Structural Effects in Amides. Crystal and Molecular Structures of Phosphoric and Carboxylic Anilides

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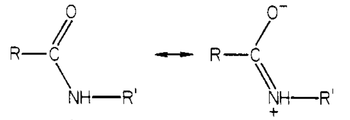
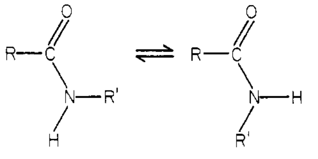
Crystal and molecular structures of three *N*-aryl carboxylic amides (RCONHAr) and three dimethyl *N*-arylphosphoramidates $(MeO)_2P(O)NHAr$ were determined and are discussed together with those of related systems described in the literature. Carboxylic amides exist in the trans configuration of the CO and NH groups, and both the *N*-aryl and *C*-aryl (for R = Ar) rings are considerably twisted with respect to the amide plane. Phosphoramidates prefer the cis orientation of the PO and NH groups, with the *N*-aryl group bisecting the MeO-P-OMe angle. Substituents in the *N*-aryl group have a weak effect on structural parameters of both amide functions. For the phosphoramidates a linear free-energy relationship between the intramolecular P=O···H—N hydrogen bonding and the acidity of the $ArNH_3^+$ ions has been obtained.

As a fundamental unit in a polypeptide chain, the amide system is one of the most important organic functional groups. In a secondary derivative (1), the nature of the molecular fragments R and R′ determines the detailed structural parameters of the amide linkage. These parameters include bonding characteristics such as CO and CN bond orders, degree of resonance interactions of the amide group with substituents R and R′, planarity of system 1, and the intermolecular hydrogen bonding effects. Resonance affects the bond orders at the carbonyl center, and therefore the C-O and C-N distances can serve as a measure of the contribution of the dipolar structure 2, which in turn should be influenced by polar effects of groups R and R′. Although a plot of the C=O vs. C—N distances of several amides suggests a reciprocal dependence,[1] some amides show significant deviations from this relationship. Any additional resonance interactions of the amide system with groups R and R′ should result in changes of the molecular parameters of 1, particularly in terms of the planarity of the molecule as a whole, and of the C-R and N-R′ distances.



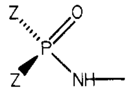
1 2

Hydrogen bonding interactions are primarily a function of the preferred conformation of the amide 1; the trans conformation 3 is generally stabilized thermodynamically over the cis (4) by a few kilocalories per mole.[2] Intermolecular hydrogen bonding in 3 results in the formation of polymeric aggregates, while 4, in the solid state, may form dimers or polymers, with the molecules often related by various symmetry elements.



3 4

Phosphoric amides 5 can be considered as close structural analogues of compounds 1. Both systems are derived from the primary amine R′-NH_2, acylated by groups (carboxyacyl and phosphoryl) of similar electronic effects.[3] However, as far as the bonding characteristics and structural effects are concerned, there are some essential differences between amides 1 and 5. Resonance interactions between the phosphoryl group and nonbonding electrons of the adjacent atom (amide nitrogen in 5) are expected to be less important[6] than the analogous conjugation in a carbonyl system. Consequently, any polar effects of the N substituent R′ should be transmitted less effectively to the P=O group than they are transmitted to the carbonyl group in structure 1.[7]



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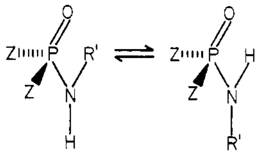
Since the phosphoryl center in 5 is not planar but tetrahedral, the cis conformation 7, with the projection of the N-R′ bond bisecting the ZPZ angle, should not suffer such destabilizing effects as the analogous conformation (4). Phosphoric amides should therefore show higher ability for the dimerization via the intermolecular hydrogen bonding than their carboxylic counterparts; such a tendency has been indeed demonstrated for these compounds in solution by IR[7] and NMR[8] spectroscopy.



6 7

Although the parallelism between carboxylic and phosphoric esters is frequently discussed,[9] comparative

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[1] M. B. Robin, F. A. Bovey, and M. Basch in "The Chemistry of Amides", J. Zabicky, Ed., Interscience, London, 1970, Chapter 1.

[2] M. D. Law, "The Organic Chemistyr of Peptides", Wiley-Interscience, London, 1970, p 155.

[3] With respect to the benzene ring (as measured by the ^{13}C NMR shielding parameters) benzoyl and diethyl phosphoryl $[(EtO)_2P(O)]$ groups show almost identical polar effects. The corresponding inductive (σ_I) and resonance ($\sigma_R{}^0$) substituent constants are 0.06 and 0.17 for the benzoyl group,[4] and 0.06 and 0.16 for the $(EtO)_2P(O)$ substituent.[5]

[4] G. C. Levy, R. L. Lichter, and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy", Wiley-Interscience, New York, 1980, Chapter 4.

