Synthesis and stereochemistry of benzamidines and acetamidines[1]

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Abstract

Phosphoric anhydride reacts with benzanilides and acetanilides in a novel self-condensation reaction to give *N*-substituted aroyl and acyl amidines (2a-g) and (4a-d) respectively. In contrast, an *N*-alkylbenzamide (5) gave dibenzamide (6). X-ray crystallographic studies of (2b), (2d), (4f) and (6) are reported. NMR spectroscopy of *N*-benzoyl-*N*,*N*′-bis(2,6-diethylphenyl)-benzamidine (2e), *N*-benzoyl-*N*,*N*′-bis(2,6-diisopropylphenyl)benzamidine (2f), *N*-acetyl-*N*,*N*′-bis(2,6-diethylphenyl)acetamidine (4e) and *N*-acetyl-*N*,*N*′-bis(2,6-diisopropylphenyl)-acetamidine (4f), revealed diastereotopic ethyl and isopropyl groups, which is attributed to chirality arising from restricted rotation about the aryl-N bonds. The barrier to rotation about the least restricted aryl-N bond of the benzamidine (4f) was 76 kJ mol^{-1} as determined by variable temperature NMR spectroscopy. Splitting of the NMR methyl signals for *N*-benzoyl-N,N′-bis(2-methylphenyl)-benzamidine was also observed. Molecular mechanics modelling, together with X-ray crystallography, indicated that this is due to the adoption of an unusual rotamer equilibrium which gives rise to two environments for the amide bound 2-tolyl methyl group. The ambident character of benzanilide and the stabilities of phosphorylated intermediates was studied by semi-empirical and *ab initio* MO calculations. Evidence for the establishment of an equilibrium mixture of O-phosphorylated and N-phosphorylated amides via phosphorotropy and the intermediate formation of nucleophilic iminol tautomers is discussed as part of a proposed reaction mechanism.

Keywords: Benzamidines stereochemistry, ab initio MO calculations, Molecular mechanics, phosphoric anhydride

Introduction

The original aim of this study was the direct preparation of acyclic phosphorylated amides which previously had been prepared by indirect methods only.[2] Due to the ambident nucleophilic character of carboxylic amides there is the possibility of forming N-phosphorylated amides and

O-phosphorylated imidates. N-Phosphorylated amides have been widely used in the synthesis of unsymmetrical phosphates,[3] pyrophosphates,[3,4] as phosphorylating agents for alcohols[5] and they have been found to be excellent pesticides[6] and antiviral agents.[7] O-Phosphorylated imidates or imidoyl phosphates have been detected as reactive intermediates in the synthesis of unsymmetrical pyrophosphate diesters[3,4] and the Pictet-Gams and Bischler-Napieralski reactions may also involve O-phosphorylated amide groups.[8]

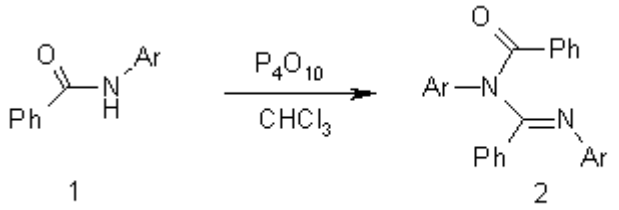
Whilst the methodology for the synthesis of phosphorylated acyclic amides is broad and well developed[3-9] many of them have limitations. Since phosphoric anhydride has been shown to be an efficient phosphorylating agent for cyclic amides, such as barbiturates,[10] this investigation was directed at its potential for the phosphorylation of acyclic amides, i.e. benzanilides, acetanilides and N-alkylbenzamides.

Results and Discussion

General Procedures. The reactions of the secondary amides with phosphoric anhydride were performed in chloroform and monitored by ^{31}P NMR spectroscopy. The spectra followed a similar complex series of patterns, throughout the three series of benzanilides and acetanilides and alkylbenzamide, which were assigned to the products of consecutive cleavage of residual phosphoric anhydride cyclic fragments. The usual sequence consisted of a number of multiplets centred at δ_P -42, -30 and -25, and -12 ppm. The signals of main intensity gradually moved from the higher to the lower field regions in accordance with continued opening of the phosphoric anhydride cage. ^{13}C NMR monitoring of the course of the reaction showed the presence of starting amide, the products of self-condensation and signals attributed to phosphorylated intermediate - the signal intensities of each changing in the expected manner.

