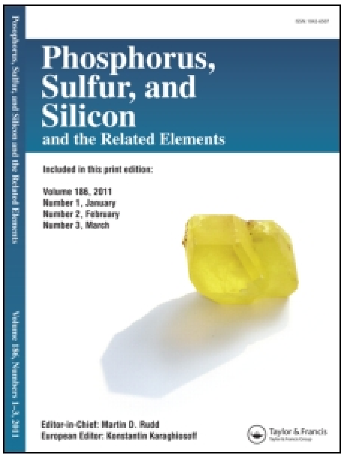


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

PHOSPHORYL TO CARBONYL MIGRATION OF AMINO GROUPS IN MIXED ANHYDRIDES. THE EFFECT OF N-SUBSTITUENTS

Jillian Symes[a]; Tomasz A. Modro[a]
[a] Department of Chemistry, University of Pretoria, Pretoria, South Africa

To cite this Article Symes, Jillian and Modro, Tomasz A.(1988) 'PHOSPHORYL TO CARBONYL MIGRATION OF AMINO GROUPS IN MIXED ANHYDRIDES. THE EFFECT OF N-SUBSTITUENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 39: 1, 113 — 117

To link to this Article: DOI: 10.1080/03086648808072861

URL: http://dx.doi.org/10.1080/03086648808072861

Phosphorus and Sulfur, 1988, Vol. 39, pp. 113–117
Reprints available directly from the publisher
Photocopying permitted by license only

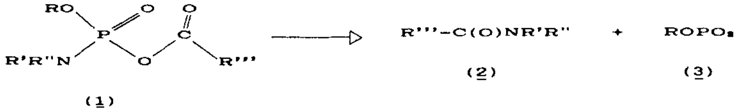
PHOSPHORYL TO CARBONYL MIGRATION OF AMINO GROUPS IN MIXED ANHYDRIDES. THE EFFECT OF N-SUBSTITUENTS

JILLIAN SYMES and TOMASZ A. MODRO
Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

(Received January 28, 1988; in final form March 10, 1988)

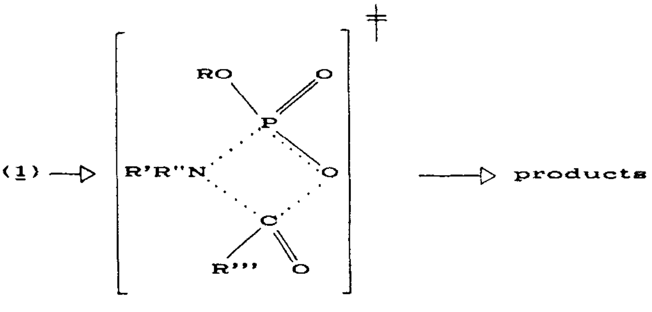
The rates of fragmentation of mixed anhydrides (MeO)(p-X-C_6H_4NMe)P(O)OC(O)Ph (**1**) (X = MeO, H, Cl, CF_3) giving carboxyamides PhC(O)NMe(C_6H_4-X-p) were measured in $CDCl_3$ at 70°C. The reaction constant $\rho = +0.85$ was obtained. The magnitude of ρ is taken as an indication of low sensitivity of rate to polar effects of substituents (in agreement with the concerted mechanism postulated), and its positive sign suggests that the cleavage of the P—N bond is more advanced in the transition state than is the formation of the N—C bond.

We have recently reported[1] on the unimolecular fragmentation of mixed anhydrides (**1**) yielding carboxyamides (**2**) and metaphosphate esters (**3**).



(1)

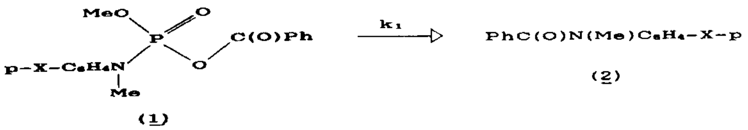
Solvent effects as well as the effect of structural changes at the carbonyl center (R''') indicated[1] little charge development in the transition state and suggested a concerted mechanism of fragmentation.