[5] T. A. Modro, *Can. J. Chem.*, **55**, 3681 (1977).

[6] J. Emsley and D. Hall in "The Chemistry of Phosphorus", Harper and Row, London, 1976, Chapter 8.

[7] G. A. Foulds, B. P. Rijkmans, and T. A. Modro, *S. Afr. J. Chem.*, *34*, 72 (1981).

[8] M. J. P. Harger, *J. Chem. Soc.*, *Perkin Trans. 2*, 1882 (1977).

[9] See for example F. H. Westheimer, *Pure Appl. Chem.*, *49*, 1059 (1977).

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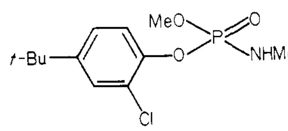
studies on the two classes of amides **1** and **5** are much more fragmentary. Following our interest in carboxylic amides[10] and their vinylogues,[11] as well as in phosphoramidates[12] and in the comparison between these two classes of compounds,[13] we decided to determine and analyze the crystal and molecular structures of some selected amides of types **1** and **5**. We wished to evaluate the changes in the geometry of the carboxyamide and phosphoramidate moieties which occur with structural modifications of the molecules.

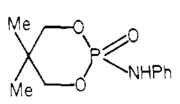
Results and Discussion

In this paper we report molecular parameters obtained by the determination of crystal structures of the *N*-aryl-substituted carboxylic and phosphoric amides shown in Chart I. All experimental data and details concerning the determination and refinement of the structures of the discussed compounds are published elsewhere.[14] Benzanilides **1a** and **1b** could be compared with benzamide itself (**1d**), whose crystal and molecular structure was described in detail by Penfold and White.[17] The para substituents in the *N*-aryl groups were selected to cover a large range of the electronic effects. *p*-Methoxyacetanilide (**1c**) could not be compared with its *p*-nitro counterpart because we failed to prepare crystals of the *p*-nitroacetanilide suitable for X-ray examination.[18] The structure of the compound **1c** could, however, be discussed together with that of the unsubstituted acetanilide **1e** described by Brown.[19]

Structural characteristics of the phosphoric anilides **5a–c** could be compared with only a few related systems. For the N-substituted diesters of amidophosphoric acid (**5**, Z = OR) the crystal and molecular structures of the insecticide crufomate (**5d**)[20] and 5,5-dimethyl-2-oxo-2-aminobenzo-1,3,2-dioxaphosphorinane (**5e**)[21] could be included in the comparison. Compound **5d** represents a model in which the nonbonding electrons at nitrogen cannot be involved in any resonance interactions with substituent R′ (methyl) and thus are fully available for the conjugation with the phosphoryl group. Amide **5e** can be compared



5d



5e

Table I. Selected Molecular Parameters[a] for Carboxylic Amides $RC_1(O)NHR'$

			bond distances, Å			bond angles, deg		dihedral angles, deg			
compd	R	R′	C_1-O	C_1-N	N-C(R′)	OC_1N	$C_1NC(R')$	Φ^b	θ^c	Ψ^d	conformation and hydrogen bonding
1a	Ph	p-$MeOC_6H_4$	1.22	1.36	1.44	124	124	1	28	38	trans, polymeric (N-H· · ·O, 3.11 Å)
1b	Ph	p-$NO_2C_6H_4$	1.23	1.38	1.42	122	125	0	28	36	trans, polymeric (N-H· · ·O, 3.11 Å)
1c	Me	p-$MeOC_6H_4$	1.23	1.35	1.42	123	127	5		22	trans, polymeric (N-H· · ·O, 2.88 Å)
1d[e]	Ph	H	1.24	1.31		122		planar	26		two sets: dimeric (N-H· · ·O, 2.96 Å), polymeric (N-H· · ·O, 2.91 Å)
1e[f]	Me	Ph	1.22	1.35	1.41	123	128	planar		18	trans, polymeric (N-H· · ·O, 2.94 Å)

[a] Bond distances in this work are accurate to within ±0.003–0.007 Å and angles to within ±0.2–0.5°. [b] Dihedral angle $O\text{-}C_1\text{-}N\text{-}C(R')$, i.e., the planarity of the amide group. [c] For R = Ph, the interplanar angle $C^{Ph}_{ortho}\text{-}C^{Ph}_{ipso}\text{-}C_1/C^{Ph}_{ipso}\text{-}C_1N$. [d] For R′ = Ar, the interplanar angle $C^{Ar}_{ortho}\text{-}C^{Ar}_{ipso}\text{-}N/C^{Ar}_{ipso}\text{-}NC_1$. [e] Reference 17. [f] Reference 19.

