PM3 Potential Energy Surfaces for Phosphoryl Transfer Reactions

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The PM3 SCF-MO potential energy surface for phosphoryl group transfer shows pathways involving both five- and a three-co-ordinate species, the relative energies and geometries of which are influenced by both the nature of the leaving group and specific solvation effects.

Phosphoryl transfer reactions are of major biological,[1] mechanistic,[2] and synthetic[3] interest. The normal aqueous mechanism is thought to involve a pre-associative five-co-ordinated species with apical incoming and leaving groups resulting in inversion of configuration[4] at phosphorus (Scheme 1), although an alternative pathway involving a three-co-ordinated metaphosphate intermediate has also been the subject of considerable speculation.[2,5]

Quantitative modelling of such a system requires a theoretical procedure that foremost can reproduce the relative geometries and energies of oxyphosphorus compounds at various levels of co-ordination. In this context, the recently introduced PM3 semi-empirical SCF-MO method[6] has been shown to agree well with *ab initio* calculations with respect to the energetics and stereochemical characteristics of three-, four-, and five-co-ordinated phosphorus[6] in the Wittig reaction,[7] and the potential surface characteristics for the Beckmann rearrangement.[8] PM3 is also the only common semi-empirical procedure to correctly reproduce the structure and vibrational spectra of small water aggregates,[6,9] the water solvation structures and energies of small positive and negative ions,[9] and the unusual structural characteristics of weak complexes between *e.g.* methane and HCN.[10] We present here an evaluation of PM3 for modelling bond breaking and hydrogen bonding interactions in phosphoryl transfer reactions.[1]

Energy contour maps at the PM3 level constructed using the P–O bond lengths of the incoming and leaving oxygen nucleophile ($R^1 = R^2 = R^3 = Me$) reveal the associative pathway forming (**4**) (Figure 1) to involve the intermediacy of a penta-co-ordinate species (**3**), *via* an 'in-line' transition state (**2**) corresponding to inversion of configuration at phosphorus. Retention of configuration[4] at phosphorus to give (**11**) would require (for $R^1 = R^2 = R^3 = Me$ specifically) pseudo-rotation in species (**7**) so that OR^2 becomes apical as in (**9**) (Scheme 1). However, such a process must decrease the angle between the two $P–O^-$ groups to 90° in (**9**). The resulting increase in lone pair repulsions is reflected in the PM3 prediction that (**9**) is not a stable minimum, with a gas phase energy (calculated using idealised angles) 30.0 kcal mol^{-1} (1 cal = 4.184 J) higher than (**3**). The other possible penta-co-ordinate intermediate (**12**) in which both $P–O^-$ groups are apical (and which therefore cannot eliminate either R^1O or R^2O) is also higher in energy than (**3**) by 8.8 kcal mol^{-1}.

A dissociative pathway involving the formation of the separate species $MeO^- + MeO^- + Me_3OPO_2$ (**5**, R = Me, Scheme 1) in which $MeOPO_2$ corresponds to a neutral metaphosphate intermediate, is lower in energy than (**2**), at least in the gas phase.[11] No reverse barrier back to (**1**) from (**5**) was found in the gas phase. Stabilisation of the oxyanion as with $R^1 = R^2 = CF_3$ virtually eliminates the distinction between (**2**) and (**3**) and lowers the energy of (**5**) significantly relative to (**3**). Experimentally, this effect is manifest in greater involvement of a metaphosphate intermediate with increasing *e.g.* nitro group ring substitution of R^2 = aryl.[2] Leaving groups such as ($R^2 = P_2O_6^{3-}$, R^3 = adenosyl),[1b] would be expected to show intermediate behaviour between our two model groups R = Me and R = CF_3.

These gas-phase pathways have very high absolute barriers due to electrostatic repulsion between the two negatively charged species. A more realistic model constructed by including six water molecules resulted in a substantial reduc-