A MNDO SCF–MO study[2] of reaction (1) fully supported the hypothesis of a concerted mechanism, and application of the localised orbitals approach[3] indicated a late rather than early transition state. Fragmentation involving anhydride (**1**) in which the phosphorus, nitrogen and (ester) oxygen atoms were incorporated into a cyclic system revealed[4] that the rate of reaction depends strongly on the steric effects of the structural environment around the reacting NPOC system. Since our calculations showed[2] that in the transition state the forming C—N and the breaking P—N bonds are stretched to different degrees, we were interested whether these bond distances were indicative of any fractional charge being developed at nitrogen along the reaction coordinate. In this work we report on the polar effects on N-substituents in (**1**) on the rate of fragmentation.

RESULTS AND DISCUSSION

We have synthesized four mixed anhydrides (**1a, b, c, d**) and measured their rates of fragmentation to the corresponding anilides (**2a, b, c, d**) in $CDCl_3$ at 70°C.



a, X = MeO; b, X = H;
c, X = Cl; d, X = CF_3

Since the steric effects of the migrating $N(Me)C_6H_4$-X-p group in the transition state should be approximately the same for all four substrates, any differences in k_1 values could provide information about the electronic demand of the nitrogen atom, and if so, could be correlated in terms of the Hammett equation.[5]

Substrates (**1**) were prepared as described before[1] and products (**2**) were identified by isolation and comparison with authentic samples. Rates of reactions were determined by monitoring the change in the N–Me group signal in the ^1H n.m.r. spectrum of the reaction mixture. In all cases the doublet (J_{HP} 10 Hz) at δ 3.2–3.3 resulting from the N–Me group in (**1**) was gradually replaced by the broad signal (δ 3.5) of the N–Me group in (**2**). Reaction (3) follows first-order kinetics, and the rate constants obtained are listed in Table I.

In agreement with the proposed mechanism for the fragmentation, the effect of ring-substitution on the reaction rate is weak; there is only a four-fold change in the reactivity between the most and the least reactive substrate. Although rate determinations involve only four substrates,[6] the k_1 values show a definite trend, and when plotted against Hammett σ_x constants, give a reasonably linear ($r = 0.981$) relationship with a reaction constant $\rho = +0.85$. It is relevant to note at this point that the benzoylation of ring substituted anilines by benzoyl chloride, *i.e.* the reaction involving significant (positive) charge development at nitrogen in

TABLE I

Rates of formation of (**2**) from (**1**) in $CDCl_3$ at 70°C

Substrate	$10^6 k_1{}^a$ (s^{-1})	$\sigma_x{}^b$
(**1a**)	0.69 ± 0.03	−0.27
(**1b**)	1.09 ± 0.04	0.00
(**1c**)	1.53 ± 0.06	0.23
(**1d**)	2.74 ± 0.09	0.40

[a] Average of two runs; $r > 0.999$.
[b] Taken from Reference 5.

the transition state,[7] is characterised by a highly negative reaction constant, $\rho = -3.21$.[8] The low positive value of ρ determined for the fragmentation (3) not only shows the low sensitivity of rate to polar effects of substituents, as expected for a concerted reaction, but also indicates an inversion of the effect observed for typical acylation reactions. This value suggests that the *departure* of the nitrogen atom from phosphorus is more important in the transition state than its association with the carbonyl centre. In support of this, the MNDO SCF–MO study[2] demonstrated that the P—N bond cleavage in (**1**) is assisted by the stereoelectronic effects of neighbouring heteroatoms. Thus, we find that "classical" electron-withdrawing effects in N-substituents destabilise the P–N bond in (**1**), and together with stereoelectronic effects, facilitate nitrogen departure and increase the fragmentation rate. The advanced P—N bond cleavage in the transition state increases the electron deficiency of the phosphorus atom, thus increasing the extent of cleavage of the C—O (anhydride) bond, and enabling formation of the incipient metaphosphate species (**3**).

