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Lipophilic ditopic guanidinium receptors: selective extractants for tetrahedral oxoanions*

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Ditopic open-chain guanidinium receptors have been developed especially for a selective extraction of tetrahedral oxoanions. The anion extraction behaviour of these host compounds has been studied in the system sodium salt-H_2O-buffer/host-$CHCl_3$. Lipophilic bisguanidines are capable of extraction of even strongly hydrated anions as hydrogen phosphate, sulfate and nucleotides over a wide pH range. A remarkable selectivity of sulfate over hydrogen phosphate was obtained using receptors 2, 5 and 7. The ditopic host 2 shows a pronounced preference for ATP versus ADP and AMP. The 1:1 complex formation observed in the organic phase points to a well-organized complex structure for the oxoanions investigated and ditopic hosts.

INTRODUCTION

The vital dependence of life on the presence and turnover of inorganic phosphate legitimates the current strive to influence its uptake and metabolism. Among all metabolic reactions the formation of phosphate esters, phosphoryl amidates or phosphoric anhydrides appears to be most fundamental. One of the multitude of biological functions of phosphorylation is simply the prevention of passive transport of substrates across compartment boundaries (membranes)[1]. Vital metabolites by virtue of covalent binding to phosphoryl groups thus may be kinetically trapped within a membrane enclosed volume unless a dedicated transport system allows the exchange of this anionic species. The reason for the inability of phosphate and its esters to pass the membrane phase by passive diffusion lies in its tremendous hydration free energy[2] ($\Delta G_{hydr}\{H_2PO_4^-\} = -465$ kJ•mol^{-1}; $\Delta G_{hydr}\{PO_4^{3-}\} = -2765$ kJ•mol^{-1}), which places these anions at the extreme hydrophilic end of the Hofmeister series[3].

Certain promising chemotherapeutic approaches for the treatment of viral infections (e.g. "antisense" nucleotide[4]), require efficient transport of externally applied polyanionic phosphoryl species across the cell membrane of the like charge. An artificial carrier would be beneficial if not essential to the success of this method[5]. This perception caused various attempts to construct synthetic host molecules which would bind phosphate esters (i.e. nucleotide) in aqueous solution[6,7]. One can distinguish approaches based on recognition of the hydrophobic ester moiety (the nucleotide base) from an alternative that is primarily directed towards the complexation of the anionic phosphate substructure. Only the latter may eventually function as a carrier system, because it is of prime importance to replace the hydration shell around phosphate by a specific ligand (receptor) in order to extract the entire guest from water into the hydrophobic membrane phase. Following this idea some very simple and some more sophisticated examples for phosphate ester transport have been tested and described in the literature[8]. The comparison and reliable assessment of these systems, however, is complicated by non-standardized experimental conditions. Transport rates as the true parameters of merit of a carrier system depend on a multitude of influential factors including even the geometry of the transport cell and the stirring speed etc. The effects of differences in the experimental set up used by different laboratories are thus quite hard to predict and hamper a straightforward evaluation of the basic transport properties of a carrier under study. As a corollary it is quite hard to pinpoint enhanced transport rates reported to well defined improvements of carrier design.

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In addition to the development of transport systems the phase transfer of phosphate and its esters may be exploited for the construction of ion-selective sensors[9]. If some receptors can be designed that would bring about the selective and fast transfer of phosphate guests from the aqueous environment to a membrane phase, this basic complexation event could be coupled to electrochemical or optical signalling to make up an on-line sensing device[10]. Phosphate sensors are in high demand as no satisfactory device is currently available, but concern about the role of phosphate in the environment, and thereby the need for analysis is ever increasing[11].

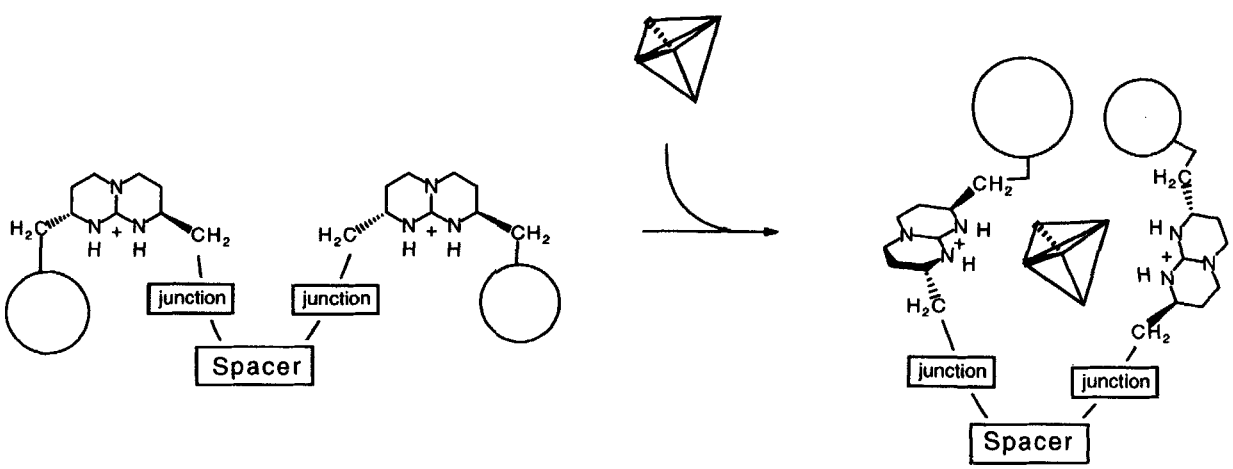
With these possible applications in mind we embarked on the construction of phosphate (ester) receptors capable to serve as carriers in the transfer of these hydrophilic guests to an apolar organic phase. Towards this goal a number of features appeared essential: i) The receptor was to interact with the anionic phosphate moiety in an highly dedicated fashion. This should outmatch the solvation energy and give an host-guest complex of decent stability. ii) Unspecific charge-charge interactions, however, had to be minimized, in order not to harm guest-selectivity and to maintain low overall hydrophilicity. iii) The host should display extreme distribution behaviour in solvent mixtures for the organic solvent to avoid leakage of the carrier into the aqueous phase. iv) The receptor design should allow for rapid complexation/decomplexation rates across phase boundaries since slow exchange rates most frequently limit overall transport or cause a sluggish response of membrane-based sensors[10].

