excellent basis to mimic such reactions. The development of hosts that can bind specifically to anions has been hampered by a number of difficulties including low solubility, high hydration energies, size constraints and geometrical diversity. Nevertheless, a growing body of research work related to anion coordination is now emerging, including the recognition of halides [15–27], phosphates and nucleotides [5, 18–45], nucleic acids [46], carboxylates [21–25, 39, 45, 47–56], nitrates [18–23, 25, 27, 57–60] and sulfates [18–23, 25, 27, 38, 39, 59, 61], mainly by organic receptors. In addition, a number of studies also describe the recognition phenomena between metalloreceptors and anions such as phosphates [32, 62–67], carboxylates [67–69], nucleic acids [70–73], nucleobases and nucleotides [74–76].

Within this field, we have recently undertaken a systematic evaluation of molecular recognition phenomena between phosphates and nucleotides based on hexaazamacrocyclic ligands containing *m*-xylylic and diethylic ether spacers [77–79]. In that work we have evaluated quantitatively the different factors involved in the recognition processes; namely, Coulombic interactions, hydrogen bonding and π–π stacking interactions.

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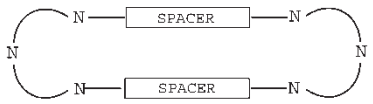
In the present paper we report the host–guest binding interactions of the ligands 3,7,11,18,22,26-hexaazatricyclo[26.2.2.2^{13,16}]tetratriaconta-1(31),13(34),14,16(33),28(32),29-hexaene (P3) and 3,6,9,16,19,22-hexaazatricyclo[22.2.2.2^{11,14}]triaconta-1(27),11(30),12,14(29),24(28),25-hexaene (P2) with tripolyphosphate (Tr) and ATP (At) substrates and compare them with those obtained by the isomeric ligands 3,7,11,19,23,27-hexaazatricyclo[27.3.1.1^{13,17}]tetratriaconta-1(33),13,15,17(34),29,31-hexaene (Bn) and 3,6,9,17,20,23-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25(27)-hexaene (Bd) (see Chart 1).

RESULTS AND DISCUSSION

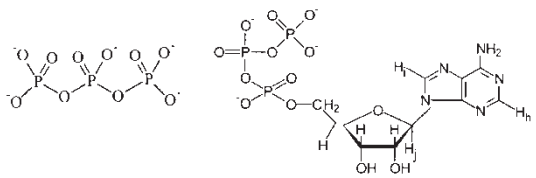
Ligands and Substrates

In the present work we describe the recognition capacities of two ligands with tripolyphosphate and ATP and compare them and their isomeric counterparts; drawings of these ligands and the substrates are presented in Chart 1. The ligands are four ditopic hexaazamacrocycles that differ from one another in their aromatic substitution, which can be *meta* or *para*, and in the number of methylenic units linking the secondary amines. Thus Bd, possessing *meta* substitution and two methylenic units, is the receptor with the smallest cavity whereas P3, which possesses *para* substitution and three methylenic units, has the largest cavity. Assuming an extended conformation of all the C and N sp^3 atoms, which is the conformation presented by Bn in its X-ray structure [80], the relative size of their cavities can be calculated normalized to Bd, the ligand with the smallest cavity. In this way the isomeric ligands are 12% larger in the *para* case as the cavity increases by two-membered ring units relative to *meta*; ligands with the same aromatic substitution but differing in the number of methylenic units increase their cavity size by 20%, due now to the increase in four-membered ring units of the cavity. From a topological viewpoint the *meta* ligands have a rectangular shape whereas the *para* substituted ligands are closer to a square. From the acid–base point of view the isomeric ligands have almost the same protonation constants, as shown in Table I [77], whereas the increase in four methylenic units increases the basicity by about 10 orders of magnitude. The species distribution diagrams shown in Fig. 1 for P2 and P3 illustrate how this difference in basicity influences the zones of predominance of the different protonated species of each ligand. Perhaps the most illustrative feature of these diagrams is that for P3 the pentaprotonated species, H_5P3^{5+}, does not start to form significantly until pH > 5 whereas for P2 at pH 2, the abundance of H_5P2^{5+} is already 9%.



Ligand (L)	Spacer	*n*	Cavity size*	Basicity
Bd		2	1.00	40.42
P2		2	1.12	40.42
Bn		3	1.20	50.32
P3		3	1.34	50.64

*Cavity size normalized for the smallest macrocycle Bd (see text).



Tr ATP (At)

CHART 1 Drawings and abbreviations for the ligands and substrates together with NMR labeling scheme for At.

The substrates used in this work are the tripolyphosphate and ATP, which have the same number of phosphorus atoms but differ in their overall charge as well as in the presence of the substituted ribose ring on one of the terminal phosphate groups. Their protonation constants are shown in Table I.

Recognition Capacity of P3 and P2

Potentiometric titrations of H_6P3^{6+} and H_6P2^{6+} were used to measure their six protonation constants, which, as expected, are very similar to those of their isomeric counterparts, H_6Bn^{6+} and H_6Bd^{6+}, as shown in Table I [77]. Species distribution diagrams as a function of p[H] for P2 and P3 are shown in Fig. 1. Tripolyphosphate and ATP anionic complex formation with P3 and P2 and their different protonated forms were also calculated using the same technique. The experimental curves are shown in Fig. 2. The mathematical treatment allows us to fully characterize the different equilibria present in solution and the results obtained are presented in Table II.