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[10] P. Wan, T. A. Modro, and K. Yates, *Can. J. Chem.*, *58*, 2423 (1980).

[11] M. P. du Plessis, R. G. F. Giles, and L. R. Nassimbeni, *S. Afr. J. Chem.*, *34*, 23 (1981).

[12] T. A. Modro and D. H. Graham, *J. Org. Chem.*, *46*, 1923 (1981).

[13] T. A. Modro, *ACS Symp. Ser.*, **No. 171**, 619 (1981).

[14] The crystal and molecular structure of **5b** have been published.[15] Publications concerning the crystallographic data on **5a,c**[16a] and **1a,b**[16b] will be available soon. Crystallographic data for of **1c** are available upon request from the Photocopying Section, CSIR Library Division, CSTL, P.O. Box 395, Pretoria 0001, South Africa.

[15] M. P. du Plessis, T. A. Modro, and L. R. Nassimbeni, *S. Afr. J. Chem.*, **33**, 124 (1980).

[16] (a) M. P. du Plessis, T. A. Modro, and L. R. Nassimbeni, *Acta Crystallogr.*, in press; (b) M. P. du Plessis, T. A. Modro, and L. R. Nassimbeni, submitted for publication in *Cryst. Struct. Commun.*

[17] B. R. Penfold and J. C. B. White, *Acta Crystallogr.*, **12**, 130 (1959).

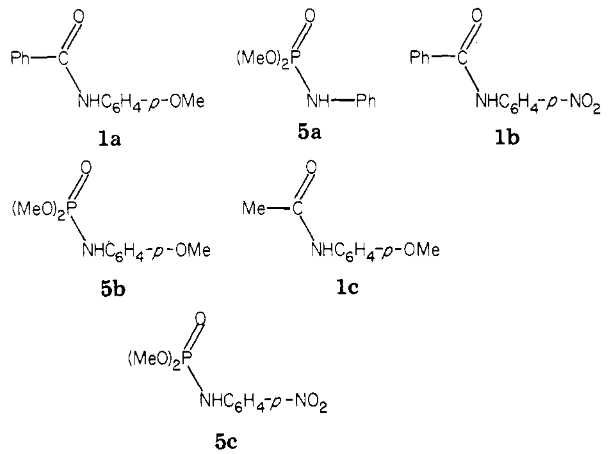
[18] Regardless of solvent, tempereature, and concentration, *p*-nitroacetanilide crystallizes in the form of soft, long needles, unsuitable for X-ray crystallographic purposes.

[19] C. J. Brown, *Acta Crystallogr.*, **21**, 442 (1966).

[20] R. G. Baughman, D. A. Eckey, and R. A. Jacobson, *J. Agric. Food Chem.*, *26*, 398 (1978).

[21] T. S. Cameron, Z. Galdecki, and J. Karolak-Wojciechowska, *Acta Crystallogr., Sect. B.*, **B32**, 492 (1976).

Chart I

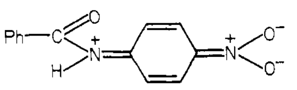


directly with **5a**, the only differences in molecular parameters stemming from the conformational restrictions introduced by the dioxaphosphorinane ring.

To avoid introducing unnecessary data, we selected only a few molecular parameters, directly related to the bonding of the amide function, planarity of the system, and hydrogen-bonding association, for the discussion.

Carboxylic Amides. Table I contains the relevant parameters obtained in this work and reported in the literature for amides of structure 1.