Our concept to meet these challenges[12] is based on foldable guanidinium hosts (scheme 1), which make use of bicyclic guanidines as the fundamental receptor units[13] connected to each other via an aromatic spacer moiety. As the guanidinium anchor group is prominent for its dedicated and structured binding of oxoanions in natural as well as in artificial receptors[14] one can predict that both guanidinium substructures will fold in an hinge motion to pinch the phosphate guest between them. Owing to the chirality of the bicycles their main planes will align in perpendicular fashion. This sets the stage for an optimum hydrogen bonding network that is complementary to the topology of tetrahedral oxoanions.

The synthesis of the ensemble of hosts **1-8** (figure 1) and the binding properties of some members with anionic guests in homogeneous protic solution have been communicated[12a,15]. Here we want to report on the anion extraction behaviour of this host series in the two phase system sodium salt-H_2O-buffer/host-$CHCl_3$. The aim of our investigations consists in the search for structure-reactivity relationships. Thus, spacer dimensions were modified and connection functions and overall hydrophobicity were altered. Liquid-liquid extraction chosen as the method for study compares favourably with respect to accuracy, reproducibility, speed and expressiveness with standard transport experiments, and allows to delineate advantages and weaknesses in the design of this family of hosts.

RESULTS AND DISCUSSION

The investigations performed show that a sufficient lipophilicity of the receptors is a prerequisite for an effective phase transfer. Using compounds **3**, **4**, **6** and **8** possessing a OH group at the molecule periphery a graduated complex formation were found, but the extraction experiments were accompanied by difficulties as the formation of a third phase, precipitation and poor coalescence behaviour. Obviously, owing to the hydrophilic character these receptors are not able to form hydrophobic complexes with oxoanions which are well-soluble in organic diluents[16]. Therefore, only the highly lipophilic



Scheme 1 Conceptual sketch of complex formation of foldable ditopic guanidinium hosts with tetrahedral oxoanions

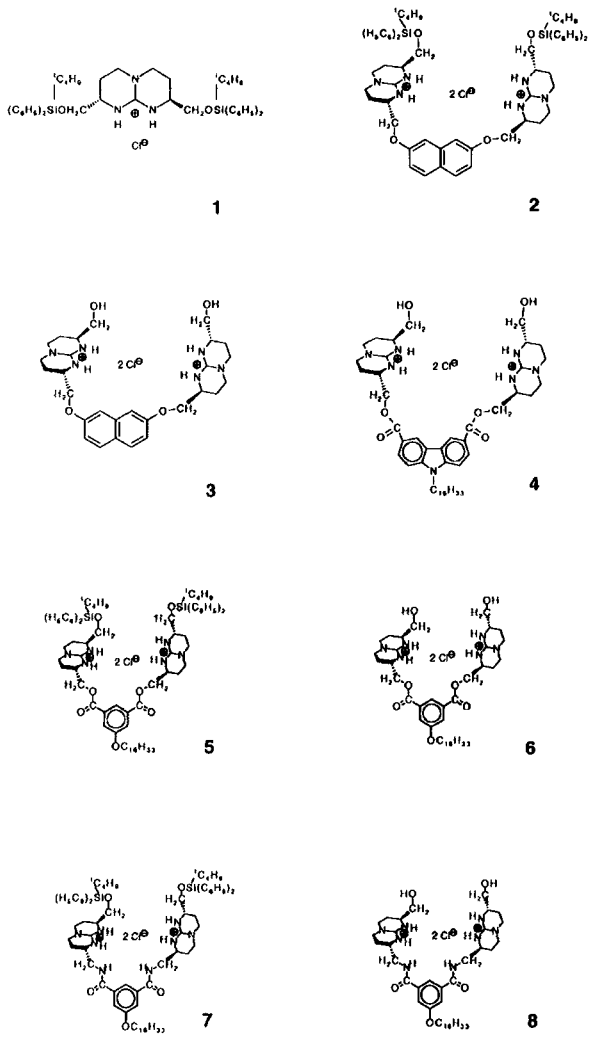


Figure 1 Investigated compounds.

ditopic guanidinium compounds **2**, **5** and **7** have been used for the subsequent extraction experiments. Furthermore, the monotopic guanidinium receptor **1** has been included in these investigations for comparison. The extraction equilibrium with these compounds is achieved very fast which is useful in view of a practical application.

The liquid-liquid extraction equilibrium of an anion X^{n-} with a guanidinium chloride $L^{m+}Cl_m^-$ is generally described by eq. (**1**):

$$pX_{(w)}^{n-} + s \cdot (L^{m+} \cdot Cl\bar{m})_{(org)} \overset{K_{Ex}}{\rightleftharpoons} (L_s^{m+} \cdot X_p^{n-})_{(org)} + (n \cdot p)Cl_{(w)}^- \quad (1)$$

with $s \cdot m = n \cdot p$; the subscripts (org) and (w) denote the organic and aqueous phase, respectively. The extraction constant is then defined by eq. (**2**):

$$K_{Ex} = \frac{\left[(L_s^{m+} \cdot X_p^{n-})\right]_{(org)} \cdot [Cl^-]_{(w)}^{(n \cdot p)}}{[X^{n-}]_{(w)}^{p} \cdot \left[(L^{m+} \cdot Cl_m^-)\right]_{(org)}^{s}} \quad (2)$$

The distribution ratio D_X of the anion X^- describes the phase transition quantitatively defined in eq. (**3**)

$$D_X = \frac{[X]_{(org)}}{[X]_{(w)}} \quad (3)$$

The composition of the extracted species can be determined from the experimental data by graphical slope analysis or nonlinear curve fitting using eq. (**2**) and (**3**)[17].