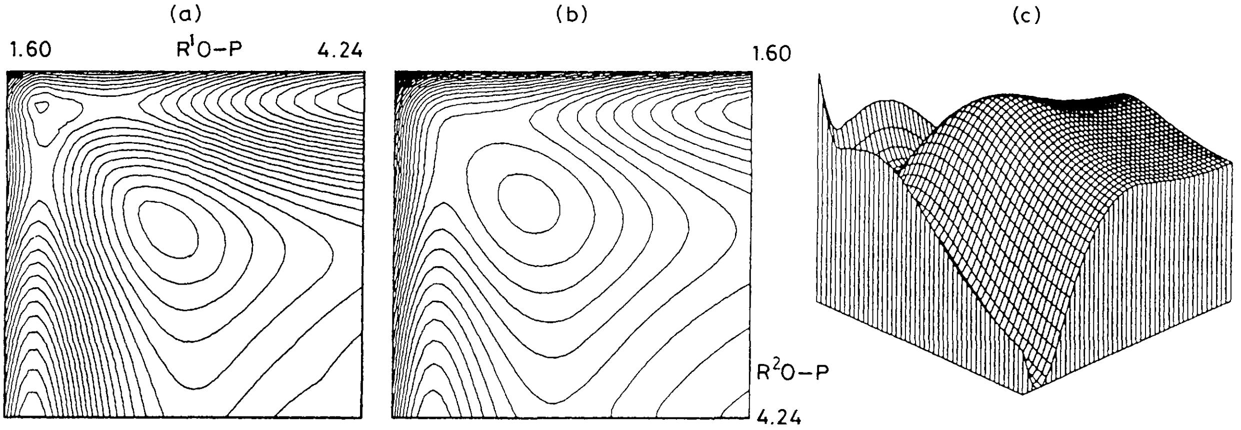


Figure 1. Contour maps for phosphoryl transfer as a function of the reaction co-ordinates $r(R^1O–P)$ and $r(R^2O–P)$, in Å, for (a) $R^1 = R^2 = R^3 = Me$ and (b) $R^1 = R^2 = CF_3$, $R^3 = Me$. All contour levels are separated by 2.0 kcal mol^{-1}. An isometric projection of the surface for $R^1 = R^2 = R^3 = Me$ is shown in (c).

tion in the calculated barriers (Table 1), along with a promotion of the associative route (**3**) relative to the dissociative pathway (**5**) by 10.9 and 17.1 kcal mol^{-1} for R = Me and CF_3 respectively. With such solvation, species (**5**) now represents a genuine minimum in the potential surface, the reverse barrier back to (**1**) being 2.1 kcal mol^{-1}. The energies of the isomers (**9**) and (**12**) solvated with 6 H_2O remain higher than (**3**) (by 19.4 and 3.5 kcal mol^{-1} respectively for R = Me), whilst such solvation increases the stability of (**3**) relative to (**2**) from 7.1 to 12.2 kcal mol^{-1}. The structure of the transition state (**2**) solvated with 6 H_2O (Figure 2) shows the expected tetrahedral co-ordination around the oxy-anion substituents, suggesting that PM3 may provide quantitative models for specific interactions with *e.g.* amino acid residues.[1] The calculated apical P–O bond lengths in (**2**) (Figure 2) indicate that equatorial $P–O^-$ solvation results in a noticeably earlier transition state. A model constructed using 15 water molecules reveals that (**2**) (R = Me) is now significantly lower in energy than (**5**), and a reasonable barrier to the associative reaction is now predicted. The effects of different R substituents, solvents, and steric effects on the PM3 potential surfaces for these and the related thiophosphoryl transfer reaction will be reported elsewhere.

