# The Mechanism of Phosphoryl to Carbonyl Migration of Amino Groups in Mixed Anhydrides. A MNDO SCF-MO Study

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A MNDO SCF-MO study of the mechanism of acyl migration in mixed carboxylic–phosphoric anhydride systems supports the hypothesis that these reactions are concerted, involving no dipolar intermediates. The calculations reveal a marked specificity for migration to an amino group rather than to an alkoxy group. The stereoelectronic contributions to this effect are revealed by inspection of the SCF molecular orbitals. These show greater localisation along the axes of the forming/cleaving C–N and N–P bonds at the transition state for migration to N than for migration to O. The cyclic transition state for the latter also shows greater destabilising 1,3-interactions between the endocyclic heteroatoms. A more quantitative analysis in terms of localised orbitals also supports the bond localisation argument.

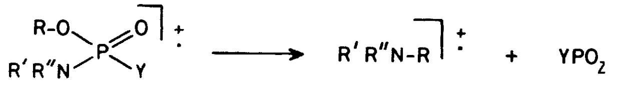
Rearrangements involving cleavage of C–O and formation of C–N bonds are well known and can be illustrated by the Chapman rearrangement of *N*-substituted imidates to disubstituted amides.[1] The results of a detailed study[2] on the O⟶N acyl group migration in *O*-acyl isoamides indicate that the transfer takes place *via* a four-membered transition state; the concerted nature of the rearrangement was confirmed later[3] by theoretical calculations. On the other hand, the analogous migration in a sulphonic system, namely the rearrangement of *O*-ethyl *N*-methyl toluene-4-sulphonimidate to *N*-ethyl-*N*-methyltoluene-4-sulphonamide has been demonstrated[4] to proceed *via* an intermolecular $S_N2$ transalkylation. Similarly, the imide–amide rearrangement in a phosphoryl series [$(RO)_3P{=}NR' \longrightarrow (RO)_2P(O)NRR'$] does not occur spontaneously, but requires the presence of an alkylating agent RX, indicating a sequence of nucleophilic displacements by nitrogen and the ion $X^-$.[5] In all these reactions the migration occurs at the $sp^2$ nitrogen doubly bonded to the acyl centre, so the rearrangement is not accompanied by fragmentation of the molecular framework.

We have recently reported[6] on the facile O⟶N migration of an acyl group in a mixed carboxylic–phosphoric anhydride system; the reaction resulted in fragmentation of the substrate and expulsion of a metaphosphate species (Scheme 1).

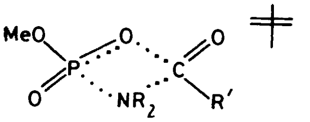
$$(MeO)(R_2N)P(O)OC(O)R' \longrightarrow R'C(O)NR_2 + MeOPO_2$$

**Scheme 1.**

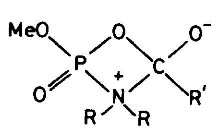
In terms of structural changes, the reaction represented by Scheme 1 parallels the fragmentation behaviour observed in the mass spectra of organic carbonates[7] and carbamates,[8] when the O⟶O or O⟶N migrations were accompanied by the expulsion of such products as $CO_2$ or alkyl isocyanate. We have demonstrated[9] that the fragmentation is also characteristic of the mass spectrometric behaviour of phosphoric amido esters, with the metaphosphate derivative $YPO_2$ being ejected from the molecular ion (Scheme 2). Contrary to the electron-impact-induced migration/fragmentations, collapse of the mixed anhydrides (Scheme 1) involves the ground state of a substrate and takes place under mild conditions. Solvent and substituent effects on the rate of fragmentation indicated[6] little charge development in the transition state, thus favouring structure (**1**) rather than the intermediate (**2**). It was observed[6] that the migration from phosphorus to the carbonyl carbon involved the amine, but not the alkoxy group; *i.e.* no carboxylic ester was detected in the reaction product. In order to obtain additional support for a concerted mechanism of fragmentation, and to investigate the reasons for the observed selectivity, a MNDO study has been carried out using structure (**3**) as a model for a mixed anhydride system.



