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A Simple Polyheterotopic Molecular Receptor Derived from Bispyrazolylmethane Showing Negative Allosteric Co-operation of Zn(II)

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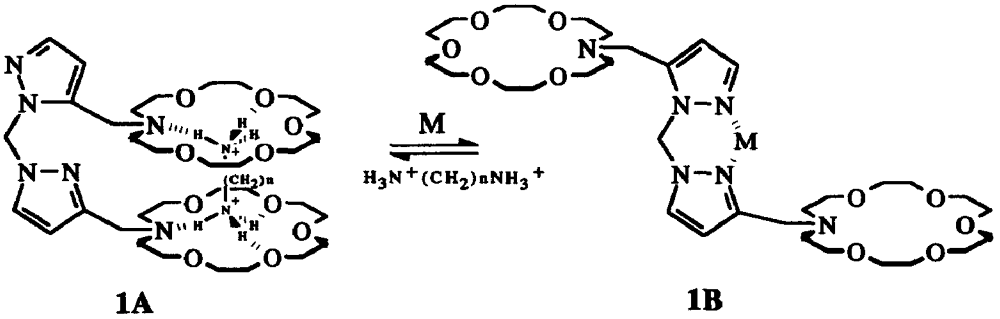
Abstract: The preparation of 1 as a model for negative allostery is described. Transport experiments (bulk liquid membrane) of alkyl di- and monoammonium cations in the presence or absence of ZnI_2 in the receiving phase evidenced strong negative allosteric effects of the metal towards ammonium complexation.

Attempts to mimic enzyme allosteric properties[1] in simplified artificial systems have been relatively numerous in the recent literature.[2] There are good examples of positive allostery in which, for instance, binding constants of lipophilic substrates or the selectivity of ionophores are dramatically increased by the addition of heavy metal ions to the receptor.[3,4] However, only a few cases of allosteric negative effects have been reported,[5] even though their investigation may lead to the development of systems finding attractive applications, such as liberation of drugs, of catalysts, of dyes *etc.* as well as selective transport.

With this aim, and based on our previous work in the pyrazole field,[6] we envisioned that molecule **1** (Scheme I) might embody the essential elements of a novel, quite simple allosteric system with potential negative co-operativity: the crown ether rings in the conformation **1A** would co-operate in anchoring aliphatic diammonium cations while chelation of the pyrazoles to a metal might arrange them as in conformer **1B**, where the co-operation between the two crown rings is no longer possible. Hence, the metal would act as a negative allosteric effector or switch[7] in dication release.

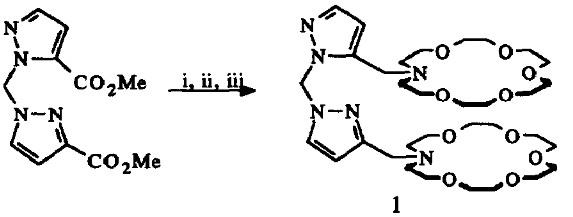


Scheme I

Simple competion of the metal in complexation to the crown ethers has of course to be ruled out. If the expected allosteric effect of the metal is in fact operative, complexation of monoammonium salts should be essentially unaffected by the metal since co-operation of the two crown rings is unlikely to be required for **1** to bind a monocation. However, if the metal directly interferes with cation complexation to the crown ethers, binding of monommonium salts should be also impeded by the presence of the metal.

A convenient method to easily make these properties manifest is to monitor transport on bulk liquid membranes. We therefore report the preparation of bis-pyrazolylmethane **1** and preliminary results concerning its ability to transport aliphatic mono- and diammonium salts which resulted strongly modulated by the presence or absence of ZnI_2.

The synthesis of **1**[8] (Scheme II) from the indicated diester [6a] is straightforward.



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Reagents and conditions: (i) LAH/THF, r.t., 6 h (98%); (ii) PBr_3/MeCN, reflux, 30 min (78%); (iii) Monoaza-18-crown-6 (slow addn.)/Ag_2CO_3/MeCN, reflux, 6 h (90%).