The partial double bond character of the carbonyl–nitrogen bond[22] requires the amide group to be planar. Since the resonance stabilization achieved in this way is large,[23] this is one of the most important geometrical conditions, as can be seen from the negligible deviations of the amide system from planarity for all compounds in Table I ($\Phi \approx 0°$). Variations in the detailed electron distribution within the amide function (as represented by the resonance structures 1 and 2) affect primarily the carbonyl–nitrogen bond order. For the unsubstituted amide **1d** the C_1–N distance is short (1.31 Å), indicating strong resonance donation effect of the nitrogen nonbonding electrons.[24] Substitution of one of the NH_2 hydrogen atoms for an aromatic group results in the decrease of this donation, as demonstrated by the increased C_1–N distance for all the remaining substrates in Table I. This competitive involvement of the aromatic ring in resonance interactions with the nitrogen atom is also a function of ring substituents. This can be clearly demonstrated by comparing structures **1a** and **1b**. In **1b** the nitrogen lone pair is strongly involved in conjugation with the *p*-nitro group (resonance structure 8), resulting in the elongation of the C_1–N bond (1.38 Å) and shortening of the nitrogen–aromatic carbon distance (1.42 Å). As expected, in compound **1a**, substituted with an electron-donating *p*-methoxy group, the values of the C_1–N and N–C(Ar) bonds (1.36 and 1.44 Å, respectively) are changed in opposite directions relative to the derivative **1b**. Comparison of **1c** and **1e** shows that, relative to the unsubstituted anilide **1e**, the presence of the *p*-methoxy group in **1c** has little effect on the nitrogen–ring interactions (identical values of the C_1–N distance). Since both the NHAc and OMe substituents are resonance donors with respect to the aromatic ring, the direct conjugation effects between these two groups are not possible.[25] It is relevant to note that all structural modifications do not significantly affect the carbonyl group; the C_1–O distance remains virtually constant throughout Table I. Similarly, the bond angles at the amide group (OC_1N and C_1NR') show almost no variations, indicating no changes in the hybridization of the atoms involved. Since all anilides included in Table I exist in the solid state in the trans configuration (3), the OC_1N and C_1NR' angles are greater than 120° due to the repulsion between aromatic moiety R′ and an electron-rich carbonyl group.[28] In all amides studied the aromatic rings, bonded to the carbonyl carbon (**1a,b,d**), as well as those substituted at nitrogen (**1a–c,e**), are twisted considerably with respect to the plane of the amide function. The deviation from the planarity at the carbonyl center is approximately constant ($\theta = 26$–$28°$); the rotation at nitrogen has a value of $\Psi = 36$–$38°$ for benzanilides and $\Psi = 18$–$22°$ for acetanilides. These conformations, resulting in the decrease of the resonance interactions of aromatic substituents with the amide group, are a consequence of close, nonbonding interactions between the ortho hydrogen atoms of the aromatic ring and the planar HNCO system of the amide.[17] In compounds containing two aromatic substituents (**1a,b**) both dihedral angles, θ and Ψ, have the same sign.[29] As a consequence, both benzene rings in **1a** and **1b** are twisted with respect to each other by an angle of 64–66° (Figure 1). The molecular geometry presented in Figure 1 indicates that any resonance interactions between the two aromatic groups are necessarily weak; therefore, the secondary amide structure ArC(O)NHAr′ cannot be considered as an extensively conjugated system. This may be the reason for the relatively small variations in the bonding



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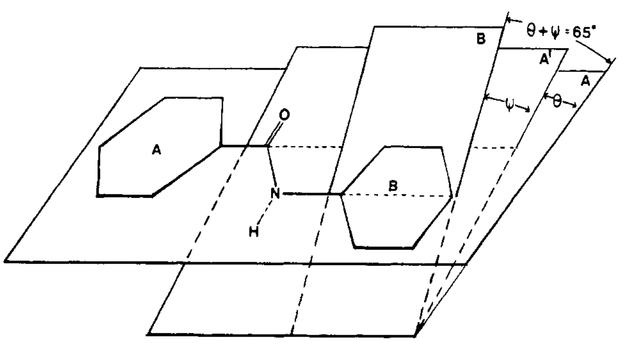

Figure 1. Projection of an *N*-arylbenzamide molecule: A, plane of the benzamide ring; A^1, plane of the amide function; B, plane of the *N*-aryl ring.

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[22] L. Pauling, "The Nature of the Chemical Bond", Cornell University Press, Ithaca, NY, 1958.

[23] The rotational barrier of the C–N bond for most of the amides is on the order of 20 kcal/mol.[1]

[24] For the *N*-methylacetamide the carbonyl–nitrogen bond is even shorter; C_1–N = 1.29 Å.[1]

[25] It is well-known from the electronic spectra of aromatic compounds that in the para-disubstituted systems, when the two substituents are of the same type there is not much change in the total substituent effect.[26] For example, while the benzanilide p-$NMe_2C_6H_4C(O)$-$NHC_6H_4NO_2$-p is a strongly conjugated system, the UV spectra of p-$NO_2C_6H_4C(O)NHC_6H_4NMe_2$-$p$ did not indicate a conjugation of two rings over the carboxamide groups.[27]

[26] E. S. Stern and C. J. Timmons, "Electronic Absorption Spectroscopy in Organic Chemistry", E. Arnold Ltd., London, 1970, Chapter 6.