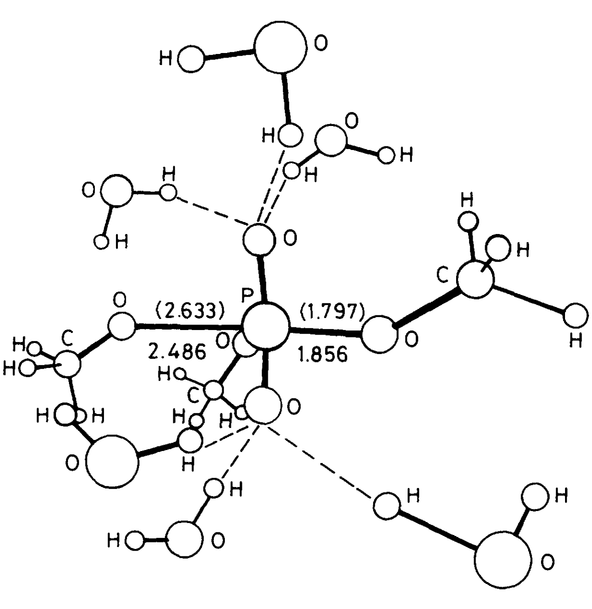
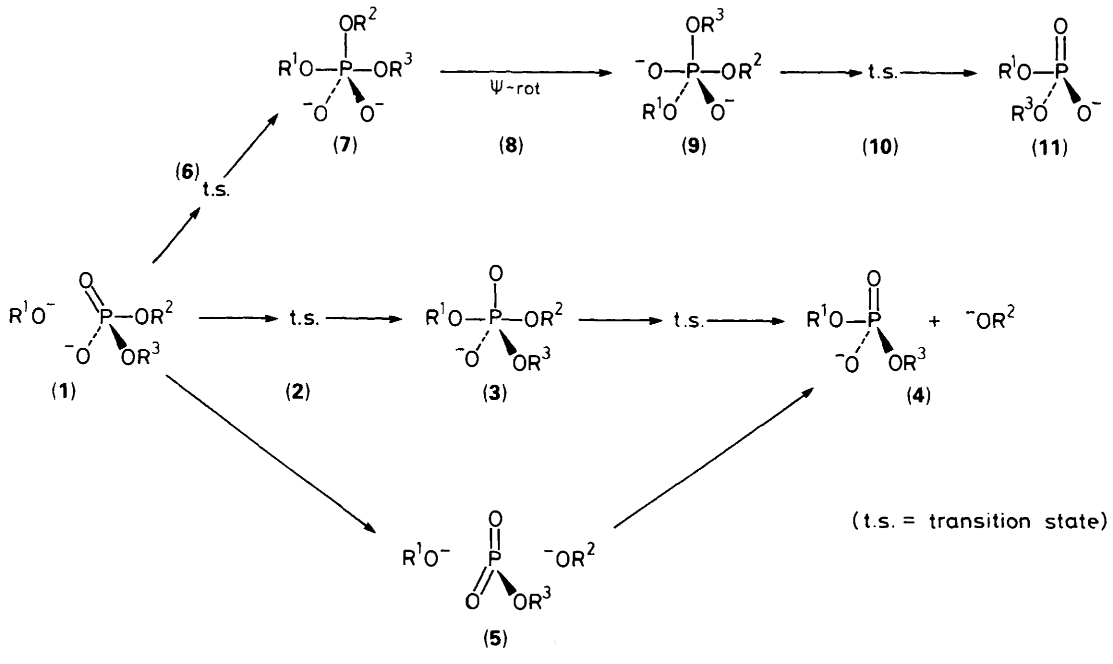


Figure 2. Calculated PM3 structure for transition state (**2**), for $R^1 = R^2 = R^3 = Me_3$, showing each $P–O^-$ group surrounded approximately symmetrically by three water molecules. Bond lengths in Å for the gas phase and (in parentheses) for solvation with six water molecules.

Table 1. Relative energies[a] of stationary points on the potential surface for phosphoryl transfer.

R^1,R^2	(**1**)	(**2**)	(**3**)	(**5**)[b]
Me	0.0 (−312.7)[c]	89.2	82.1	69.3
Me + 6 H_2O	0.0 (−680.4)[d]	42.4	30.2	(30.4)[e]28.3[f]
Me + 15 H_2O	0.0 (−1233.5)[g]	21.2	11.1	24.1[h]
CF_3	0.0 (−713.3)	74.8	74.7	33.1
CF_3 + 6 H_2O	0.0 (−1067.1)[i]	34.7	33.1	8.6[j]

[a] All energies in kcal mol^{-1} relative to (**1**). [b] Species (**5**) represents the supermolecule $R^1O^- + R^2O^- + R^3OPO_2$. [c] Standard calculated enthalpy of formation. [d] Minimum with *r*(R^1O–P), *r*(R^2O–P) = 10.8, 1.75 Å. A second minimum with *r*(R^1O–P), *r*(R^2O–P) = 4.9, 1.755 Å was 20.1 kcal mol^{-1} higher in energy. [e] Transition state with *r*(R^1O–P), *r*(R^2O–P) = 14.65, 3.05 Å. [f] Minimum with *r*(R^1O–P), *r*(R^2O–P) = 14.7, 5.3. [g] *r*(R^1O–P), *r*(R^2O–P) = 9.01, 1.76. [h] Minimum with *r*(R^1O–P), *r*(R^2O–P) = 14.5, 5.9. [i] *r*(R^1O–P), *r*(R^2O–P) = 10.4, 1.85. [j] Minimum with *r*(R^1O–P), *r*(R^2O–P) = 13.7, 5.7.



Scheme 1

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