EXPERIMENTAL

^{1}H n.m.r. spectra were determined with a 90 MHz Bruker WH 90, 80 MHz Bruker WP80 or 60 MHZ Varian EM360 spectrometer, using Me_4Si or DDS as internal standard. Elemental analyses were carried out at the University of Cape Town and the C.S.I.R. All solvents and commercial reagents were dried and purified by conventional means before use. Dimethyl phosphorochloridate (**4**) was prepared from PCl_3, MeOH and SO_2Cl_2.[9]

Substrates. Dimethyl N-methyl-N-aryl phosphoroamidates, $(MeO)_2P(O)N(Me)Ar$ (**5**, **a**, aryl = p-anisyl; **b**, aryl = phenyl) were prepared as follows. A solution of (**4**) in benzene was added dropwise to a benzene solution of the corresponding N-methylaniline (1.5 mole-equivalent) and triethylamine (1.1. mole-equivalent) with stirring and cooling in an ice–salt bath. The mixture was then stirred at 0°C for 3 h and left at room temperature overnight. Triethylammonium chloride was filtered off and the filtrate washed three times with aq. KOH (pH 9), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Products (**5**) were obtained as oils, and were identified by ^{1}H n.m.r. spectra. (**5a**): 65%; δ ($CDCl_3$) 3.14 (3H, d, J_{HP} 10 Hz, NMe), 3.72 (6H, d, J_{HP} 12 Hz, 2 × POMe), 3.75 (3H, s, ArOMe) 6.44 – 7.44 (4H, d of d, C_6H_4). (**5b**): 42%; δ ($CDCl_3$) 3.22 (3H, d, J_{HP} 9 Hz, NMe), 3.77 (6H, d, J_{HP} 11 Hz, 2 × POMe), 6.55 – 7.50 (5H, br s, Ph).

Dimethyl N-methyl-N-(p-chlorophenyl) phosphoroamidate (**5c**) was prepared[10] as follows. N-methyl-p-chloroanilinium chloride (2.45 g, 0.014 mol) was dissolved in $POCl_3$ (4.14 g, 0.027 mol) and the solution was heated under reflux for 4 h. Excess $POCl_3$ was removed under reduced pressure, and N-methyl-N-(p-chlorophenyl)phosphoramidic dichloride, $Cl_2P(O)N(Me)C_6H_4Cl$-p (**6**) was obtained as an oil. 3.58 g (99%); δ ($CDCl_3$) 3.30 (3H, d, J_{HP} 14 Hz, NMe), 7.50 (4H, m, C_6H_4).

3.58 g (**6**) in 70 ml MeOH was added to a solution of MeONa (2 mole-equivalent) in 50 ml MeOH and the solution heated under reflux for 1 h. Methanol was removed under reduced pressure, $CHCl_3$ (50 ml) was added and the solution was washed with water (3 × 10 ml). After drying and evaporation (**5c**) was obtained as an oil. 2.24 g (53%); δ ($CDCl_3$) 3.22 (3H, d, J_{HP} 9 Hz, NMe), 3.75 (6H, d, J_{HP} 12 Hz, 2 × POMe), 7.33 (4H, m, C_6H_4) (Found: C, 43.9; H, 5.3; N, 5.8%. Calculated for $C_9H_{13}ClNO_3P$: C, 43.4; H, 5.2; N, 5.6%).

Dimethyl N-methyl-N-(p-trifluoromethylphenyl) phosphoramidate (**5d**) was prepared as follows. p-Trifluoromethylanilinium chloride (5.59 g, 0.028 mol) was dissolved in $POCl_3$ (12.93 g, 0.085 mol) and heated under reflux for 4 h. After evaporation of excess $POCl_3$, yellow crystals of N-(p-trifluoromethylphenyl)phosphoramidic dichloride, $Cl_2P(O)NHC_6H_4CF_3$-p (**7**) were obtained. 7.03 g (89%); δ ($CDCl_3$) 7.30 (2H, d, J_{HH} 8 Hz, 2,6-H_2), 7.53 (2H, d, J_{HH} 8 Hz, 3,5-H_2).