For the P2-Tr system ($\sigma_{fit} = 0.0065$) eight equilibrium species are detected and their formation can be expressed as follows:

$$HP2^{+} + Tr^{5-} \rightleftharpoons HP2Tr^{4-} \quad \log K_1^R = 2.99 \qquad (1)$$

$$H_2P2^{2+} + Tr^{5-} \rightleftharpoons H_2P2T^{3-} \quad \log K_2^R = 2.88 \qquad (2)$$

$$H_3P2^{3+} + Tr^{5-} \rightleftharpoons H_3P2Tr^{2-} \quad \log K_3^R = 3.66 \qquad (3)$$

$$H_4P2^{4+} + Tr^{5-} \rightleftharpoons H_4P2Tr^{-} \quad \log K_4^R = 4.27 \qquad (4)$$

TABLE I Logarithms of the protonation constants for ligands (L = P3, Bn, P2 and Bd) and substrates (S = At and Tr) at 25.0 °C and $\mu = 0.10$ M (KCl). Charges have been omitted for clarity

Equilibrium quotient (L)	P2	Bd*	P3	Bn*	Equilibrium quotient (S)	Tr	At
K_1^H [HL]/[L][H]	9.54	9.46 (9.51)	10.55	10.35 (10.33)	K_1^H [HS]/[S][H]	8.02	6.56
K_2^H [H_2L]/[HL][H]	8.90	8.72 (8.77)	10.06	9.76 (9.73)	K_2^H [H_2S]/[HS][H]	5.54	4.02
K_3^H [H_3L]/[H_2L][H]	8.26	7.98 (7.97)	8.56	8.54 (8.56)	K_3^H [H_3S]/[H_2S][H]	1.98	1.57
K_4^H [H_4L]/[H_3L][H]	7.50	7.12 (7.09)	7.67	7.78 (7.77)			
K_5^H [H_5L]/[H_4L][H]	3.18	3.75 (3.78)	7.12	7.22 (7.22)			
K_6^H [H_6L]/[H_5L][H]	3.04	3.40 (3.27)	6.70	6.67 (6.64)			
$\sum \log K_i^H$	40.42	40.42 (40.40)	50.64	50.32 (50.24)			
$\sigma_{fit} \times 1000$ and (ref.)	1.5	1.9 (43)	1.9	2.1 (80)			

* Values previously reported in the literature are indicated in parentheses.

$$H_5P2^{5+} + Tr^{5-} \rightleftharpoons H_5P2Tr \quad \log K_5^R = 8.88 \quad (5)$$

$$H_6P2^{6+} + Tr^{5-} \rightleftharpoons H_6P2Tr^{+} \quad \log K_6^R = 12.02 \quad (6)$$

$$H_6P2^{6+} + HTr^{4-} \rightleftharpoons H_7P2Tr^{2+} \quad \log K_7^R = 9.17 \quad (7)$$

$$H_6P2^{6+} + H_2Tr^{3-} \rightleftharpoons H_8P2Tr^{3+} \quad \log K_8^R = 6.61 \quad (8)$$

where values for K_i^R, the recognition constant of protonation degree i, are listed in order of appearance from low to high p[H].

Figure 3 shows the species distribution diagrams for these ternary systems. In the case of the P2:Tr:H system, the complexed species always have higher concentrations than the free P2 ligand or its protonated species within the pH range 2.0–8.2; this is also the case for the other three systems described here, indicating the strength of the corresponding ternary species. The recognition constant values obtained for this system are within the range of those previously reported for host–guest interactions with hexaaza macrocyclic amines and phosphates containing aromatic and aliphatic spacers [28–33, 46, 77–79].

The highest equilibrium constant for the present ternary recognition complexes P2:Tr:H corresponds to the formation of the species H_6P2Tr^+, with $\log K_6^R = 12.02$. This complex can be formally described as a H_6P2^{6+} positive cation bonded to Tr^{5-} by Coulombic forces and hydrogen bonds. In this complex the Coulombic interactions and hydrogen bonding reach a maximum.

Taking into consideration that the protonation constants for Tr and P2 (Table II), there are other possible sets of equilibria that could lead to the formation of H_iP2Tr ternary species:

$$HP2^{+} + HTr^{4-} \rightleftharpoons H_2P2Tr^{3-} \quad \log K_2^{R'} = 3.76 \quad (9)$$

$$H_2P2^{2+} + HTr^{4-} \rightleftharpoons H_3P2Tr^{2-} \quad \log K_3^{R'} = 3.90 \quad (10)$$

$$H_3P2^{3+} + HTr^{4-} \rightleftharpoons H_4P2Tr^{-} \quad \log K_4^{R'} = 3.74 \quad (11)$$

$$H_4P2^{4+} + HTr^{4-} \rightleftharpoons H_5P2Tr \quad \log K_5^{R'} = 4.03 \quad (12)$$

$$H_5P2^{5+} + HTr^{4-} \rightleftharpoons H_6P2Tr^{+} \quad \log K_6^{R'} = 7.01 \quad (13)$$

$$H_4P2^{4+} + H_2Tr^{3-} \rightleftharpoons H_6P2Tr^{+} \quad \log K_6^{R''} = 4.65 \quad (14)$$

$$H_5P2^{5+} + H_2Tr^{3-} \rightleftharpoons H_7P2Tr^{2+} \quad \log K_7^{R'} = 6.64 \quad (15)$$

$$H_6P2^{6+} + H_2Tr^{3-} \rightleftharpoons H_8P2Tr^{3+} \quad \log K_8^{R'} = 6.61 \quad (16)$$

$$H_5P2^{5+} + H_3Tr^{2-} \rightleftharpoons H_8P2Tr^{3+} \quad \log K_8^{R''} = 7.64 \quad (17)$$

For each species all the equilibria operate simultaneously and their relative importance is a function of p[H].