In case of a 1:1 complex formation between a ditopic guanidinium salt $L^{2+}Cl_2^-$ and a divalent anion X^{2-} the extraction reaction can be analyzed using eq. (**4**):

$$Log\ D_X = Log\ K_{Ex,1} + s \cdot Log[L^{2+}Cl_2^-]_{(org)} - 2 \cdot Log\ [Cl^-]_{(w)} \quad (4)$$

Under experimental conditions of constant ionic strength in the aqueous phase and excess of the receptor compared with the anion concentration, the slope of the line in the Log D_X − Log $c_{Receptor}$ diagram gives the stoichiometric coefficient s of the formed complex[18].

Figure 2 shows the results of extraction investigations of different anions with compounds **1** and **2**. The monotopic guanidinium compound **1** extracts only the hydrophobic monocharged anions bromide and iodide. Under the experimental conditions chosen[19] the oxoanions hydrogen phosphate, sulfate and the nucleotides AMP, ADP and ATP are practically not extracted.

In contrast to this, high extractabilities of oxoanions, in particular for sulfate, ADP and ATP, are obtained with the ditopic guanidinium receptor **2**. Amazingly, a high selectivity of sulfate over hydrogen phosphate is found. Sulfate and hydrogen phosphate are similar anions with respect to their size, geometry and Lewis-basicity[20]. One possible reason for the preference of sulfate over hydrogen phosphate during extraction might be the lower hydration free energy for sulfate[2, 21]. In the case of hydrogen phosphate the remaining proton can form additional hydrogen bonds to water, and consequently the host-guest complex should be more hydrophilic with respect to sulfate.

Furthermore, a remarkable graduation of nucleotide extraction[22] was observed. Thus, a pronounced selectivity of ATP over ADP and AMP is found correlating with the rising charge of the nucleotides.

Slope analyses of straight lines obtained in the Log D_X-Log $c_{Receptor}$ diagram (figure 3) indicate the stoichiometry of complex formation of the monotopic guanidinium compound **1** with the monovalent anions

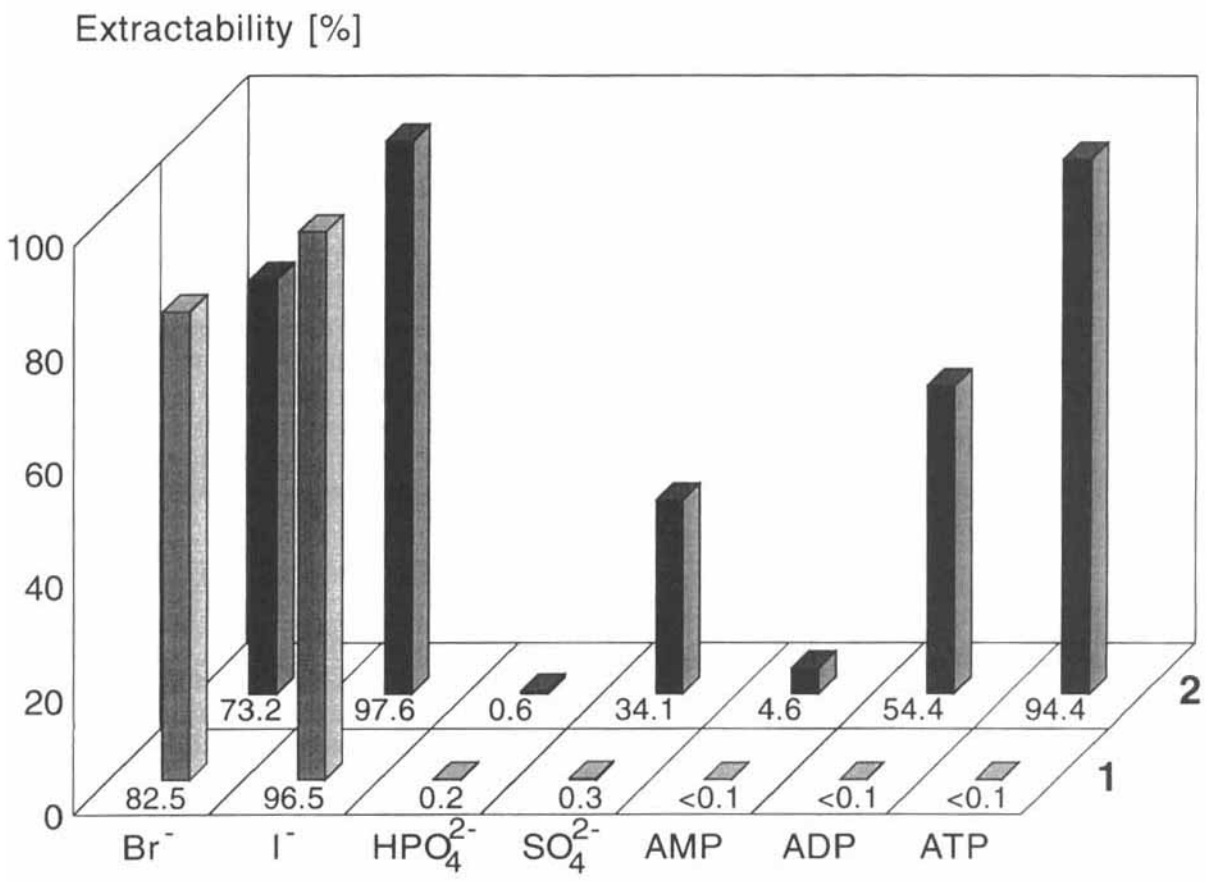


Figure 2 Extractability of anions with the monotopic and ditopic guanidinium compound **1** and **2.**
{[NaX, (Na_2X)] = $1 \cdot 10^{-4}$ M (X = Br^-, I^-, SO_4^{2-}, HPO_4^{2-}); pH = 8.7 (TAPS/NaOH-buffer); [nucleotide] = $1 \cdot 10^{-4}$ M; pH = 7.4 (HEPES/NaOH-buffer); [receptor] = $1 \cdot 10^{-3}$ M in chloroform}

bromide and iodide as 1:1 (anion : receptor), and with the divalent sulfate and hydrogen phosphate ions as 1:2.