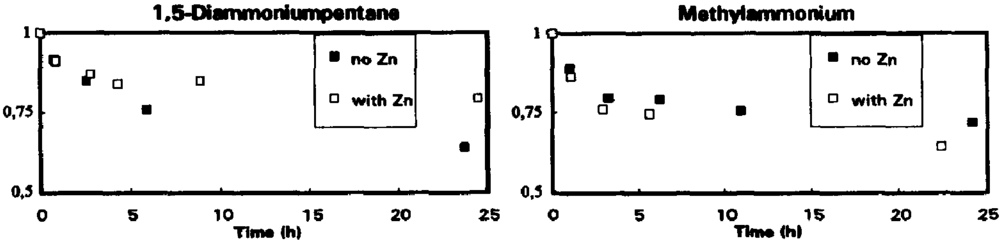
Scheme II

While the solubility of pentane-1,5-diammonium dipicrate in $CDCl_3$ was almost negligible, the presence of **1** permitted up to *ca.* 0.9 equivalents of the picrate to dissolve suggesting a 1:1 stoichiometry for the complex, in agreement with the expected co-operation of the crown rings as in **1A** (Scheme I). The ^1H NMR spectra of the complex **1**.pentane-1,5-diammonium dipicrate showed[9] a *ca.* 1:1 intensity ratio between the signals of both components, the small induced shifts in **1** being compatible with conformational changes necessary for the formation of the proposed 1:1 complex. The stability constant measured by Cram's method[10] ($CHCl_3$: $K_a=2.99.10^5$ M^{-1}; $-\Delta G^o$ = 7.47 kcal/mol; CH_2Cl_2: $K_a=3.26.10^5$ M^{-1}; $-\Delta G^o$ = 7.52 kcal/mol) proved to be similar to stability constants measured in systems with well established co-operation between two crowns.[11]

Figure 1 shows the rate of transport (bulk liquid membrane) of pentane-1,5-diammonium dipicrate and methylammonium picrate (initial c = 1 mM) by **1**, measured from the diminution of picrate content of source phase *vs.* time,[12] in the presence (□) or absence (■) of ZnI_2 (1 mM) in the receiving phase. It is evident that, as expected, Zn(II) retarded the transport of pentane-1,5-diammonium dipicrate (after 24h, *ca.* 31% less picrate was transported when Zn(II) was present in the receiving phase) but, quite interestingly, methylammonium transport was enhanced in turn (*ca.* 15% more picrate was transported with Zn(II) in the receiving phase after 24 h). These transport changes induced by Zn(II) may be easily explained in terms of a metal induced shift of the carrier's equilibrium (Scheme I) to **1B** conformer where, on one hand, co-operation between crown ethers to bind diammonium salts is not possible (transport diminished) and, on the other, repulsive steric and/or electrostatic interactions between the complexed monocations are minimized (transport augmented).

Albeit it has been noticed that Zn(II) may be either complexed[13] or transported[14] by macrocyclic ligands containing nitrogen-oxygen donors, *the observed enhancement in monocation transport excludes the possibility of simple competition of the metal in complexation to the crown ether and strongly supports the proposed switching allosteric effect (Scheme 1) exerted by Zn(II) to the carrier 1 in the transport of diammonium cations.*[15]

Figure 1.- Rate of transport of ammonium picrates by **1**, measured as diminution of picrate content of source phase *vs.* time, in the presence or absence of ZnI_2 in the receiving phase.



Since Zn(II) induced retardation or enhancement in the transport of di- and monocations by **1**, respectively, the metal may act as an effective selectivity regulator in competitive transport. Further investigations concerning this point and others are in progress.