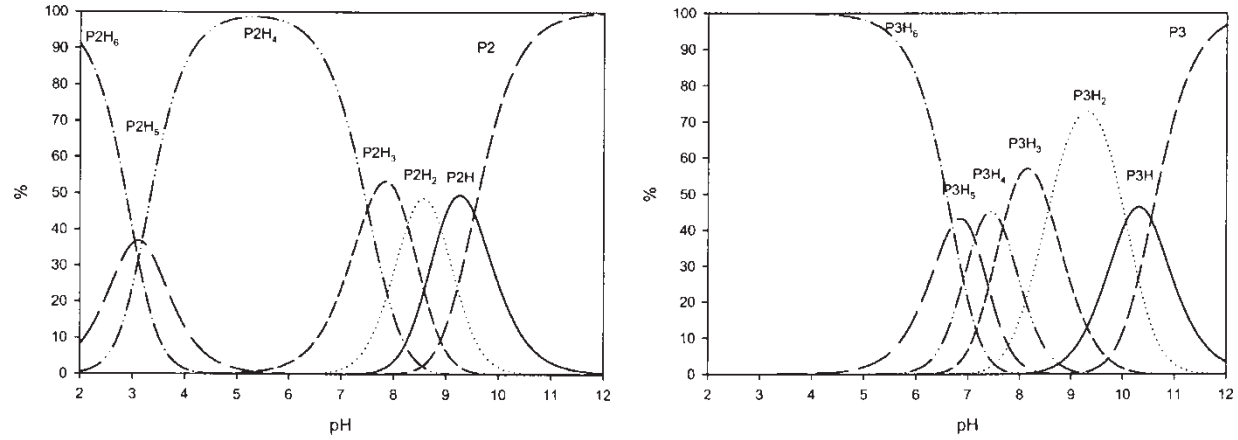


FIGURE 1 Species distribution diagrams for the P2 and P3 ligands a function of p[H].

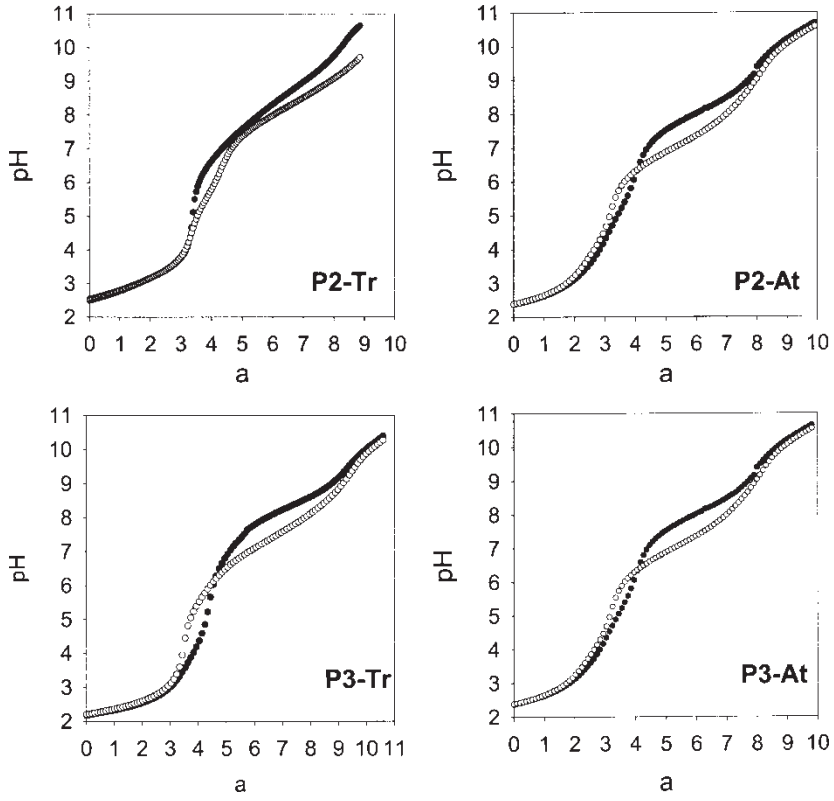


FIGURE 2 (•) Experimental curves obtained for the potentiometric titrations of equilibrated Tr and ATP substrates with the P2 and P3 ligand receptors. All ligands at a concentration of 2.0×10^{-3} M with $\mu = 0.1$ M (KCl) at 25.0 °C. (○) Calculated potentiometric curves for the same systems assuming there is no interaction between the substrate and the ligand.

^{1}H NMR experiments with 1:1 mixtures of free ligand and substrate were also carried out for the ligands P2 and P3 with the Tr and At substrates at pH 4.5–5.9 The results of these experiments for the P3-Tr and P3-At systems are shown in Table III together with their coordination induced shift (CIS) values. The shift in nearly all the resonances of the ligands together with the shift in the aromatic resonances of the nucleotide provide further evidence not only of the coordination of the substrate by the ligand receptor but also of the existence of $\pi-\pi$ interactions between the aromatic rings of the ligands and of the At substrate.