As shown in figure 4, the slope of the extraction line for hydrogen phosphate with the ditopic guanidinium receptor **2** in the Log D_X-Log $c_{Receptor}$ diagram points to the preferred formation of a 1:1 complex in the organic phase. In the case of sulfate extraction, the relating slope is lower than 1 and indicates additional interactions. The reason of this behaviour is probably a coextraction of the buffer anion[23]. At the pH of 8.7 the used buffer TAPS (pK_a = 8.55) is preponderantly in its anionic form. Switching the pH to 7.8 the coextraction is considerable suppressed, since the major buffer species now is the zwitterion. As can be seen in figure 5, at the pH of 7.8 the slope of the Log D_X-Log $c_{Receptor}$ diagram indicates the expected 1:1 complex formation of the ditopic host **2** with sulfate in the organic phase. In addition the extractability of sulfate is improved by twofold.

Likewise, the bisguanidinium host **2** forms only 1:1 complexes with the nucleotides investigated (figure 5). This fact in the case of AMP is readily understandable. At pH 7.8 AMP dissociates almost completely in aqueous solution[24]. But the same behaviour is characteristic for ADP and ATP, too. Nevertheless, a 1:1 complex formation of the dication **2** with ADP and ATP was observed indicating also the presence of dianions of these nucleotides in the organic phase, which might eventually be formed by supplementary association of sodium ions. To clarify these findings further investigations especially on the structure of the complexes formed are necessary. Another noticeable result is the decreasing slope[25] of the curves in the region of higher receptor concentrations which can be caused by a limited lipophilicity of the complexes formed in the organic phase. Altogether, the selectivity of nucleotide extraction using the ditopic host **2** is considerable. Under the experimental conditions given in figure 5, the distribution ratios for the extraction of ATP are more than one or even two orders of magnitude higher relative to ADP and AMP extraction, respectively.

The separation selectivity as a whole strongly depends on both the pH and the composition of the aqueous phase. This is illustrated in figure 6 using three different buffer systems. As expected the nucleotide extraction is rather poor at the low pH region where AMP, ADP and ATP are not completely dissociated. At a pH higher than 7, especially ATP can be efficiently extracted with pronounced selectivity towards ADP and AMP, respectively.

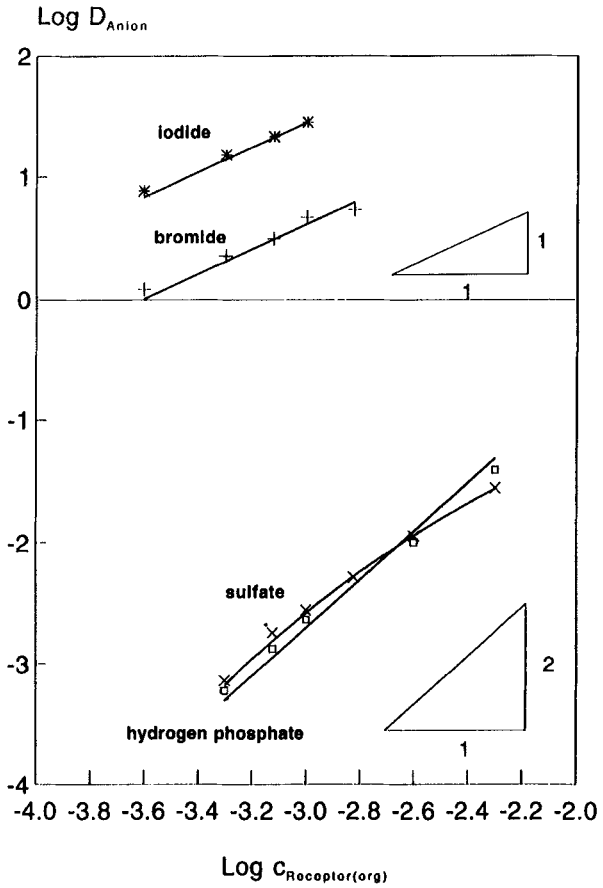


Figure 3 Extraction of anions with a monotopic guanidinium compound **1** as a function of receptor concentration.
{[NaX, (Na_2X)] = $1 \cdot 10^{-4}$ M (X = Br^-, I^-, SO_4^{2-}, HPO_4^{2-}); pH = 8.7 (TAPS/NaOH-buffer); [receptor **1**] = $2.5 \cdot 10^{-4}$...$5 \cdot 10^{-3}$ M in chloroform}