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8. Spectroscopic data of **1**. ^{1}H NMR 300 MHz ($CDCl_3/CD_3OD$ 9:1): δ 2.68 (m, 8H, $OCH_2\mathit{CH_2}N$), 3.4-3.6 (m, 42H, $O\mathit{CH_2}$ and $Pz\mathit{CH_2}N$), 3.79 (s, 2H, $Pz\mathit{CH_2}N$), 6.04 (d, 1H, J=1.7 Hz, $H_{4'}Pz$), 6.10 (s broad, 1H, H_4Pz), 6.47 (s, 2H, $N\mathit{CH_2}N$), 7.30 (d, 1H, J=1.7 Hz, $H_{3'}Pz$), 7.62 (s broad, 1H, H_5Pz); ^{13}C NMR from proton detected $^1J_{CH}$ 2D NMR correlation ($CDCl_3$): δ 55 (corr. to 2.68), 71 (corr. to 3.58), 50 (corr. to 3.79), 53 (corr. to 3.60), 108 (corr. to 6.10), 132 (corr. to 7.62), 141 (corr. to 7.30), 109 (corr. to 6.04), 64 (corr. to 6.47); ^{13}C NMR of quaternary carbons from proton detected $^nJ_{CH}$ (n>1) 2D NMR correlation ($CDCl_3$): δ 152 (corr. to 3.60 and 7.62), 142 (corr. to 3.79, 6.47, 6.04 and 7.30).
9. ^{1}H NMR 300 MHz ($CDCl_3/CD_3OD$ 9:1): δ 1.41 (m, 2H, $NCH_2CH_2\mathit{CH_2}CH_2CH_2N$), 1.62 (m, 4H, $NCH_2\mathit{CH_2}CH_2\mathit{CH_2}CH_2N$), 2.57 (m, 4H, $OCH_2\mathit{CH_2}N$), 2.65 (m, 4H, $OCH_2\mathit{CH_2}N$), 2.87 (m, 4H, $N\mathit{CH_2}CH_2CH_2CH_2\mathit{CH_2}N$), 3.3-3.6 (m, 40H, $O\mathit{CH_2}$), 3.65 (s broad, 2H, $Pz\mathit{CH_2}N$), 4.00 (s broad, 2H, $Pz\mathit{CH_2}N$), 6.00 (d, 1H, J=1.9 Hz, H_4Pz), 6.06 (d, 1H, J=1.8 Hz, $H_{4'}Pz$), 6.36 (s broad, 2H, $N\mathit{CH_2}N$), 7.37 (d, 1H, J=1.9 Hz, $H_{3'}Pz$), 7.60 (d, 1H, J=1.8 Hz, H_5Pz), 8.69 (s, 2H, C_6H_2).
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12. Transport conditions: All transport experiments were carried out at room temperature. The glass cell used was a cylinder (6 cm high, inner diameter 6 cm) containing another smaller one at the bottom (3 cm high, inner diameter 3 cm) where the chloroform phase (30 ml) containing **1** (0.099 mM) lay below the aqueous phases. The source and receiving phases (10 ml) were separated by a 3 mm glass wall which did not reach the bottom of the small cylinder, leaving a 1 cm clearance where a Teflon-coated magnetic bar (1 cm long, 5 mm diameter) stirred the organic phase. Aliquots (75 µl) of both aqueous phases were simultaneously taken at given periods, separately diluted to 5 ml with acetonitrile and their absorption measured at 380 nm for picrate content by UV-vis. In Figure 1, the rate of transport was deduced from the variation of the absorbance of the source phase relative to its value at $t = 0$.
13. See for example Kim, S.-J.; Kim, J.-H.; Huh, H.; Choi, K.-S. *Pure & Appl. Chem.* **1993**, *65*, 499.
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15. Since transport measurement in Fig. 1 is based on diminution of picrate content of source phase *vs.* time, countertransport of I^- might be another problem to take into account. However, it has been reported that this ion is transported *ca.* five orders of magnitude slower than picrate (see Olsher, U.; Hankins, M.G.; Kim, Y.D.;Bartsch, R.A. *J. Am. Chem. Soc.* **1993**, *115*, 3370 and references 4-6 of this paper) and its influence should be thus negligible.

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