**Scheme 2.**



**(1)**



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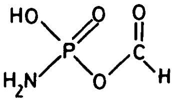


**(3)**

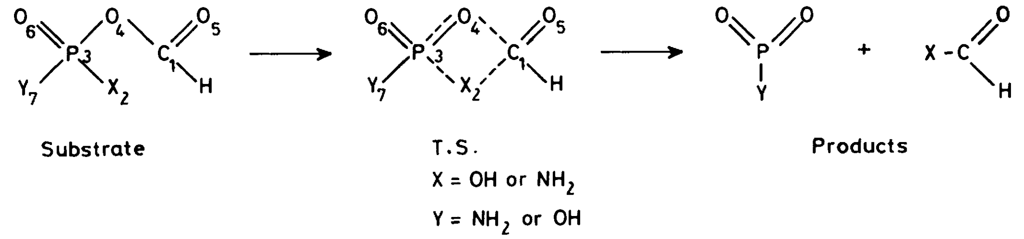
*Computational Details.*—Calculations were carried out using the standard MNDO procedure[10] employing an *s*/*p* valence shell basis set only, and carrying out full optimisation of all $3N - 6$ geometrical variables. Putative transition states were located by minimising the sum of the square scalar gradients, using as a starting point an estimated structure for the transition state. The stationary points so located were shown to be true transition states by calculating the force constant matrix[11] and showing it to have only one negative root, with eigenvectors corresponding to interconversion of reactant and product. No other energy minima intermediate between reactant and product were located, suggesting a concerted reaction as predicted.

## Results and Discussion

The calculated energies and geometrical variables for the two possible courses of the fragmentation (Scheme 3) are shown in the Table.

**Table.** Calculated MNDO energies and other parameters for species occurring in Scheme 3

| | Substrate | $X = NH_2$, T.S. | $Y = OH$ Product | $X = OH$, T.S. | $Y = NH_2$ Product |
|---|---|---|---|---|---|
| $\Delta H_{298}$/kcal mol$^{-1}$ | −183.1 | −130.2 | −146.7 | −119.1 | −148.5 |
| Dipole moment/D | 1.28 | 3.53 | 4.24 | 2.60 | 3.78 |
| Imaginary frequency at T.S./cm$^{-1}$ | | 504 | | 499 | |
| Bond lengths/Å | | | | | |
| 1–2 | | 1.554 | 1.473 | 1.479 | 1.355 |
| 2–3 | 1.667 | 1.851 | | 1.796 | |
| 3–4 | 1.610 | 1.529 | 1.484 | 1.531 | 1.471 |
| 4–1 | 1.351 | 1.892 | | 1.879 | |
| 5–1 | 1.272 | 1.218 | 1.214 | 1.219 | 1.227 |
| 6–3 | 1.497 | 1.481 | 1.483 | 1.480 | 1.470 |
| 7–3 | 1.667 | 1.594 | 1.596 | 1.646 | 1.604 |



Scheme 3.