[27] J. Reichel, R. Bacaloghi, And W. Schmidt, *Rev. Roum. Chim.*, **9**, 299 (1964); *Chem. Abstr.*, **61**, 12798 (1964).

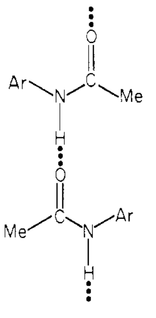
[28] R. J. Gillespie and R. S. Nyholm. *Q. Rev., Chem. Soc.*, 11, 339 (1957).

[29] In a system viewed down the J–K bond, the dihedral angle ω (I–J–K–L), i.e., the angle between I–J and K–L, is considered positive if the I–J bond has to be rotated clockwise into the K–L bond.[30]

[30] W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

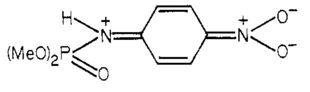
parameters of the amide functions observed for a series of derivatives 1.

All anilides are connected by a set of N–H···O type hydrogen bondings, joining molecules into endless chains. A fragment of such a chain formed by *p*-methoxyacetanilide (**1c**) can be represented as follows:



The orientation of molecules in the polymeric chain allows each aromatic group to interact with two (from above and below) methyl groups of the acetyl functions and thus to minimize intermolecular repulsions between two aromatic rings. Such a geometry is probably responsible for the relatively short (2.88 Å) hydrogen-bonding distance. In the case of benzanilides **1a,b**, regardless the orientation of molecules, the aggregation via hydrogen bonding is necessarily followed by intermolecular ring–ring interactions. This results in longer distances between units of the aggregate (N–H···O distance ≈ 3.1 Å), even for the *p*-nitroderivative **1b** for which relatively high acidity of the N–H group should be expected.

Phosphoric Amides. The molecular parameters obtained in this work for three dimethyl *N*-arylphosphoramidates, together with those reported for two other phosphoric amido esters, are listed in Table II. Since the phosphorus–nitrogen distance in the dipolar molecule of phosphoramidic acid H_3N^+–PO_3H^- ("pure" single P–N bond) is ca. 1.78 Å,[31] Table II indicates a significant increase of the P–N bond order in all amidates studied (P–N = 1.61–1.65 Å). This effect is stronger for the *N*-alkyl derivative **5d** since in this compound the nitrogen lone pair of electrons is fully available for interaction with the phosphoryl center. For the closely related series **5a–c**, ring substitution affects the nitrogen–ring interactions in an expected fashion. In the *p*-nitro compound **5c** the contribution of the dipolar resonance structure **9** is responsible



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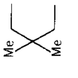
for the shortest [1.40 Å, C(Ar)–N] and longest [1.64 Å, N–P] distances. The fact that the nitrogen (amide)–carbon (aromatic) bond in **5c** is shorter than the same bond in its carboxylic analogue **1b** (1.40 vs. 1.42 Å)[32] either demonstrates that the phosphoryl group competes with respect to the nitrogen nonbonding electrons less effectively than the carbonyl group,[33] or results from the difference in the angle of the twist (hence conjugation) of the N-aromatic substituent relative to the plane determined by the amide

Table II. Selected Molecular Parameters[a] for Phosphoric Anilides (RO)(R′O)P(O$_1$)NHR″

				bond distances, Å			bond angles, deg		dihedral angles, deg		
compd	R	R′	R″	P–O$_1$	P–N	N–C(R′)	O$_1$–P–N	P–N–C(R″)	Φ[b]	Ψ[c]	conformation and hydrogen bonding
5a	Me	Me	Ph	1.46	1.62	1.42	111	131	3	8	cis, dimer (N-H···O, 2.86, 2.88 Å)[d]
5b	Me	Me	*p*-MeOC$_6$H$_4$	1.46	1.63	1.42	111	129	9	2	cis, dimer (N-H···O, 2.88, 2.89 Å)[e]
5c	Me	Me	*p*-NO$_2$C$_6$H$_4$	1.46	1.64	1.40	109	129	2	0	cis, polymeric (N-H···O, 2.83 Å)
5d[f]	Me	2-Cl-4-*t*-BuC$_6$H$_3$	Me	1.46	1.61	1.46	113	123	planar		cis[g]
5e[h]			Ph	1.48	1.65	1.42	116	123	almost planar	24	trans, polymeric (N-H···O, 2.80 Å)

[a] Bond distances determined in this work are accurate to within ±0.002–0.007 Å and angles to within ±0.1–0.6°. [b] Dihedral angle O$_1$–P–N–C(R″), i.e., the planarity of the amide group. [c] For R″ = Ar, the interplanar angle C^{Ar}_{ortho}–C^{Ar}_{ipso}–N/C^{Ar}_{ipso}–NP. [d] Hydrogen bonds in two crystallographically independent molecules of 5a. [e] Pair of crystallographically independent hydrogen bonds. [f] Reference 20. [g] No data on hydrogen bonding given. [h] Reference 21.