TABLE II Stepwise association constants (K) for the interaction of ligand (L = P2, Bd, P3 and Bn) and substrate (S = Tr and At) at 25.0 °C and $\mu = 0.10$ M (KCl). Charges have been omitted for clarity

Stoichiometry L S H	Equilibrium	P2	Bd	P3	Bn
Tripolyphosphate (Tr)					
111	[HLTr]/[HL][Tr]	2.99	3.51	–	–
112	[H_2LTr]/[H_2L][Tr]	2.88	–	2.57	–
113	[H_3LTr]/[H_3L][Tr]	3.66	4.71	3.28	–
114	[H_4LTr]/[H_4L][Tr]	4.27	6.47	4.31	4.56
115	[H_5LTr]/[H_5L][Tr]	8.88	10.85	5.56	6.61
116	[H_6LTr]/[H_6L][Tr]	12.02	14.19	7.01	8.60
117	[H_7LTr]/[H_6L][HTr]	9.17	11.06	5.87	6.76
118	[H_8LTr]/[H_6L][H_2Tr]	6.61	7.57	4.33	4.52
	$\sigma_{fit} \times 1000$ or ref.	6.5	37	6.9	77
ATP (At)					
111	[HLAt]/[HL][At]	2.61	–	2.14	–
112	[H_2LAt]/[H_2L][At]	2.75	–	2.59	–
113	[H_3LAt]/[H_3L][At]	3.25	3.35	3.00	2.59
114	[H_4LAt]/[H_4L][At]	3.97	5.27	3.71	4.07
115	[H_5LAt]/[H_5L][At]	7.44	8.69	4.76	5.76
116	[H_6LAt]/[H_6L][At]	9.83	11.16	5.67	7.13
117	[H_7LAt]/[H_6L][HAt]	7.05	7.88	4.42	4.97
118	[H_8LAt]/[H_6L][H_2At]	6.01	5.42	3.79	4.20
	$\sigma_{fit} \times 1000$ or ref	5.3	30	7.4	77

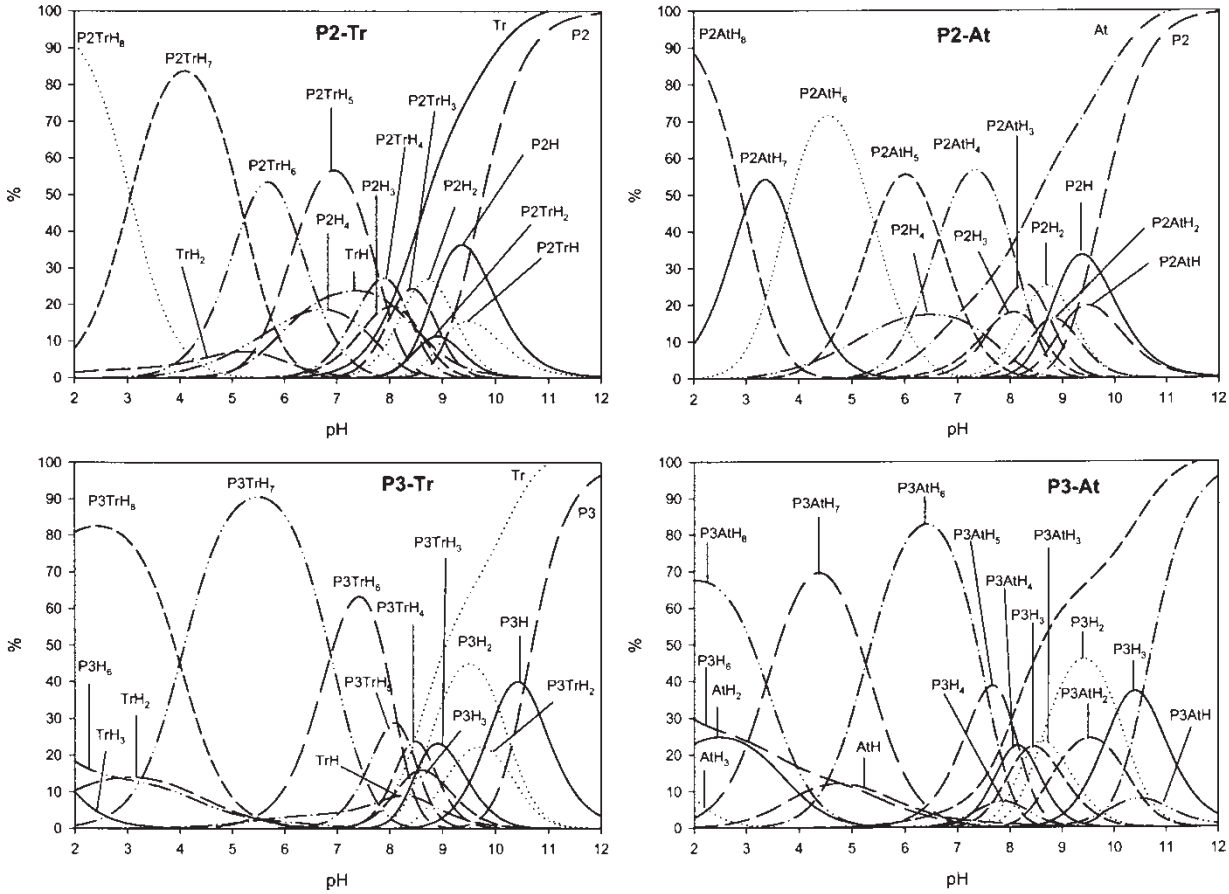
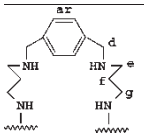


FIGURE 3 Species distribution diagrams as a function of p[H] for the P2-Tr, P2-At, P3-Tr and P3-At systems.