Reaction of benzanilides with phosphoric anhydride. The reaction of benzanilide and its analogues (1a-g) with phosphoric anhydride proceeded at different rates depending on the nature of the substituents on the anilide group. As the reaction proceeded, the reactants slowly dissolved, and the reaction mixture developed a range of colours from pale yellow to dark red. Upon completion of the reaction and evaporation of the solvent, the residue was treated with a protic solvent such as ethanol to gently cleave the residual P-O-P bonds of phosphoric anhydride. Following extraction and recrystallisation, crystalline aroyl benzamidines (2a-g) (Equation 1) were isolated in 41-84% yields. The highest yields of the benzamidines were obtained by reacting phosphoric anhydride with benzanilide in the ratio of 1:3, using chloroform as solvent at room temperature (20^{o}C) for 0.25 to 56 h depending on the aryl substituents. With respect to the reaction rates, electron-donating substituents such as methoxy and alkyl groups facilitated the reaction, whereas the electron-withdrawing nitro group inhibited the condensation and promoted hydrolysis of the benzanilide. When the alkyl substituents were ortho orientated steric shielding of the reactive centre tended to partially counter the inductive effect. As

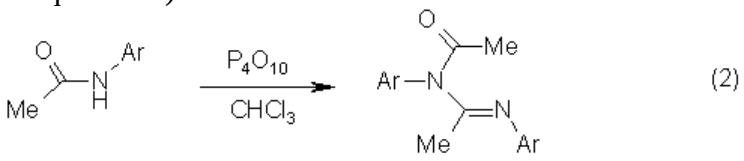
expected the steric hindrance was greater for the isopropyl analogues than for the methyl analogues. The benzanilide bearing the strong electron-donating dimethylamino group in the para position of the aniline ring reacted readily as indicated by the rapid dissolution of the phosphoric anhydride in the chloroform. However characterisation of the product was inhibited by the extreme insolubility of the isolated product.



1 2 (1)

a, Ar = Ph
b, Ar = 2-MeC_6H_4
c, Ar = 2,6-$Me_2C_6H_3$
d, Ar = 2,4,6-$Me_3C_6H_2$
e, Ar = 2,6-$Et_2C_6H_3$
f, Ar = 2,6-$iPr_2C_6H_3$
g, Ar = 4-OMeC_6H_4

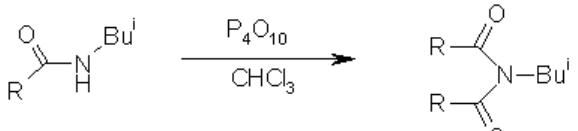
Reaction of acetanilides with phosphoric anhydride. Acetanilide and its homologues (3a-f) with different substituents in the aniline ring reacted under similar conditions with phosphoric anhydride to give the products of self-condensation, i. e. substituted acyl acetamidines (4a-f) (Equation 2, Ar as in Equation 1).



3 4 (2)

Whilst the ortho diethyl and diisopropyl substituted acetanilides were the most reactive - slightly exothermic reactions occurring- the *o*-methylacetanilide and non-substituted acetanilide required reflux conditions. Although acyl acetamidines were obtained from the latter acetanilide on one occasion, the reaction could not be reproduced. An isolation procedure, similar to benzamidines, was applied. Recrystallisation from ethanol gave pure products in 2-74 % yield.