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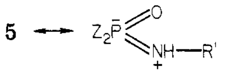
(31) (a) E. Holiles, D. E. C. Corbridge, and B. Raistrick, *Acta Crystallogr.*, **6**, 621 (1953); (b) D. W. J. Cruickshank, *J. Chem. Soc.*, 5858 (1961).

(32) Similarly, the N–C(Ar) distance in **5b** is shorter (1.42 Å) than that in **1a** (1.44 Å).

(33) The identical conclusion has been reached[34] on the basis of the ^{13}C NMR spectroscopy of the N-acylated and phosphorylated aniline derivatives.

(34) T. A. Modro, *Phosphorus Sulfur*, **5**, 331 (1979).

group. The characteristic feature of all the acylic structures **5a–d** is a constant value of the phosphoryl bond length (1.46 Å). It can be interpreted in terms of the constant P=O bond order, regardless of the degree of the p_π–d_π back-donation effect of the amide nitrogen atom. If the short P—N bond (e.g., **5d**) indicates high bond order, then the constant value of the P=O distance suggests contribution of a resonance structure (**10**) involving an hexavalent phosphorus atom.[35] Data for the cyclic structure **5e** point to the sensitivity of the molecular parameters of a phosphoramidate group to steric requirements. When compared with the noncyclic analogue **5a**, the dioxaphosphorinane structure **5e** is characterized by relatively long P=O and P—N bonds (1.48 and 1.65 Å, respectively). This is certainly the result of a tendency by the phosphoryl oxygen and the NHPh group to avoid destabilizing interactions with the 4,6-hydrogen atoms and 5,5-methyl groups of the six-membered ring. If the nitrogen atom in **5** is substituted by a particularly bulky group, the unfavorable interactions between this group and the (RO)$_2$P(O) moiety can result also in the elongation of the N–C bond. This was demonstrated in the recently published[37] structure of the methyl phenyl phosphoramidate of ethyl L-phenylalaninate, where the distance between the nitrogen atom and the bulky phenylalaninate ester group is increased to 1.49 Å.[38]



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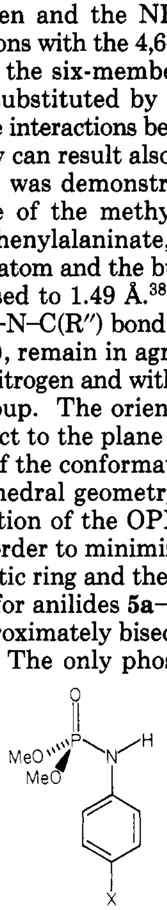
The values of the P-N-C(R″) bond angles, together with values of Φ (Table II), remain in agreement with the sp^2 hybridization of the nitrogen and with the planarity of the phosphoramidate group. The orientation of the N-aromatic ring with respect to the plane of the amide system is clearly a function of the conformation of the molecule. Because of the tetrahedral geometry of the phosphorus atom, the cis orientation of the OPNH linkage requires small values of Ψ in order to minimize steric interactions between the N-aromatic ring and the two phosphate ester groups. This occurs for anilides **5a–c** where the plane of the benzene ring approximately bisects the MeO-P-OMe angle (structure I). The only phosphoramidate which exists in a trans conformation (**6**) is the dioxaphosphorinane derivative **5e**.[21] This conformation is necessary in order to avoid unfavorable interactions between the phenyl group and the axial hydrogen atoms at the 4- and 6-positions of the phosphorinane ring. In a trans conformation the phenyl moiety is not twisted considerably (Ψ = 24°) with respect to the plane of the phosphoramidate group, as a result of steric interactions between the phosphoryl oxygen and the ortho CH fragment of the *N*-phenyl substituent.



I, X = H, OMe, NO$_2$

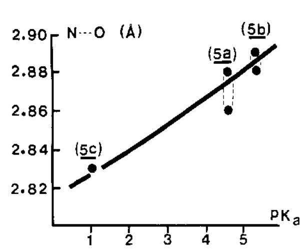
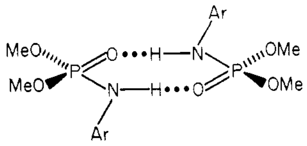


Figure 2. Intermolecular hydrogen bonding distance in (MeO)$_2$P(O)NHAr vs. acidity of the ArNH$_3^+$ ions.

