Theoret. Chim. Acta (Berl.) 40, 71–74 (1975)

Relationes

Binding of Cations and the Conformation of the Phosphodiester Linkage

Bernard Pullman, Nohad Gresh and Hélène Berthod

Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Théorique
associé au C.N.R.S., Paris

Received July 21, 1975

Contrary to CNDO results, *ab initio* SCF computations indicate that binding of Na^+ and Mg^{++} to the phosphodiester linkage leaves unperturbed its preferences for a *gg* conformation about the $P–O_{ester}$ bonds.

Key word: Phosphodiester linkage

The phosphodiester linkage is an essential constituent of the structure of the nucleic acids and of the phospholipid components of membranes. As a continuation of our quantum-mechanical exploration of its electronic and conformational properties and of the effect of environmental factors upon these properties [1–5] we have now investigated the influence of cation binding upon its conformational preferences.

As in References [2–5] we have used the dimethylphosphate anion (DMP^-, Fig. 1) as a model compound. The computations have been performed within the SCF *ab initio* procedure using the STO 3G basis set [6]. The cations studied in the present work are Na^+ and Mg^{++}, using the exponents optimized by W.J. Hehre *et al.* [7]. (Studies are in progress on K^+ and Ca^{++} ions).

The construction of complete conformational energy maps being highly expensive in an *ab initio* treatment we have limited our investigation to the fixation of the metal cations in *a priori* most plausible sites and to the evaluation of the

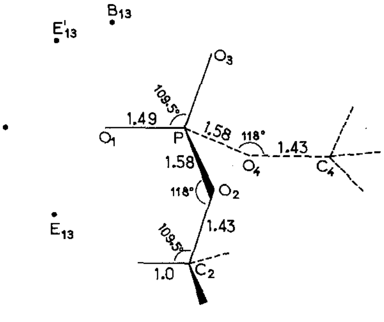

Fig. 1. Dimethylphosphate anion and the principal sites of Na^+ and Mg^{++} binding

effect of such attachments upon the relative energies of the three fundamental conformations resulting from possible rotations about the P–O_{ester} bonds: gauche-gauche (*gg*), gauche-trans (*gt*) and trans-trans (*tt*) [1–4]. In the selection of the most plausible sites of location of the cations we have been guided by the results obtained previously in a similar search for the preferred sites of fixation of protons [2] and water molecules [3, 4]. Four directions of approach have been retained which will be named by analogy to notations used for the water fixation scheme [3, 4]: B_{13} on the bissectrix of the O_1PO_3 angle, E_{13} and E'_{13} along directions which make an angle of 120° with the O_1P axis, respectively on the external and internal side of the O_1PO_3 angle; the fourth site is along the PO axis (Fig. 1). in each case the O... cation distance was optimized for each of the three conformations, *gg*, *gt* and *tt*.

It must be kept in mind that the cation binding energies computed with the STO 3G basis set are overestimated (scaling factor needed$\simeq$0.6) and that the distances of approach are too small [8]. However, a number of examples show that all the qualitative features of the binding are satisfactorily reproduced [8–11] and allow the obtention of valuable information in an exploratory study like the present one. A detailed comparison with the hydration energies and a discussion of the effect of the basis set will be given separately. The principal results are presented in Table 1. The essential conclusions which may be drawn from them are two-fold.

1. In the first place they indicate that the preferred site of attachment of the cation to DMP^- is along the bissectrix of the O_1PO_3 angle (site B_{13}), a position in which the cation is exposed strongly to the effect of both anionic oxygens. Among the three other binding sites explored in the case of Na^+, the next in the order of decreasing binding energy is the E'_{13} site already 32 kcal/mole less efficient than the B_{13} site. The E_{13} site and the binding site along O_1P are still weaker. In the case of Mg^{++} only the B_{13} and E'_{13} were taken into consideration. The latter is already 63 kcal/mole less stable than the former. The above stated preferences refer of course to the isolated DMP^-. In condensed state or in solution the possibility of intermolecular bridging must be considered.

2. The second conclusion is that the cation binding leaves unperturbed the order of conformational preferences with respect to the torsion about the P–O ester bonds: the *gg* conformation remains the most stable one, followed by the *gt* one, followed in turn by the *tt* one, as in free DMP^- [1–12]. In fact, the cation binding in its preferred B_{13} site seems even to increase the relative stability of the *gg* form with respect to the two others: the energy difference in *ab initio* computations on free DMP^- is 3.4 kcal/mole between the *gg* and *gt* form and 8.0 kcal/mole between the *gg* and *tt* forms [12]. The two values become, respectively, 4 and 10 kcal/mole in the Na^+ adduct and 4.9 and 12.2 kcal/mole in the Mg^{++} adduct.