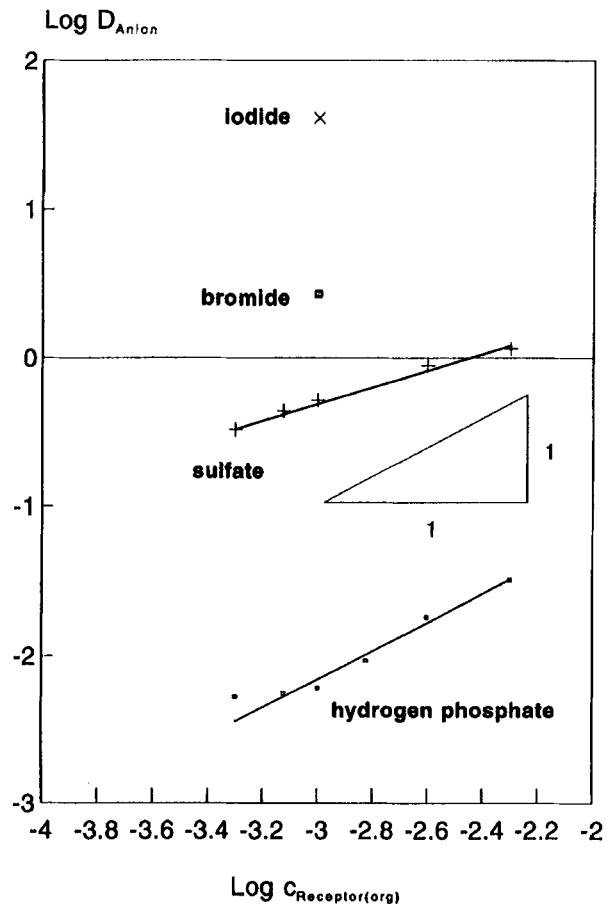


Figure 4 Extraction of anions with a ditopic guanidinium compound **2** as a function of receptor concentration.
{[NaX, (Na_2X)] = $1 \cdot 10^{-4}$ M (X = Br^-, I^-, SO_4^{2-}, HPO_4^{2-}); pH = 8.7 (TAPS/NaOH-buffer); [receptor **2**] = $2.5 \cdot 10^{-4}$...$5 \cdot 10^{-3}$ M in choloroform}

Remarkable, the nucleotide extraction decreases with rising pH in all buffer systems investigated. This is probably caused by the coextraction of the buffer anion discussed above. On the other hand the concentration of sodium increases with rising pH. Due to the increasing formation of nucleotide complexes with sodium[26] in the aqueous phase the concentration of free nucleotides is degraded, and consequently the nucleotide extraction goes down.

By variation of the spacer and junction elements the size and rigidity of the ditopic guanidinium compounds can be altered, and thus the oxoanion extraction efficiency and selectivity is influenced. Figure 7 shows the results of anion extraction with the ditopic receptors **5** and **7** having a isophthalic acid spacer moiety. As can be seen (cf. figure 2), the replacement of the naphthalene spacer element (host **2**) in the molecule by the smaller and more flexible isophthalic acid (host **5**) leads to a decrease of the nucleotide extraction. This result indicates that the dimension of the spacer strongly determines the extraction properties. Introducing an amide group as junction element (host **7**), the receptor becomes more rigid. On top, the secondary amide groups may form additional hydrogen bonds to the guest. The ditopic host **7** strongly extracts all the oxoanions investigated. Surprisingly, the strongly hydrated sulfate anion is almost quantitatively transferred into the organic phase. The extractability of sulfate is even higher than the extraction of the hydrophobic iodide. Certainly, the strong complex formation leads to a loss of separation selectivity proven especially for the nucleotide extraction.

The remarkable anion extraction behavior of host **7** is obviously caused by the cooperative effect of the hydrogen bonding of the amide groups superimposed on the general ionic interactions of the guanidinium moieties with the guest.

CONCLUSIONS

Selective anion recognition and their effective phase transfer from aqueous into organic phase require a perfect complementarity of the topology of the host designed and the anionic substrate connected with a high

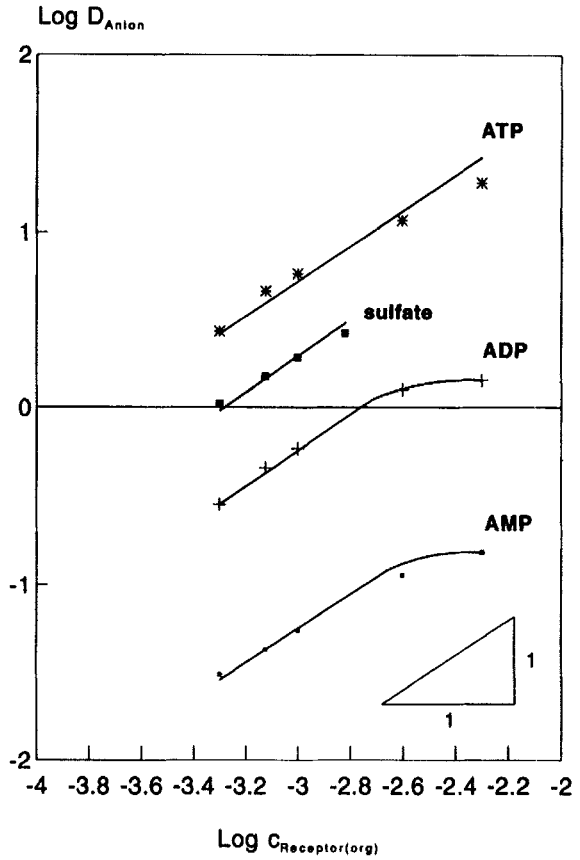


Figure 5 Extraction of sulfate and nucleotides with guanidinium compound **2** as a function of receptor concentration.
{[Na_2SO_4, (nucleotide)] = $1 \cdot 10^{-4}$ M; pH = 7.8 (TAPS/NaOH-buffer); [receptor **2**] = $5 \cdot 10^{-4} \ldots 5 \cdot 10^{-3}$ M in chloroform}