All amides **5** form intermolecular hydrogen bonds of the P=O···H—N type. Anilides **5a** and **5b**, existing in the cis conformation, form centrosymmetric dimers **11**, while compound **5c**, although also having cis orientation, is arranged in the form of a polymeric aggregate. Polymeric structure is, of course, a necessary arrangement for the trans-orientated anilide **5e**.



11

Since the anilides **5a–c** differ only by a substituent at the para position of the *N*-aryl group, the variations in the hydrogen bonding can be considered as a direct function of the polar effects of these substituents. The electronic effects of ring substituents should be expected to modify the acidity of the N–H group and thus to vary the strength of the corresponding hydrogen bond. For these three anilides the hydrogen bonding (measured as the intermolecular N···O distance) gives fairly linear correlation with the pK_a values[39] of the corresponding anilinium ions ArNH$_3^+$ (Figure 2). Although the lfe relationship represented in Figure 2 is an approximate one, there seems to be a direct correlation between the acidic properties measured in solution and the intermolecular interactions in the solid state. The plot indicates that the electronic effects of the N substituent are poorly transmitted to the phosphoryl group. If it were otherwise, any increase in donating ability of the N–H function should decrease the accepting ability of the P=O group (and vice versa), so the net N···O distance should not vary significantly with ring substitution. The P=O distance in structures **5a–c** is constant within the experimental error (average P=O = 1.460 ± 0.005 Å), which is in agreement with this conclusion.

Experimental Section

Anilides **1a–c** were prepared from the corresponding acyl chlorides and substituted anilines. Their melting points were identical with those reported in the literature, and their ^{1}H NMR spectra and elemental analyses were in full agreement with the expected structures. Phosphoramidates **5a,b** were prepared from dimethyl phosphorochloridate and the corresponding aniline in the presence of triethylamine. For **5a**, mp 83–85 °C (from petroleum ether). Anal. Calcd for $C_8H_{12}NO_3P$: C, 47.76; H, 6.01; N, 6.96. Found: C, 47.75; H, 5.95; N, 6.90. **5b**, mp 68–69 °C (from petroleum ether). Anal. Calcd for $C_9H_{14}NO_4P$: C, 46.76; H, 6.10; N, 6.06. Found: C, 46.45; H, 6.10; N, 5.95. **5c** was prepared from *N*-(*p*-nitrophenyl)phosphoramidic dichloride and sodium methoxide; mp 164–165 °C (from benzene). Anal Calcd for

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[35] A resonance structure analogous to **10** has been postulated in discussion of the UV spectra of aromatic phosphonic acids.[36]

[36] R. F. Husdon. "Structure and Mechanism in Organophosphorus Chemistry", Academic Press, London, 1965, Chapter 3, Section VIII.E.

[37] T. Koizumi, Y, Kobayashi, E. Hoshii, M. Takamoto, K. Kamiya, and H. Asakawa, *Tetrahedron Lett.*, 3995 (1980).

[38] T. Koizumi, personal communication.

[39] C. D. Johnson, "The Hammett Equation", Cambridge University Press, Cambridge, 1973, p 29.

$C_8H_{11}N_2O_5P$: C, 39.03; H, 4.50; N, 11.38. Found: C, 39,05; H, 4.45; N, 11.45.

All the crystal structures were determined from diffractometer intensity data. Structure solutions were carried out by direct methods and refined by full-matrix least-squares routines using the SHELX-76 program.

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Registry No. 1a, 7472-54-0; **1b**, 3393-96-2; **1c**, 51-66-1; **5a**, 58046-12-1; **5b**, 25627-05-8; **5c**, 78258-13-6.

Substituent Effects. 9. Two Charged Groups. Remarks on the Eucken/Kirkwood-Westheimer Model and the Reversed-Field Effect

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Thermodynamic dissociation constants are given for 3,5-$(NMe_3^+)_2$-, 3,5-$(SO_3^-)_2$-, and 3-NMe_3^+-5-$SO_3^-C_6H_3COOH$ in water and ethanol-water mixtures. These follow the extended Hammett equation $\Delta = \rho\sigma^L + \delta^B$ (δ^B is the electrostatic Bjerrum term). This equation also accounts for the phenolic dissociation of the zwitterionic form of tyrosine (VI) and *N,N,N*-trimethyltyrosine (VII). In the latter compound the "reversed field" is acid weakening; nevertheless, acid strengthening is observed. Some other reversed-field models are given. The data strongly favor the view that the electrostatic field is not the prevailing factor. Substituent effects in 0-4 M NaCl are also presented; the zwitterionic compounds (V and VII) conform to the behavior of dipole-substituted acids.