7.03 g (**7**) in 30 ml of MeOH was added to a solution of MeONa (2.3 mole-equivalent) in MeOH (90 ml) and the solution was refluxed for 2 h. After removal of solvent, the residue was re-dissolved in chloroform (90 ml) and washed with water (3 × 25 ml). The aqueous layer was extracted with chloroform (30 ml), organic portions were combined, dried ($MgSO_4$), and solvent was removed under reduced pressure. Dimethyl N-(p-trifluoromethylphenyl) phosphoroamidate,

$(MeO)_2P(O)NHC_6H_4CF_3$-p (**8**) was obtained as a yellow solid; 5.43 g (79%); δ ($CDCl_3$) 3.79 (6H, d, J_{HP} 11.6 Hz, 2 × POMe), 7.08 (2H, d, J_{HH} 8.7 Hz, 2,6-H_2), 7.51 (2H, d, J_{HH} 8.7 Hz, 3,5-H_2).

4.01 g (0.015 mol) (**8**) was dissolved in THF (50 ml) and added dropwise to a stirred suspension of NaH (0.865 g, 80% w/w in oil, 0.029 mol) in THF (20 ml). Once evolution of hydrogen had ceased, a solution of Me_2SO_4 (1.86 g, 0.015 mol) in THF (20 ml) was added dropwise, and the mixture was stirred overnight at room temperature. After filtration and evaporation of solvent, the residue was dissolved in chloroform (80 ml) and washed with water (3 × 20 ml). After drying ($MgSO_4$) and removing solvent under reduced pressure, (**5d**) was obtained as orange oil. 3.03 g (73%); δ ($CDCl_3$) 3.25 (3H, d, J_{HP} 8.5 Hz, NMe), 3.74 (6H, d, J_{HP} 11.6 Hz, 2 × POMe), 7.33 (2H, d, J_{HH} 10.5 Hz, 2,6-H_2), 7.57 (2H, d, J_{HH} 10.5 Hz, 3,5-H_2).

Tetramethylammonium salts of methyl N-methyl-N-aryl phosphoramidic acids, $[Ar(Me)N](MeO)PO_2^- \; Me_4N^+$ (**9**) were obtained by heating solutions of (**5**) and trimethylamine (3–4 mole-equivalents) in acetonitrile in sealed tubes at 80°C for *ca.* 20 h. After cooling, the precipitated salts were filtered off and dried under reduced pressure. Tetramethylammonium methyl N-methyl-N-(p-anisyl) phosphoramidate (**9a**): 40%; v. hygroscopic; δ (D_2O) 3.03 (3H, d, J_{HP} 9 Hz, NMe), 3.20 (12 H, s, NMe_4^+), 3.55 (3H, d, J_{HP} 11 Hz, POMe), 3.85 (3H, s, ArOMe), 6.90–7.55 (4H, m, C_6H_4) (Found: C, 45.85; H, 8.9; N, 8.7%. Calcd for $C_{13}H_{25}N_2O_4P{\cdot}2H_2O$: C, 45.85; H, 8.5; N, 8.2%).

Tetramethylammonium methyl N-methyl-N-phenyl phosphoramidate (**9b**): 42%; v. hydroscopic; δ (D_2O) 3.03 (3H, d, J_{HP} 9 Hz, NMe), 3.20 (12 H, s, NMe_4^+), 3.53 (3H, d, J_{HP} 11 Hz, POMe), 7.00 – 7.50 (5H, m, Ph) (Found: C, 50.75; H, 8.35; N, 10.15%. Calcd for $C_{12}H_{23}N_2O_3P{\cdot}0.5H_2O$: C, 50.9; H, 8.5; N, 9.9%).

Tetramethylammonium methyl N-methyl-N-(p-chlorophenyl) phosphoramidate (**9c**): 75%; δ (D_2O) 3.02 (3H, d, J_{HP} 9 Hz, NMe), 3.22 (12H, s, NMe_4^+), 3.50 (3H, d, J_{HP} 11 Hz, POMe), 7.12 – 7.40 (4H, m, C_6H_4) (Found: C, 46.5; H, 7.15; N, 9.1%. Calcd for $C_{12}H_{22}ClN_2O_3P$: C, 46.75; H, 7.1; N, 9.1%).