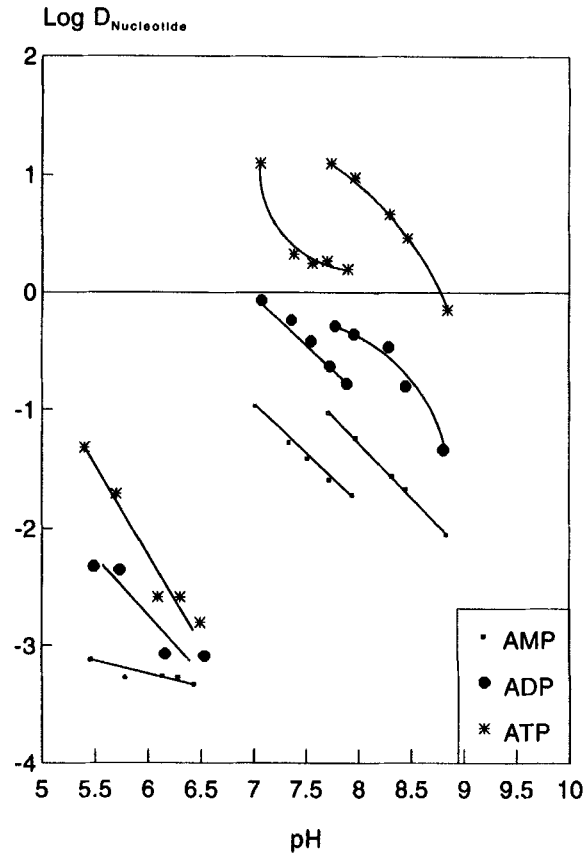


Figure 6 Extraction of nucleotides with guanidinium compound **2** as a function of pH.
{[nucleotide] = $1 \cdot 10^{-4}$ M; [receptor **2**] = $1 \cdot 10^{-3}$ M in chloroform; pH = 5.4...6.5 (MES/NaOH-buffer); 7.0...8.0 (HEPES/NaOH-buffer); 7.7...8.9 (TAPS/NaOH-buffer)}

lipophilicity of the host guest complex formed. A series of ditopic guanidinium compounds was developed especially for the extraction of tetrahedral oxoanions, wherein the selectivity is governed by a combination of electrostatic interactions and ligand-anion complementarity of shape, size, and functionality.

A high lipophilicity of the receptor is a prerequisite for an effective phase transfer. Bisguanidinium compounds possessing OH groups at the molecule periphery are not capable of an effective oxoanion extraction. On the other hand highly lipophilic bisguanidinium receptors extract even strongly hydrated oxoanions like sulfate, hydrogen phosphate and nucleotides from water into chloroform. Remarkable selectivity of sulfate over hydrogen phosphate, and ATP over ADP and AMP extraction are obtained. In all cases the composition of the extracted anion complexes of sulfate, hydrogen phosphate and nucleotides with ditopic hosts is 1:1 reflecting a well-defined complex structure. In contrast to the bisguanidinium compounds the oxoanions investigated are practically not extracted by a monoguanidinium salt.

EXPERIMENTAL

The extraction studies were performed at 25 ± 1°C in 2 ml micro test tubes by means of mechanical shaking. The phase ratio $V_{(org)}:V_{(w)}$ was 1:1 (0.5 ml each); the shaking time was 30 min. In this time the equilibrium was achieved. All samples were centrifuged after extraction. The determination of anion concentration in both phases was carried out radiometrically using the γ-radiation measurement of ^{82}Br and ^{131}I in a NaI(Tl) scintillation counter (Cobra II, Canberra-Packard), and the β-radiation of ^{14}C (nucleotides), ^{32}P and ^{35}S in a liquid scintillation counter (Tricarb 2500, Canberra-Packard). In each case two independent experiments were performed. The experimental error is ≤ 2 % for $D = 10^{-2} \ldots 10^{2}$; in the case of lower extraction ≤ 10 %. The radioisotopes were supplied by Medgenix Diagnostics GmbH, Rathingen. The pH of aqueous solutions were adjusted using Good's buffers; 4-morpholino ethane-sulfonic acid (MES) / NaOH (buffering range 5.4...6.5), 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES) / NaOH