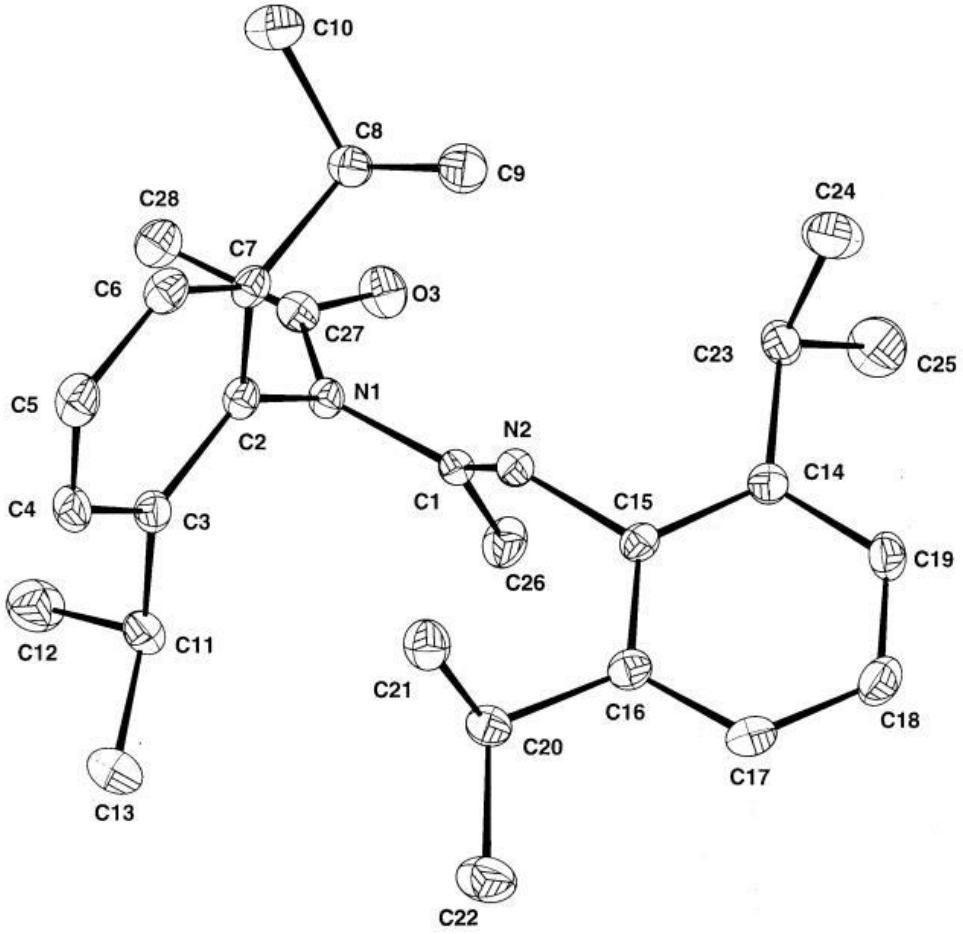
Reaction of N-alkyl amides with phosphoric anhydride



5; (a) R = Ph
(b) R = Me

6 (3)

N-Isobutylbenzamide (5a) reacted slowly with 3 equivalents of phosphoric anhydride to give N-isobutyldibenzamide (6a) as shown in Equation 3. The reaction was carried out in chloroform at room temperature over a period of 41 h . Column chromatography gave a 24 % yield of the imide. While the method cannot be used for the synthesis of N-alkylamidines, the reaction did provide some key information on the reaction mechanism (discussed below). N-Isobutylacetamide (5b) was unreactive under these reaction conditions.



Structure determination of benzamidines. The proton decoupled ^{13}C NMR spectra of substituted benzamidines contained two low intensity signals, broadened by the nitrogen atom, one in the region of δ_C 170.4 - 173.5 ppm and the other in the region of δ_C 155.3 - 158.3 ppm attributed to the amide C=O and C=N groups, respectively (Table 1). The presence of only one carbonyl signal indicated one geometric isomer about the amide bond. X-ray crystallographic analysis of benzamidines 2b and 2d showed the aryl groups on the amide group to be *trans* orientated (Figures 1 and 2, Table 2). An appropriate number of signals in the region 135.9-114.0 ppm arising from the presence of four aromatic rings, was evident. The remainder of the aliphatic region depended on the aryl substituents, non-equivalence being observed for three compounds. The infra-red spectra of the products contained a strong amide I band in the region

1675 - 1648 cm^{-1} which was generally of higher wave number than the parent anilides, i.e. 1654 - 1639 cm^{-1} (Table 3). The increase is attributed to additional delocalisation of the amide nitrogen lone pair of electrons with the imine group. Also present in the spectra was a band in the region 1646 - 1619 cm^{-1} assigned to the imine stretching mode and a band near 1300 cm^{-1} assigned tentatively to an amide III band due to overlap with other bands.