The rearrangement is calculated to be concerted, with no detectable intermediate intervening. We do note however that it is not entirely synchronous, since the P–N bond in the transition state for *N*-transfer is stretched by only 11% relative to the reactant, whereas the C(carbonyl)–O(anhydride) bond is extended by 40%. Such asymmetry is not unexpected in an intrinsically unsymmetrical reaction, and similar effects have been found in other four-centre reactions.[12] The predicted concerted nature of this reaction is noteworthy, particularly since there has been considerable controversy over the character of other pericyclic reactions such as cycloaddition (*e.g.* the Diels–Alder) or sigmatropic rearrangement (*e.g.* the Cope reaction). Dewar[13] has argued strongly that the majority of multibond reactions are stepwise, involving the cleavage of one bond at a time *via* diradical-type intermediates, and that a direct concerted pathway is the exception rather than the rule, and is likely to be more asynchronous. In contrast, *ab initio* calculations predict that concerted transition states tend to be symmetrical (synchronous) and are an energetically competitive alternative to stepwise pathways involving diradicals.[14] Dewar has shown[13] that the MNDO method does tend to predict stepwise diradical mechanisms for reactions involving the cleavage of non-polar C–C bonds. Stationary points corresponding to the symmetrical (synchronous) route tend not to be genuine transition states, having *two* negative roots in the calculated MNDO force constant matrix. We were aware of this tendency of MNDO in our previous study of N/O acyl-transfer reactions[3] but were unable to detect any diradical characteristics, finding only genuine, essentially synchronous transition states with only one negative root in the calculated force constant matrix. A typical diagnostic of diradical character in a species is that the HOMO–LUMO energy gap in a spin-restricted Hartree-Fock MNDO calculation has an unusually low value (*e.g.* $< 8$ eV), indicating that an open-shell singlet state has a particularly low energy.[15] This characteristic is not present in the present calculations, the HOMO–LUMO gap being greater than 10 eV for both the transition states studied. A similar effect was observed in the other four-centre transition states previously studied.[3,12] The MNDO characteristics discussed by Dewar[13] may therefore be typical only for reactions involving the cleavage/formation of C–C bonds. Interestingly, a re-parametrised version of MNDO (AM1) which differs principally in the treatment of the core–core repulsion terms[16] does predict a synchronous (symmetrical) pathway for the cycloaddition of ethene and butadiene at the spin-restricted Hartree-Fock level (unlike MNDO), but a diradical pathway is nevertheless still the favoured one if an open-shell wavefunction is used. We conclude that since the known tendency of MNDO is to predict highly asynchronous transition states, or stepwise mechanisms for the majority of pericyclic reactions where an intermediate is possible, the present prediction of a concerted and fairly synchronous mechanism is likely to be valid.

The calculated changes in dipole moments (see the Table) reveal quite large differences between the reactant, transition state, and product, whereas the observed solvent effect for these reactions is modest.[6] The calculations were carried out using only an *s*/*p* basis set of orbitals, which tends to emphasise the ionic contributions to the wavefunction, particularly for higher oxidation states in phosphorus. It is quite probable therefore that inclusion of *d*-functions in the basis set would reduce the charge polarisation for the reaction, as well as decreasing the calculated activation energy.

As can be seen from the Table, both possible pathways of fragmentation ($NH_2$ or OH transfer; Scheme 3, $X = NH_2$ or OH) are predicted to be endothermic with very high activation barriers ($\Delta H^{\ddagger} = 52.9$ and 64.0 kcal mol$^{-1}$, respectively). Although large errors are to be expected in the predicted energies of third period elements of a high formal oxidation state,[17] the relative comparison of energies involved in the two possible reactions may be expected to show smaller errors. In

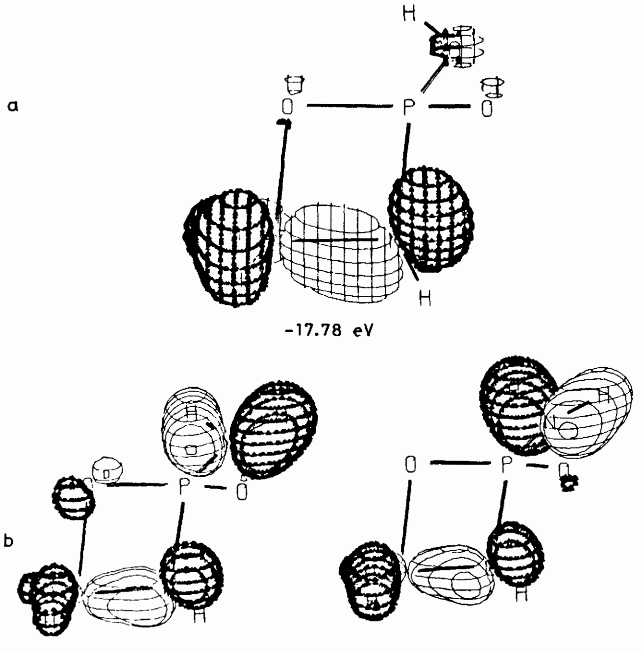


**Figure 1.** The molecular orbital (and its energy) corresponding to the formation of the σ bond between X and C in the transition state (Scheme 3); a, X = $NH_2$; b, X = OH