TABLE III ^{1}H NMR chemical shifts (δ) for the P3-At and P3-Tr complexes together with complexation-induced ^{1}H NMR chemical shifts (CIS, ppm)* for selected protons

		^{1}H NMR chemical shift and (CIS)/δ						
H-labeling scheme	Complex	ar	d	e, g	f′	h	i	j
	H_6P3At^{2+}	7.42	4.17	3.06	2.10	8.42	8.15	6.09
	(pH = 4.7)	(0.12)	(0.09)	(−0.04)	(−0.08)	(0.12)	(0.14)	(0.07)
	H_6P3Tr^{+}	7.59	4.26	3.13	2.19			
	(pH = 5.9)	(−0.06)	(−0.04)	(−0.13)	(−0.19)			

*Negative CIS values are upfield.

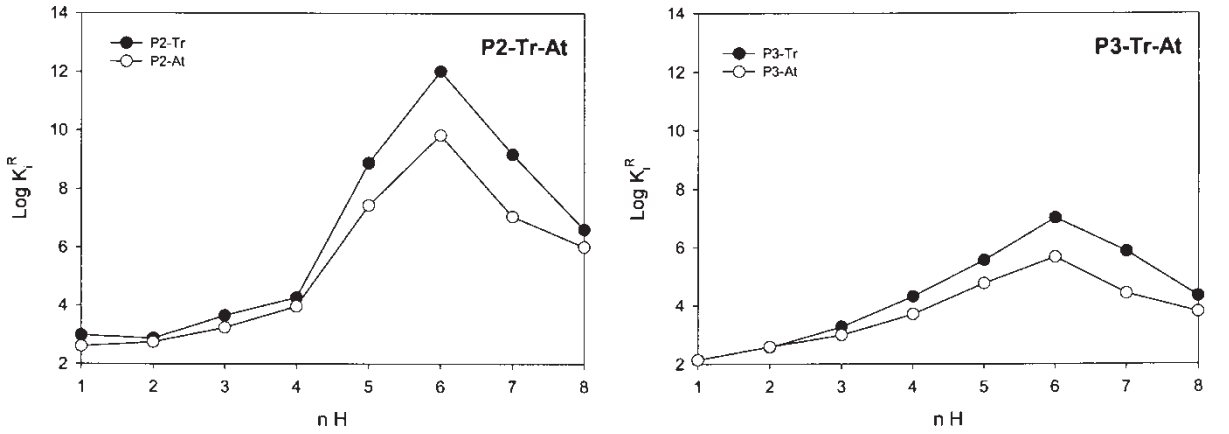
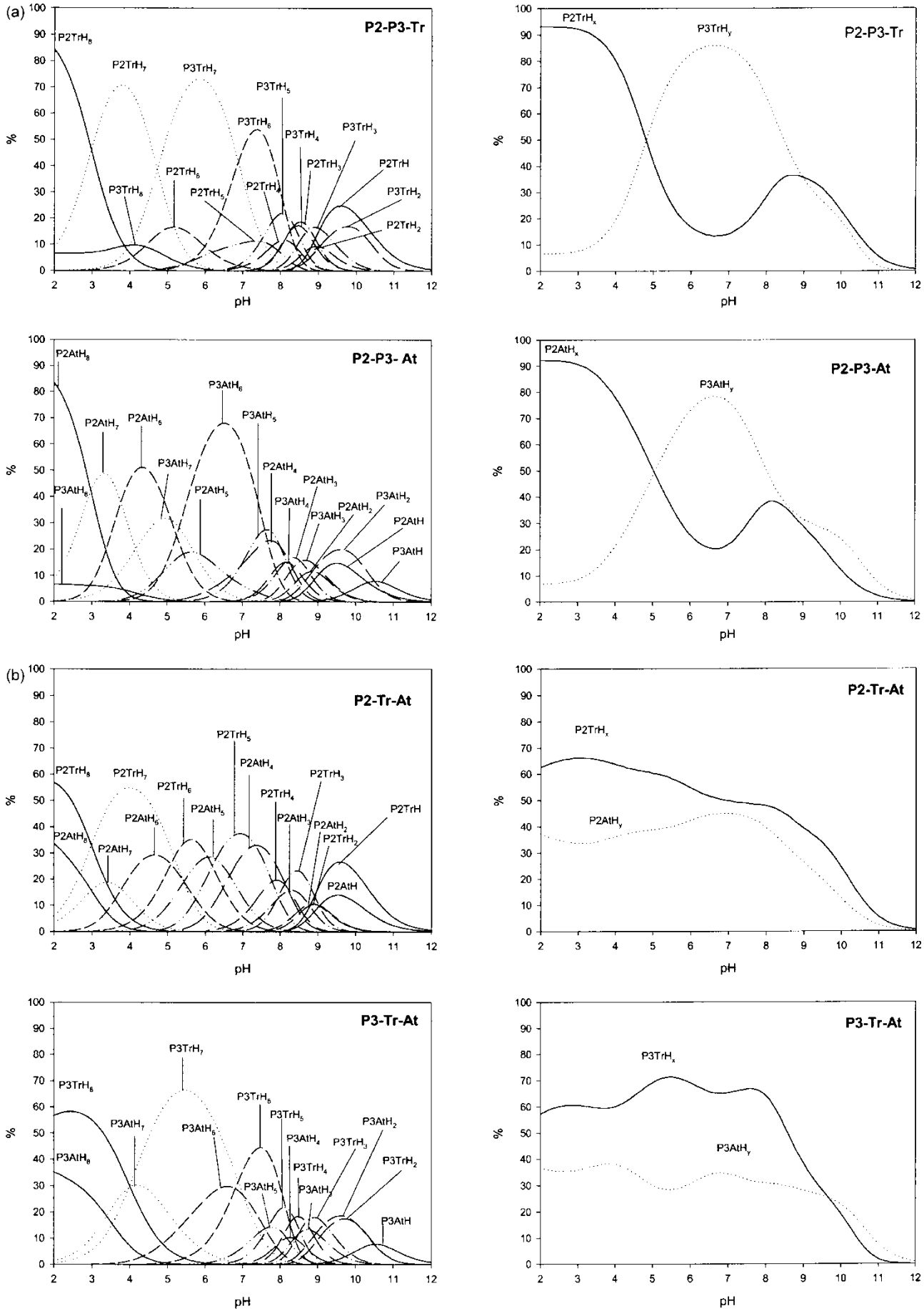