Tetramethylammonium methyl N-methyl-N-(p-trifluoromethylphenyl) phosphoramidate (**9d**): 99%; δ (D_2O) 3.18 (12H, s, NMe_4^+), 3.19 (3H, d, J_{HP} 7.9 Hz, NMe), 3.49 (3H, d, J_{HP} 11.3 Hz, POMe), 7.40 (2H, d, J_{HH} 8 Hz, 2,6-H_2), 7.65 (2H, d, J_{HH} 8 Hz, 3,5-H_2).

Substrates (**1**) were prepared as follows. Freshly distilled benzoyl chloride (0.7 mole-equivalent) was dissolved in MeCN and added to a suspension of (**9**) (one mole-equivalent) in MeCN and the mixture was stirred at room temperature for 3 h. The precipitate was filtered off, CCl_4 or benzene was added to the filtrate and the further precipitate was filtered off again. After evaporation of solvents, the residue was redissolved in a minimum volme of CCl_4 or benzene, filtered through cotton wool and evaporated under reduced pressure. The products were obtained as viscous oils. (**1a**): 84%; δ ($CDCl_3$) 3.22 (3H, d, J_{HP} 10 Hz, NMe), 3.73 (3H, s, ArOMe), 3.88 (3H, d, J_{HP} 12 Hz, POMe), 6.60 – 8.12 (9H, m, C_6H_4, Ph) (Found: C, 57.0; H, 5.4; N, 4.2%. Calcd for $C_{16}H_{18}NO_5P$: C, 57.3; H, 5.4; N, 4.2%).

(**1b**): 52%; δ ($CDCl_3$) 3.33 (3H, d, J_{HP} 10 Hz, NMe), 3.91 (3H, d, J_{HP} 12 Hz, POMe), 7.00 – 8.30 (10H, m, 2 × Ph) (Found: C, 58.8; H, 5.35; N, 4.65%. Calcd for $C_{15}H_{16}NO_4P$: C, 59.0; H, 5.2; N, 4.6%).

(**1c**): 61%; δ ($CDCl_3$) 3.30 (3H, d, J_{HP} 10 Hz, NMe), 3.98 (3H, d, J_{HP} 12 Hz, POMe), 7.10 – 8.30 (9H, m, C_6H_4, Ph) (Found: C, 52.45; H, 4.55; N, 4.15%. Calcd for $C_{15}H_{15}ClNO_4P$: C, 53.1; H, 4.4; N, 4.1%).

(**1d**): 73%; δ ($CDCl_3$) 3.37 (3H, d, J_{HP} 9.6 Hz, NMe), 3.96 (3H, d, J_{HP} 11.6 Hz, POMe), 7.53 – 8.00 (9H, m, C_6H_4, Ph) (Found: C, 45.25; H, 5.01; N, 4.51%. Calcd for $C_{16}H_{15}F_3NO_4P$: C, 51.5; H, 4.0; N, 3.75%). Poor microanalysis results can be related to the presence of small amounts of tetramethylammonium chloride evident in the n.m.r. spectrum. This side product is difficult to remove because of the instability of the anhydride and the hygroscopic nature of the salt. Previous experiments have shown that the presence of this salt in no way affects the fragmentation reaction.

Product identification. Carboxyamides (**2a**) and (**2b**) were prepared independently in the following way. PhCOCl (0.01 mole) in ether (5 ml) was added slowly to a solution of the corresponding aniline (0.02 mole) in ether (10 ml) with cooling and stirring. After 2.5 h of stirring at room temperature the precipitate was filtered off and evaporation of the solvent gave products (**2**) as oils. (**2a**): δ ($CDCl_3$) 3.50 (3H, s, NMe), 3.77 (3H, s, OMe), 6.67 – 7.53 (9H, m, C_6H_4, Ph) (Found: C, 74.7; H, 6.35; N, 5.85%. Calcd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.2; N, 5.8%). (**2b**): δ ($CDCl_3$) 3.50 (3H, s, NMe), 7.30 (10H, m, 2 × Ph) (Found: C, 79.3; H, 6.25; N, 6.65%. Calcd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2; N, 6.6%).