In previous papers[1,2] we have discussed and applied an extended Hammett equation which covers not only the effects of dipole substituents but also those of charged (pole) substituents:

$$\Delta = \rho\sigma^{Ln} + \delta^B \qquad (1)$$

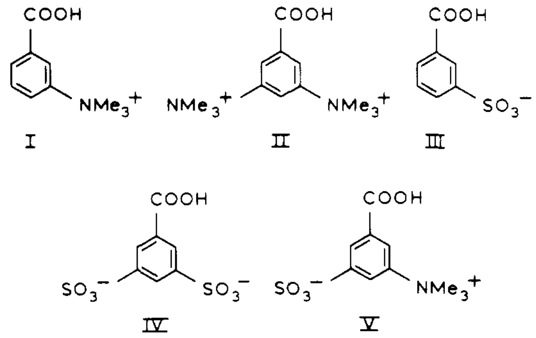
In this equation Δ is the substituent effect ($\log K - \log K^0$), $\rho = \rho_m$ is the reaction constant obtained with a set of standard meta σ values, σ^{Ln} is a "normal" σ value (for dipole substituents $\sigma^{Ln} = \sigma^n$ or σ^0; for pole substituents σ^{Ln} values were derived and tabulated),[1] and δ^B is the Bjerrum term. This last term is believed to account for, e.g., the work involved in bringing a dissociating proton to infinity against the electrostatic field of the pole or dipole of the substituent and is considered to be (almost) structure independent. The $\rho\sigma$ term, then, covers the ionization and is structure dependent.[3] For solvents with a high dielectric constant, D_s, δ^B is small for dipole substituents, so that eq 1 practically reduces to the Hammett equation; for charged substituents, δ^B cannot be neglected. For ionic reactions in the gas phase, δ^B is already large for dipole substituents[1,4] and should be taken into account when investigating structural correlations of the Hammett type.

For proton dissociation in water at 25 °C with $D_s = 78.5$ and a singly charged substituent, Bjerrum[5] obtained:

$$\delta^B = 3.1/r \qquad (2)$$

where δ^B is in pK units and r is the distance between substituent charge and proton (in angstroms). Generalizing for media with dielectric constant D_s, eq 3 can be written:

Chart I



$$\delta^B = 243/D_s r \qquad (3)$$

In what follows we shall also refer to ${}^eD_E$, the "empirical effective dielectric constant".[1] The concept was introduced by Eucken[6] (discussing dipole effects) and is simply defined as the dielectric constant number[7] required to obtain the observed substituent effect from an equation representing coulombic interactions like eq 3. Hence, ${}^eD_E$ for pole-pole interaction is defined by

$$\Delta = 243/{}^eD_E r \qquad (4)$$

Thus, for 3-$NMe_3^+C_6H_4COOH$ in water, with $\Delta = 1.03$ and $r = 6.3$ Å,[1] ${}^eD_E = 37$.

For dipoles δ^B can be obtained from eq 2 or 3 treating the effect of the dipole as the sum of the effects of two point charges with the appropriate (fractional) charges at the ends of the dipole vector. Often, the approximate eq 5 corresponding with eq 2 is used,

$$\delta^B = (0.65\mu \cos\theta)/r^2 \qquad (5)$$

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[1] Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720.

[2] van de Graaf, B.; Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1981**, *46*, 653.

[3] For recent work treating protonic dissociation as a two-stage process see: Blandamer, M. J.; Scott, J. W. M.; Robertson, R. E. *J. Chem. Soc., Perkin Trans. 2* **1981**, 447.

[4] Cf.: Topsom, R. D. *Tetrahedron Lett.* **1980**, *21*, 403; *J. Am. Chem. Soc.* **1981**, *103*, 39. Hehre, W. J.; Taagepera, M.; Taft, R. W.; Topsom, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 1344. Yoder, C. S.; Yoder, C. H. *Ibid.* **1980**, *102*, 1245.

[5] Bjerrum, N. *Z. Phys. Chem., Stoechiom. Verwandtschaftsl.* **1923**, *106*, 219.

[6] Eucken, A. *Angew. Chem.* **1932**, *45*, 203.

[7] King, E. J. "Acid-Base Equilibria"; Pergamon Press: Oxford, 1965; p 160: "... 'effective dielectric constant' constant"...is only a convenient locution to preserve the formalities of the Bjerrum and Eucken equations".

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