FIGURE 4 Plots of log K_i^R versus nH (the different ternary species with various degree of protonation) for the P2-Tr and P2-At systems (left) and the P3-Tr and P3-At systems (right).



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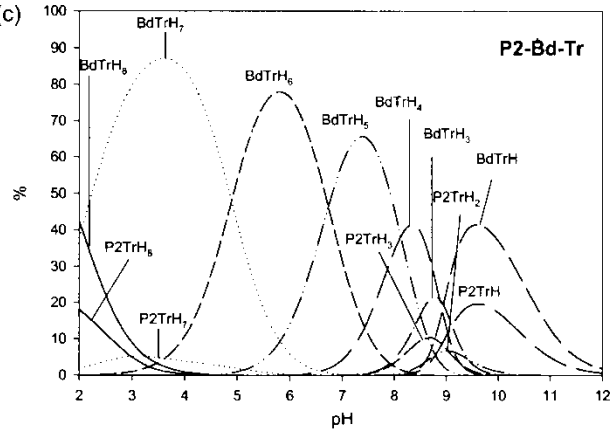

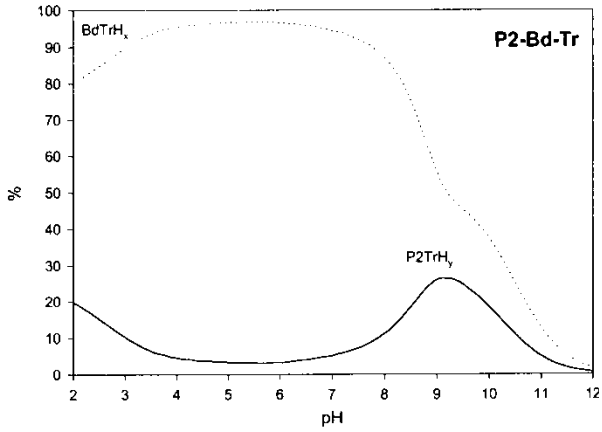

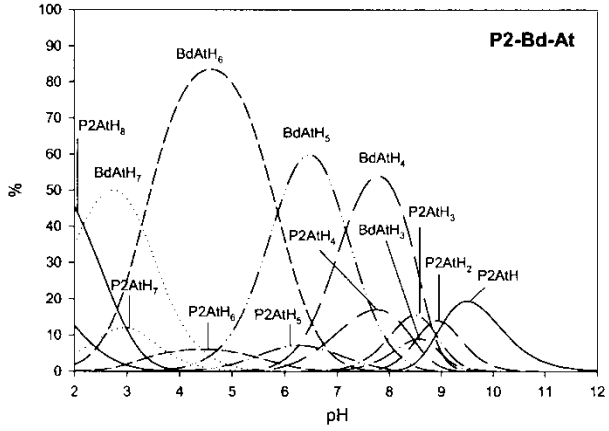

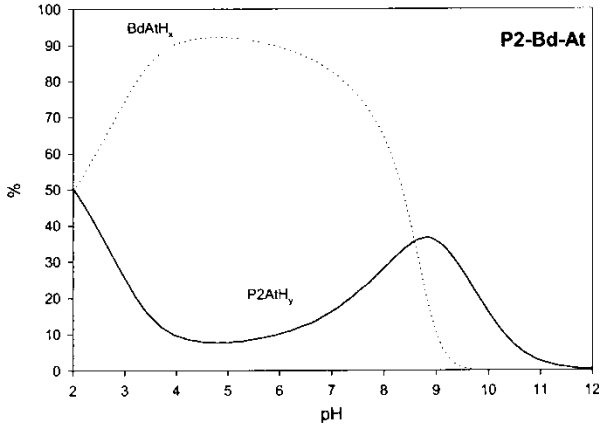

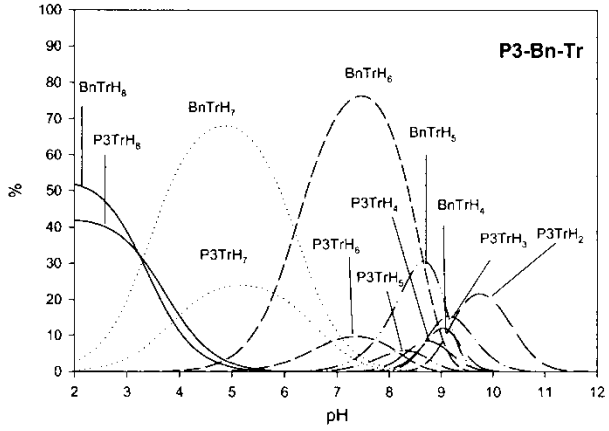

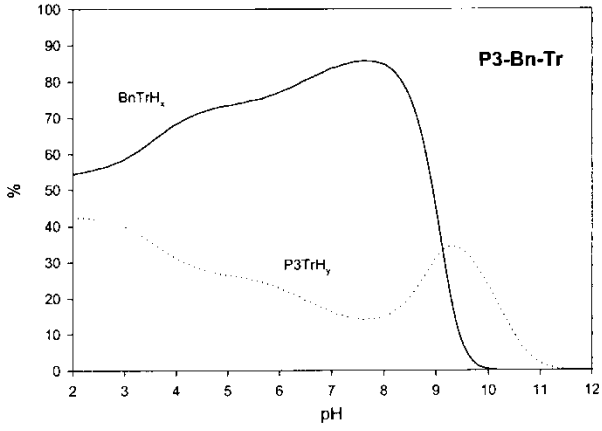

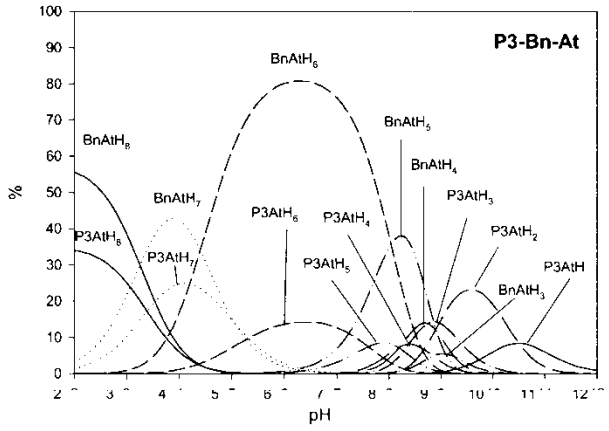

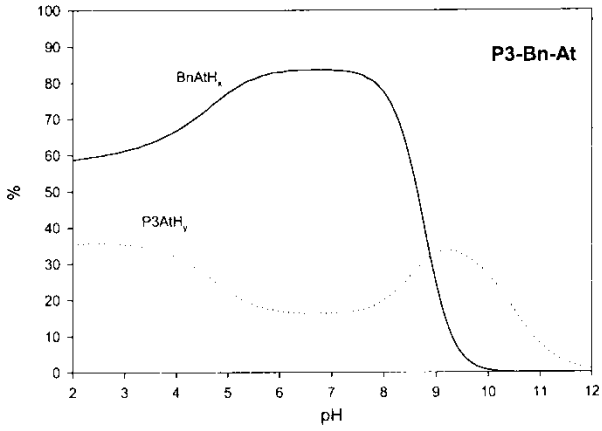

Competitive Diagrams and Selectivity

Figure 4 shows graphical representations of the different recognition constants as a function of proton content obtained for the P2 and P3 ternary systems formed with the Tr and At substrates. From these plots it is clear that the $\log K_i^R$ values are all larger for the P2-Tr than for the P2-At system, thus indicating a stronger complexation strength for the tripolyphosphate than for the ATP nucleotide. The same phenomenon is also observed for the P3-Tr and P3-At systems, thus clearly indicating that for polyphosphates with the same number of phosphorus atoms the Coulombic interaction is a dominant factor and that the potential π-stacking interactions in the nucleotide cases are of a much lower strength. This is further illustrated in Fig. 5b, where for the P2-Tr-At competitive system the P2:Tr:H_i species always predominate over the P2:At:H_i species in the entire pH range. The same is also true for the P3-Tr-At competitive systems except for a small pH range between 10.0 and 12.0.

When comparing the two diagrams of Fig. 4 it is clear that the less basic P2 (40.42) ligand in all cases presents higher $\log K_i^R$ values for a specific substrate than the P3 (50.64), that is a similar ligand but containing four more methylenic units within the secondary amines. However, the formation of stronger ternary complexes does not ensure a predominance of the stronger receptor over the entire pH range as shown in Fig. 5a. For instance, for the P2-P3-Tr competitive system at low pH the P2:Tr:H_i species dominate but for the pH range 5.0−8.0 the selectivity is reversed. This is because of the way the different protonated species of the free ligands P2 and P3 are distributed over the pH range as shown in Fig. 1.

At this point it is interesting to describe the isomeric effect produced over the substrates due to the different *meta* and *para* substitutions of the receptor ligands. This is an important comparison because the two isomers have nearly the same basicity (P2, 40.42; Bd, 40.42; P3, 50.64; Bn, 50.32) and thus the differences in the strengths of the ternary complexes will be a direct measure of the fit of the substrate with the size and shape of the receptors.