Isolation of products (**2**) formed in the fragmentation of (**1**) was carried out as follows. Freshly prepared anhydride (**1**) was dissolved in dry MeCN and the solution was heated under reflux for at least 60 h. After cooling and evaporating the solvent, the residue was dissolved in chloroform, washed three times with dil. aq. NaOH (pH *ca.* 9), the chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure. Products (**2**) were obtained as oils or low melting solids. ^1H

n.m.r. spectra of these products were identical to those of the independently prepared (**2**) and corresponded closely to the final spectral obtained from the kinetic runs. (**2a**): 82%. Found: C, 73.0; H, 6.3; N, 5.45%. (**2b**): 77%. Found: C, 76.05; H, 6.25; N, 6.0%. (**2c**): 78%. Found: C, 68.2; H, 5.15; N, 5.55%. Calcd for $C_{14}H_{12}ClNO$: C, 68.6; H, 4.9; N, 5.7%. δ ($CDCl_3$) 3.44 (3H, s, NMe), 6.92 (2H, d, J_{HH} 8.1 Hz, 2,6-H_2), 7.08 – 7.26 (7H, m, 3,5-H_2, Ph). (**2d**): 88%. δ ($CDCl_3$) 3.52 (3H, s, NMe), 7.15 (2H, d, J_{HH} 8.7 Hz, 2,6-H_2), 7.26 (5H, b.s, Ph), 7.49 (2H, d, J_{HH} 8.7 Hz, 3,5-H_2).

No attempts were made to identify the phosphorus-containing product, (**3**) (R = Me).[11]

Kinetics. Approximately 60 μL of (**1**) was dissolved in 0.4 ml of $CDCl_3$, the solution was transferred to an n.m.r. tube, sealed and incubated in a water bath at 70°C. The ^1H n.m.r. spectra of these solutions were recorded periodically and the progress of the reaction was followed by comparing the growth of the broad singlet at δ *ca.* 3.5 and the reduction of the doublet at δ *ca.* 3.3. The amounts of products (**2**) present at various times and the first-order rate constants, k_1 were determined as before.[1] All runs gave linear plots with r values greater than 0.999. Reactions were followed to at least three half-lives and were allowed to go to completion for the purpose of identifying the expected carboxyamide products.

ACKNOWLEDGEMENTS

Financial assistance from the Council for Scientific and Industrial Research and the University of Pretoria is gratefully acknowledged.

REFERENCES

1. J. Symes and T. A. Modro, *Can. J. Chem.* **64,** 1702 (1986).
2. T. A. Modro, H. S. Rzepa and J. Symes, *J. Chem. Soc., Perkin Trans.* **2,** 767 (1987).
3. P. G. Perkins and J. J. P. Stewart, *Trans. Faraday Soc.* **2,** 78, 285 (1982).
4. J. Symes, T. A. Modro and M. L. Niven, *Phosphorus and Sulfur,* **29,** (1988) in press.
5. C. D. Johnson. In *The Hammett Equation*; Cambridge University Press; p. 3 (1973).
6. Because of their non-crystalline character and their thermal and hydrolytic instability, the N-aryl substituted anhydrides (**1**) are difficult to prepare in a state of high purity. Our attempts to synthesize the p-nitroderivative (**1**, X = NO_2) were unsuccessful.
7. A. Kivinen. In *The Chemistry of Acyl Halides*; Patai, S., Ed.; Interscience: London, Chapt. 6 (1972).
8. H. van Bekkum, P. E. Verkade and B. M. Wepster, *Rec. Trav. Chim.* **78,** 815 (1959).
9. B. Fischer and J. Michalski. *Rocz. Chem.* **26,** 688 (1952).
10. K. Rorig, *J. Am. Chem. Soc.* **71,** 3561 (1949).
11. The formation of the metaphosphate product (3) in reaction (1) was demonstrated previously[1] by trapping experiment.