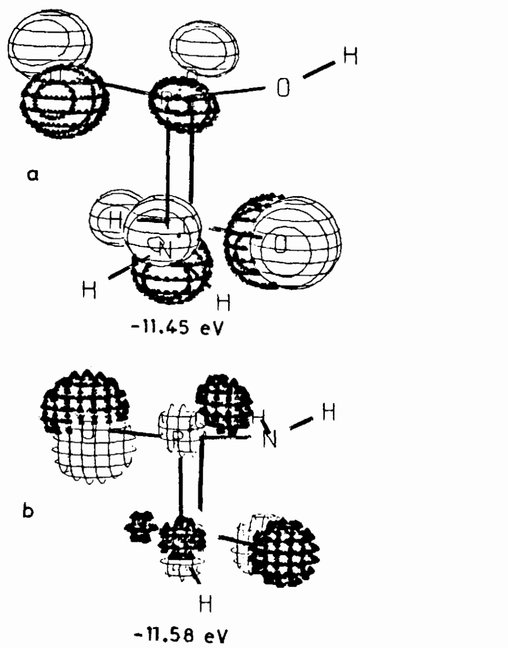


**Figure 2.** The first molecular orbital (and its energy) with electron density in the plane of the ring in the transition state (Scheme 3); a, X = $NH_2$; b, X = OH

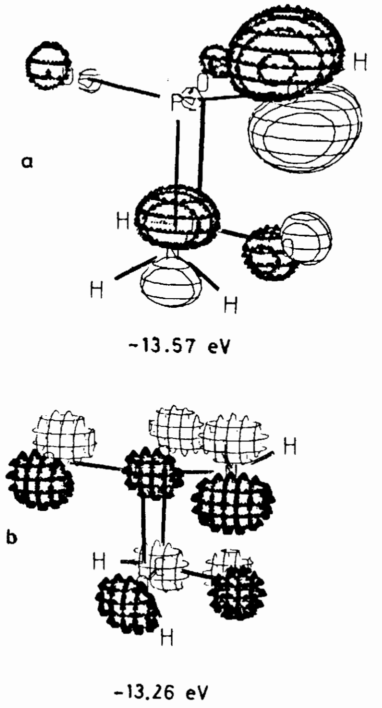


**Figure 3.** Second molecular orbital (and its energy) with electron density in the four-centre plane; a, X = $NH_2$; b, X = OH

this context, we note that the combined MNDO energies for the pairs of products shown in Scheme 3 are very similar. This result suggests that the observed selectivity in fragmentation is not due to the relative stabilities of the reaction products. MNDO Predicts that the T.S. (X = $NH_2$) is 11 kcal $mol^{-1}$ lower in energy than the T.S. (X = OH); this difference is large enough to explain the absence of the oxygen-group transfer under experimental conditions. The origins of this effect were investigated by analysing several of the highest occupied molecular orbitals for the corresponding transition sites. The low-energy molecular orbitals corresponding to the forming σ bond between X and the carbonyl carbon (Figure 1a and 1b) show striking differences. For X = $NH_2$, only one such orbital has been found with the electron density essentially localised along the axis of the forming C–N bond. In the case of X = OH, no single orbital has such properties but two orbitals can be located which correspond to symmetric and antisymmetric combinations of a C–O sigma bond with N–H sigma bonds of the $NH_2$ ring substituent. However, both these orbitals have less electron density in the region of the forming bond than does the transition state for X = $NH_2$. This result also suggests that the transition state for the OH group transfer may be more susceptible to the effects of substituents, particularly on the nitrogen atom.