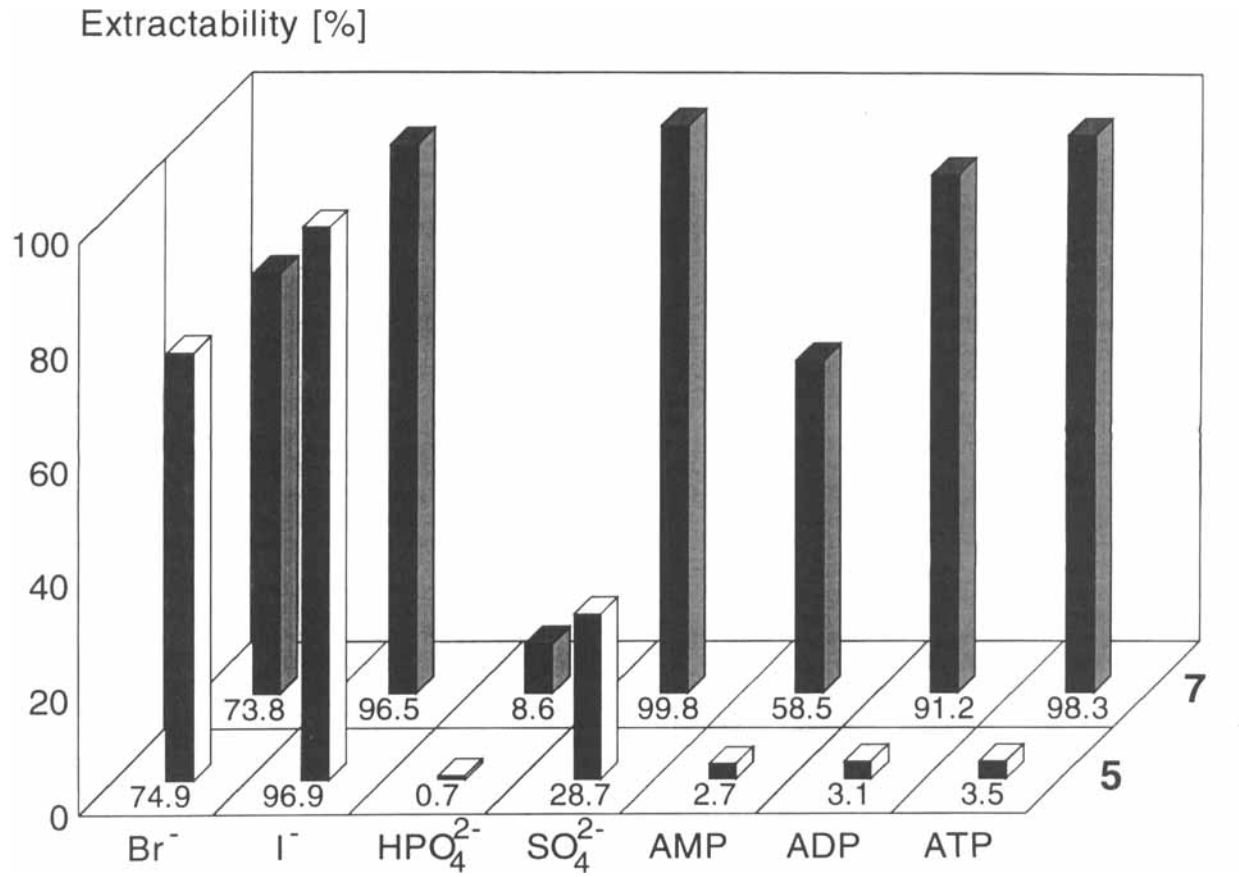


Figure 7 Extractability of anions with ditopic guanidinium compounds **5** and **7**.
{[NaX, (Na_2X)] = $1 \cdot 10^{-4}$ M (X = Br^-, I^-, SO_4^{2-}, HPO_4^{2-}); pH = 8.7 (TAPS/NaOH-buffer); [nucleotide] = $1 \cdot 10^{-4}$ M; pH = 7.4 (HEPES/NaOH-buffer); [receptor] = $1 \cdot 10^{-3}$ M in choloroform}

(7.0...8.0), and 3-([2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-amino)-1-propanesulfonic acid (TAPS) / NaOH (7.7...8.9). 0.05 M buffer solutions were prepared. The TAPS buffer concentration in the organic phase after extraction was determined by ICP-AES (IY38plus, Instruments S. A.) at 181,978 nm (sulfur).

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REFERENCES AND NOTES

1 a) Williams, R.J.P.; Frausto da Silva, J.J.R. *New Trends Bio-Inorg. Chem.* **1978**, 449-84; *idem*, Struct. Bonding **1976**, *29*, 67-121. b) Westheimer, F.H.; in *Phosphorous Chemistry*, ACS Symp. Series 486, ACS, Washington DC, 1992, p. 1-17.
2 Marcus, Y. *J. Chem. Soc. Faraday Trans.* **1991**, *87*, 2995-99.
3 a) Hofmeister, F. *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247. b) Wegmann, D.; Weiss, H.; Ammann, D.; Morf, W. E.; Pretsch, E.; Sugahara, K.; Simon, W. *Microchim. Acta* **1984**, *III*, 1-16.
4 Englisch, K.; Gaus, D.H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 613.
5 Loke, S.L.; Stein, C.A.; Zhang, X.H.; Mori, K.; Nakaniski, M.; Subasinghe, C.; Cohen, J.S.; Neckers, L.M. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 3474-3478.
6 leading references for phosphate/phosphate ester recognition: a) Schieβl, P.; Schmidtchen, F.P. *J. Org. Chem.* **1994**, *59*, 509. b) Hamilton, A.D.; Geib, S.J.; Dixon, R.P. *J. Am. Chem. Soc.* **1992**, *114*, 365-366. c) Rudkevic, D.M.; Stauthamer, W.P.R.V.; Verboom, W.; Engbersen, J.F.J.; Harkema, S.; Reinhoudt, D.M. *J. Am. Chem. Soc.* **1992**, *114*, 9671-9673. d) Kimura, E.; Kuramoto, Y.; Koike, T.; Fujioka, H.; Kodama, M. *J. Org. Chem.* **1990**, *55*, 42-46. e) Valiyaveettil, S.; Engbersen, J.F.J.; Verboom, W.; Reinhoudt, D.N. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 900. f) Iverson, B.L.; Shreder, K.; Kral, V.; Sessler, J.L. *J. Am. Chem. Soc.* **1993**, *115*, 11022-11023. g) Beer, P.D.; Chen, Z.; Goulden, A.J.; Graydon, A.; Stockes, S.E.; Wear, T. *J. Chem. Soc. Chem. Comm.* **1993**, 1834-1836. h) Gross, R.; Bats, J.W.; Göbel, M.W. *Liebig's Ann. Chem.* **1994**, 205-210. i) Bencini, A.; Bianchi, A.; Paoletti, P.; Paoli, P. *Pure Appl. Chem.* **1993**, *65*, 381-386. j) Ariga, K.; Anslyn, E.V. *J. Org. Chem.* **1992**, *57*, 417-419.
7 some recent references on nucleotide binding: a) Marecek, J.F.; Fischer, P.A.; Burrows, C.J. *Tetrahedron Lett.* **1988**, *29*, 6231-34.

b) Bencini, A.; Bianchi, A.; Burguete, M.I.; Domenech, A.; Garcia-España, E.; Luis, S.V.; Niño, M.A.; Ramirez, J.A. *J. Chem. Soc. Perkin Trans. 2*, **1991**, 1445-1451. c) Schneider, H.-J.; Blatter, T.; Palm, B.; Pfingstag, U.; Rüdiger, V.; Theis, I. *J. Am. Chem. Soc.* **1992**, *114*, 7704-7708. d) Dhaenens, M.; Lehn, J.-M.; Vigneron, J.-P. *J. Chem. Soc. Perkin Trans 2*, **1993**, 1379-1381. e) Sasaki, D.Y.; Kurihara, K.; Kunitake, T. *J. Am. Chem. Soc.* **1992**, *114*, 10994-10995. f) Cordier, D.; Mir Hosseini, W. *New J. Chem.* **1990**, *14*, 611-616. g) Furuta, H.; Magda, D.; Sessler, J.L. *J. Am. Chem. Soc.* **1991**, *113*, 978-985. h) Kuroda, Y.; Hatakeyama, H.; Inakoshi, N.; Ogoshi, H. *Tetrahedron Lett.* **1993**, *34*, 8285-8288. i) Schmidtchen, F.P. *Tetrahedron Lett.* **1989**, *30*, 4493-4496. j) Lacy, S.M.; Rudkevich, D.H.; Verboom, D.M.; Reinhoudt, D.N. *Tetrahedron Lett.* **1994**, *35*, 5953-5956.