The present results are in contradiction with results obtained recently for the same problem using the CNDO/2 method [13], which predict that the *tt* conformation becomes the most favorable one in $DMP^-...Na^+$ and $DMP^-...Mg^{++}$ complexes. It seems probable that the indications of the CNDO method are artifacts of the procedure. The more so as the available although limited

Table 1. Binding energies in DMP^-...cation adducts for different conformations of DMP^- (kcal/mole)

Site of cation binding	O...M^+ (Å) optimized distance	Energy of cation binding: ΔE with respect to DMP^- and cation at infinite separation			Difference in energy of cation binding		Difference in energy between conformers	
		gg	*gt*	*tt*	$\Delta E(gt-gg)$	$\Delta E(tt-gg)$	$\Delta E(gt-gg)$	$\Delta E(tt-gg)$
Free DMP^-							3.4	8.0
DMP^-...Na^+								
E_{13}	1.9	−167.6	−167.6		0		3.4	
Along O_1P	1.9	−169.0						
E'_{13}	1.9	−182.5	−182.4		0.1		3.5	
B_{13}	2.0	−214.6	−214.0	−212.6	0.6	2.0	4.0	10.0
DMP^-...Mg^{++}								
E'_{13}	1.7	−436.3						
B_{13}	1.9	−499.2	−497.8	−495.0	1.4	4.2	4.8	12.2

experimental indications seem rather in favor of the *ab initio* conclusions. Both crystallographic X-ray studies and different solution studies seem to indicate that the phosphodiester linkage conserves the *gg* conformation upon cation binding. Thus, e.g. the *gg* conformation is observed in the crystal of barium diethylphosphate [14], of magnesium diethylphosphate [15] and of glycerylphosphorylcholine $CdCl_2$ trihydrate [16]. It is also maintained in the aqueous solution of barium diethylphosphate [14].

A number of authors indicate also that the conformation of model compounds for the polar head of phospholipids (e.g. [17]) and the conformation of the polar head of phosphatidylcholines [18, 19], which intrinsically prefer the *gg* orientation about the $P{-}O_{ester}$ bonds, are not influenced by the presence of cations.

References

1. Perahia,D., Pullman,B., Saran, A.: Biochim. Biophys. Acta **340**, 299 (1974)
2. Berthod,H., Pullman,A.: Chem. Phys. Letters **32**, 233 (1975)
3. Pullman,A., Berthod,H., Gresh,N.: Chem. Phys. Letters **33**, 11 (1975)
4. Pullman,B., Pullman,A., Berthod,H., Gresh,N.: Theoret. Chim. Acta (Berl.) in press
5. Perahia,D., Pullman,A., Berthod,H.: Theoret. Chim. Acta (Berl.), in press
6. Hehre,W.J., Stewart,R.F., Pople,J.A.: J. Chem. Phys. **51**, 2657 (1969)
7. Hehre,W.J., Ditchfield,R., Stewart,R.F., Pople,J.A.: J. Chem. Phys. **52**, 2769 (1970)
8. Perricaudet,M., Pullman,A.: FEBS Letters **34**, 222 (1973)
9. Pullman,A.: Int. J. Quant. Chem.; Quant. Biol. Symp. **1**, 33 (1974)
10. Pullman,A., Brochen,P.: Chem. Phys. Letters **34**, 7 (1975)
11. Rode,B.M., Breuss,M., Schuster,P.: Chem. Phys. Letters **32**, 34 (1975)
12. Newton,M.D.: J. Am. Chem. Soc. **95**, 256 (1973)
13. Nanda,R.K., Govil,G.: Theoret. Chim. Acta (Berl.) **38**, 71 (1975)
14. Kyogoku,Y., Iitaka,Y.: Acta Cryst. **21**, 49 (1966)
15. Ezra,F.S., Collin,R.L.: Acta Cryst. **B29**, 1398 (1973)
16. Sundaralingam,M., Jensen,L.H.: Science **150**, 1035 (1965)
17. Papakostidis,G., Zundel,G.: Z. Naturforsch. **28b**, 323 (1973)
18. Misiorowski,R.L., Wells,M.A.: Biochem. **12**, 967 (1973)
19. Yabusaki,K.K., Wells,M.A.: Biochem. **14**, 162 (1975)

Prof. Dr. B. Pullman
Institut de Biologie Physico-Chimique
Laboratoire de Biochimie Théorique
associé au C.N.R.S.
13 rue P. et M. Curie
F-75005 Paris, France