Significant differences in behaviour were noted for the HOMO-1 in both transition states which comprised combinations of the exocyclic O or N lone pairs. The first molecular orbital with significant electron density in the plane of the four-membered PO(4)CX ring in the transition state is shown in Figure 2 (2a, X = $NH_2$; 2b, X = OH). In addition to significant density on the N or O atom comprising the nucleophile, there were components on the ring (anhydride) O atom, the two exocyclic (C=O and P=O) oxygens, and the H atom of the formyl group. The component on the N atom for $NH_2$ group transfer (Figure 2a) is significantly greater than on the corresponding O atom in the T.S. for OH transfer, Figure 2b. The implication is that substituents, particularly on the carbonyl group, would stabilise this orbital more in the T.S. for X = $NH_2$ than in the T.S. for X = OH. The larger coefficient on the N atom also indicates that this atom is acting as a better nucleophile than the O atom in the oxygen-transfer process.

The next significant orbital for the transition state is shown in Figure 3a and 3b. The electron density on the nucleophilic (migrating) N or O atom is approximately directed along the N–P or O–P bond that must cleave to form the reaction products. Such orientation enables this bond to interact with the lone pair of the exocyclic OH or $NH_2$ substituent, a phenomenon that Kirby[18] has shown leads to the lengthening of such bonds in the ground-state structures of numerous acetals and phosphorus compounds. In their study on the application of the theory of stereoelectronic effects to reactions of phosphorus, Gorenstein *et al.* demonstrated[19] that a cleavage of the bond at phosphorus in the product-determining step is *ca.* 11 kcal $mol^{-1}$ lower in energy when the bond between phosphorus and the departing group is oriented in an antiperiplanar fashion to one of the lone pairs of another heteroatom at the phosphorus centre. The strength of this interaction presumably controls the relative strength of the P–N bond and P–O bonds being broken in the two respective reaction paths.

Revealing differences are seen between the two transition states, as shown in Figures 2a,b and 3a,b. (*i*) With the nitrogen atom attacking the carbonyl centre ($X = NH_2$), most of the density is concentrated on the N atom itself and on the OH lone pair. In the case of oxygen attack (X = OH), there is significant density on the other (anhydride) in-plane oxygen atom, in such a manner as to lead to a destabilizing 1,3-interaction between the two endocyclic oxygen atoms. (*ii*) In the case of $X = NH_2$, the electron density is directed almost exactly along the axis of the N–P bond. The interaction with the OH lone pair is antibonding, and these two factors presumably weaken the N–P bond, thus facilitating its cleavage. In the case of oxygen attack (X = OH), the corresponding electron density is not directed along the O–P bond, but instead resembles more closely an oxygen lone pair. Consequently, interaction with the $NH_2$ lone pair has a destabilizing effect on the nucleophilic oxygen lone pair rather than on the O–P bond, and hence the stereoelectronic effect does not assist the OH group transfer.

These qualitative conclusions can be expressed in a more quantitative form by transforming the SCF molecular orbital into localised orbitals according to the scheme suggested by Perkins and Stewart.[20] Such an analysis for the T.S. ($X = NH_2$) reveals one orbital localised along the forming C(1)–C(2) axis and another along the cleaving N(2)–P(3) bond. The localisation indices for these two orbitals have the values 1.857 and 1.444 respectively. In this analysis,[20] a value of 1.00 indicates a localised lone pair, a value of 2.0 corresponds to a two-centre orbital, (as in *e.g.* $H_2O$) and a value of 3.0 would correspond to a three-centre bond as in *e.g.* diborane. The corresponding orbital localisation values for the T.S. (X = OH) are 1.785 and 1.318. These results support a late rather than early transition state, and also dramatically confirm that the specificity observed in this reaction is a result of greater localisation of electron density along the reactive bonds for the T.S. ($X = NH_2$) at least in part as a result of the type of stereoelectronic effect first proposed by Deslongchamps.[18b]

## Acknowledgements

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