8 a) Tabushi, I.; Kobuke, Y.; Imuta, J. *J. Am. Chem. Soc.* **1981**, *103*, 6152-6157. b) Li, T.; Diederich, F. *J. Org. Chem.* **1992**, *57*, 3449-3454. c) Li, T.; Krasne, S.J.; Persson, B.; Kaback, H.R.; Diederich, F. *J. Org. Chem.* **1993**, *58*, 380-384. d) Deslongchamps, G.; Galan, A.; de Mendoza, J.; Rebek Jr., J. *Angew. Chem.* **1992**, *104*, 58-60. e) Galan, A.; de Mendoza, J.; Toiron, C.; Bruix, M.; Deslongchamps, G.; Rebek Jr., J. *J. Am. Chem. Soc.* **1991**, *113*, 9424-9425. f) Andreu, C.; Galan, A.; Kobiro, K.; de Mendoza, J.; Park, T.K.; Rebek Jr., J. *J. Am. Chem. Soc.* **1994**, *115*, 5501-5502. g) Fluri, K.; Koudelka, J.; Simon, W. *Helv. Chim. Acta*, **1992**, *75*, 1012. h) Furuta, H.; Cyr, M.J.; Sessler, J.L. *J. Am. Chem. Soc.* **1991**, *113*, 6677-6678. i) Kral, V.; Sessler, J.L.; Furuta, H. *J. Am. Chem. Soc.* **1992**, *114*, 8704-8705.

9 a) Huser, M.; Morf, W.E.; Fluri, K.; Seiler, K.; Schulthess, P.; Simon, W. *Helv. Chim. Acta*, **1990**, *73*, 1481-1496. b) Chaniotakis, N.A.; Jurkschat, K.; Rühlemann, A. *Anal. Chim. Acta*, **1993**, *282*, 345-352. c) Umezawa, Y.; Kataoka, M.; Takami, W.; Kimura, E.; Koike, T.; Nada, H. *Anal. Chem.*, **1988**, *60*, 2392-2396.

10 Cammann, K.; Lemke, U.; Rohen, A.; Sander, J.; Wilken, H.; Winter, B. *Angew. Chem.* **1991**, *103*, 519-541.

11 Simon, W. *Chimia*, **1990**, *44*, 395.

12 a) Schmidtchen, F.P.; Schießl, P. *Tetrahedron Lett.* **1993**, *34*, 2449-2452. b) Schmidtchen, F. P.; Gleich, A.; Schummer, A. *Pure Appl. Chem.* **1989**, *61*, 1535-1546.

13 a) Gleich, A.; Schmidtchen, F. P. *Chem. Ber.* **1990**, *123*, 907-915. b) Schmidtchen, F. P.; Oswald, H.; Schummer, A. *Liebig's Ann. Chem.* **1991**, 539-543. c) Kurzmeier, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, *55*, 3749-3755. d) Schmidtchen, F. P. *Chem. Ber.* **1980**, *113*, 2175-2182. e) Echavarren, A.; Galan, A.; de Mendoza, J.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 685-693.

14 a) Hannon, C. L.; Anslyn, E. V.; The Guanidinium Group: Its Biological Role and Synthetic Analogs. In *Bioorganic Chemistry Frontiers*, Vol. 3, Dugas, H.; Schmidtchen, F. P. (Eds.), Springer, Heidelberg, 1993, pp 193-225. b) Gleich, A.; Schmidtchen, F. P.; Miculic, P.; Müller, G. *J. Chem. Soc. Chem. Commun.* **1990**, 55-57.

15 Schießl, P.; Schmidtchen, F. P.; submitted.

16 The conversion of the OH group into a methoxy or ethoxy function should overcome these problems.

17 Petrich, M.; Beyer, L.; Gloe, K.; Mühl, P. *Anal. Chim. Acta* **1990**, *228*, 229-234.

18 A 1:1 complex formation (anion : receptor) gives a stoichiometric coefficient s = 1, and 1:2 complex formation s = 2, respectively.

19 In most cases the pH value were adjusted by buffer solutions (TAPS, HEPES) in order to guarantee a constant species distribution of the anions.

20 Thatcher, G.R.J.; Cameron, D. R.; Nagelkerbe, R.; Schmitke, J. *J. Chem. Soc. Chem. Commun.* **1992**, 386-388.

21 Extraction experiments using a quaternary ammonium salt (Aliquat 336) support this assumption. Aliquat 336 extracts traces of sulfate, whereas hydrogen phosphate is not transfered into the organic phase.

22 Under the experimental conditions chosen there is no detectable dephosphorilation of the nucleotides. The distribution ratios are constant in a 2 h extraction period.

23 At the pH of 8.7 compound **2** ($c_{receptor} = 1 \cdot 10^{-3}$ M in chloroform) extracts 1% TAPS ($c_{TAPS(w)} = 5 \cdot 10^{-2}$ M). Thus, the concentration of TAPS in chloroform is $5 \cdot 10^{-4}$ M, and consequently 50% of the receptor is complexed by the buffer. At the pH of 7.8 only 0.33 % TAPS was transferred into chloroform (17 % of **2** is loaded with TAPS). TAPS was not extracted in the absence of the anion receptor **2**.

24 Perrin, D.D.; in *Stability Constants of Metal-ion Complexes-Part B-Organic Ligands*, Pergamon Press, Oxford-New York-Toronto-Sydney-Paris-Frankfurt, 1978.

25 The deviation from the slope of 1 is significant in the high concentration range. To verify the shape of the curves obtained three independent experimental cycles were performed.

26 Smith, R. M., Martell, A.E., Chen, Y. *Pure Appl. Chem.* **1991**, *63*, 1015.