For the ternary systems with the Tr substrate the Bd ligand forms stronger complexes than the P2 ligand. In the particular case of K_6^R they differ by more than two orders of magnitude as shown in Eqs. (6) and (18).

$$H_6Bd^{6+} + Tr^{5-} \rightleftharpoons H_6BnTr^{+} \quad \log K_6^R = 14.19 \qquad (18)$$

Hence the competitive distribution diagram (Fig. 5c) shows a strong predominance of the Bd:Tr:H over the P2:Tr:H ternary species (from pH 2 to 12). At pH 5.0, for instance, the selectivity of Bd-containing species over P2 is 97.6% (the selectivity for Bd-containing species over P2 at a particular pH is defined according to the following equation: $\{\Sigma_i(\%H_i : Bd : Tr)/[\Sigma_i(\%H_i : Bd : Tr) + \Sigma_i(\%H_i : P2 : Tr)]\} \times 100$). This phenomenon is also observed for the other two pairs of isomer receptors Bn and P3, although to a slightly smaller extent (see Fig. 5c). In the former case the selectivity of Bn-containing species over P3 is 85.7%. A parallel phenomenon also takes place for the nucleotide substrate At with 98% and 45% selectivities of Bd and Bn over P2 and P3, respectively.

The results just described for the formation of anionic complexes with the Tr and At substrates clearly indicate that the Bn and Bd ligand receptors are more capable of recognizing these substrates than their isomeric P3 and P2 ligands. This recognition capacity, given the similarity in the chemical nature of Bn and P3 and of Bd and P2, arises only because of the different shape and/or size of the cavity of those two pairs of ligands. Thus the Bn and Bd ligands, which have a smaller and more rectangular cavity than their P3 and P2 isomeric counterparts, are capable of better fitting the Tr and At substrates and thus form much stronger complexes.

EXPERIMENTAL

Materials

GR grade KCl was obtained from Aldrich and CO_2-free Dilut-it ampoules of KOH were purchased from J. T. Baker Inc. Sodium tripolyphosphate (technical grade, 85%) was purchased from Aldrich Chemical Co. and was purified by repeated crystallization from aqueous solution by the addition of methanol [81]. Adenosine-5′-triphosphate disodium salt hydrate (ATP) was purchased from Aldrich Chemical Co. The KOH solution was standardized by titration against standard potassium acid phthalate with phenolphthalein as indicator and was checked periodically for carbonate content (<2%) [82]. Ligands P2 and P3 (see Chart 1 for abbreviations used) were synthesized and characterized according to previously published procedures [55, 79].

Potentiometric Titrations

Potentiometric measurements were conducted in a jacketed cell thermostated at 25.0 °C and kept under an inert atmosphere of purified and humidified argon. A Crison pH meter (model 2002) was used equipped with a glass electrode and a Ag/AgCl reference

FIGURE 5 (a) Competitive calculated species distribution diagrams for systems with equimolecular amounts of the Tr and At substrates with the P2 ligands together with the corresponding total species distribution diagrams and for the P3-Tr-At competitive system. (b) The same for the competitive systems P2-P3-Tr and P2-P3-At. (c) The same for the systems P2-Bd-Tr, P2-Bd-At, P3-Bn-Tr and P3-Bn-At.

electrode with saturated KCl as internal solution. The volume of titrating agent added to the reaction mixture was controlled by means of an electronic Crison burette with a nominal volume of 2.5 mL. The support electrolyte used to keep the ionic strength constant at 0.10 M was KCl. The electrodes were calibrated by titrating a small amount of HCl at an ionic strength of 0.10 M and a constant temperature of 25 °C and determining the titration end point by the Gran method [83], which allows calculation of the electrode standard potential (E^0). $\log K_w$ for the system, defined in terms of $\log([H^+][OH^-])$, was found to be -13.78 at the ionic strength used [84] and was kept fixed during refinements.

Acid dissociation constants for the ATP and tripolyphosphate were determined under the same conditions used in this work and were found to agree well with data from the literature [84].

Potentiometric measurements of solutions containing either the ligand or the ligand plus equimolecular amounts of ATP or tripolyphosphate were run at a concentration of 2.0×10^{-3} M and an ionic strength of $\mu = 0.10$ M (KCl). At least 10 points per neutralization of every hydrogen ion equivalent were acquired, repeating titrations until satisfactory agreement was obtained. A minimum of three consistent sets of data was used in each case to calculate the overall stability constants and their standard deviations. The standard deviations calculated for the different recognition constants have a value of ± 0.02. The range of accurate p[H] measurements was considered to be 2–12. Equilibrium constants and species distribution diagrams were calculated using the programs BEST [82] and SPEXY‡, respectively.

^{1}H NMR Experiments

^{1}H NMR spectra were recorded on a Bruker 200 MHz spectrometer in D_2O using DSS as internal standard (chemical shifts are reported downfield from DSS) The measurements were carried out on equilibrated Tr or At substrates (1.0×10^{-3} M) with the ligands P3 or P2 (1.0×10^{-3} M) at 300 K. The pH was adjusted to the desired value upon addition of small amounts of a 0.1 M KOD solution in D_2O.

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‡SPEXY is a program created by R. J. Motekaitis that generates an X–Y file that contains the concentration of all the existing species in solution as a function of p[H] using BEST output files.

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