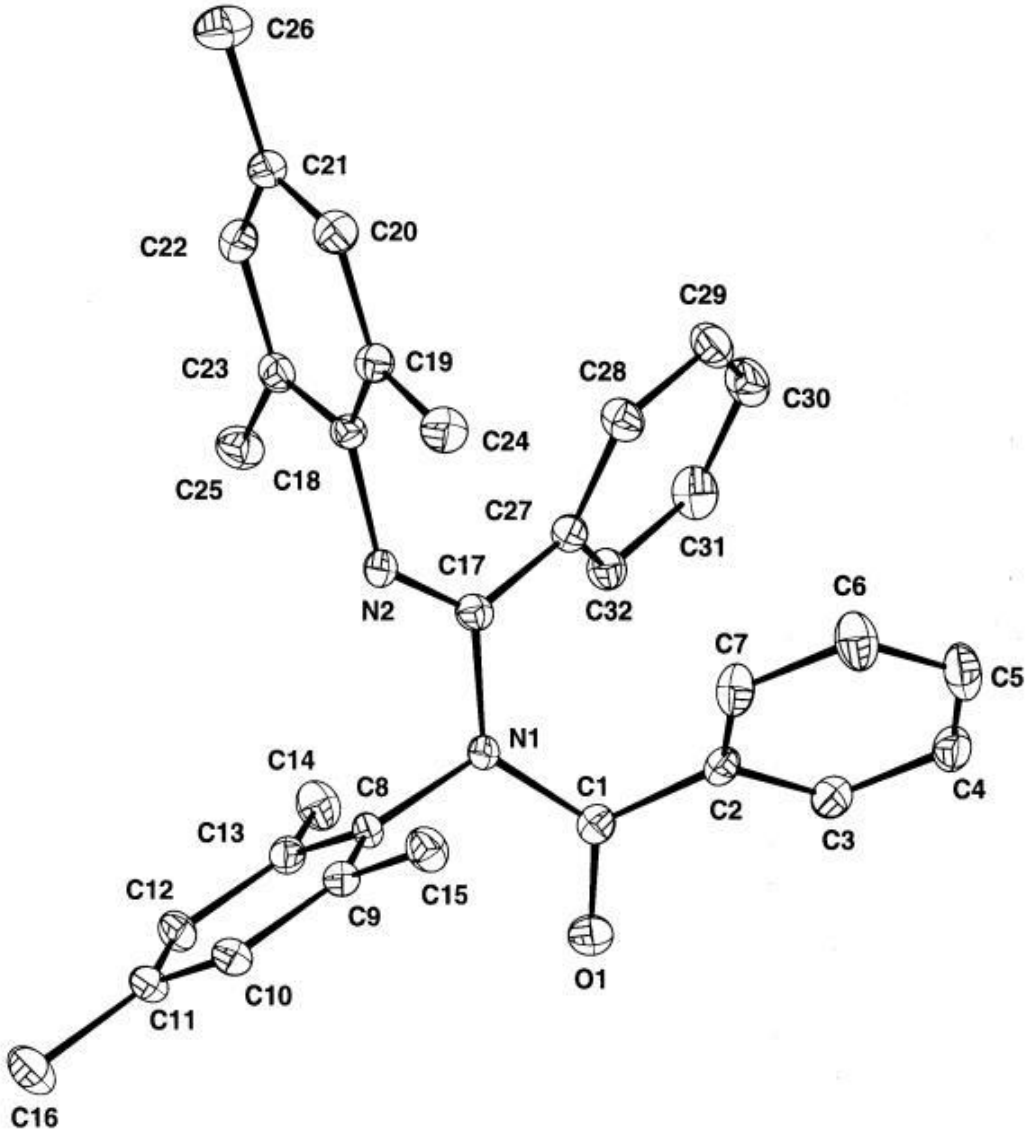


Table 1. ^{13}C NMR chemical shifts of the N-substituted aroyl benzamidines (2a-g)

		Chemical shift, ppm				
Compound	Solvent	=O	C=N	Aromatic carbons	Aliphatic substituents on the aniline rings	
					a	i
	$C_2D_2Cl_4$	170.5	158.3	148.4-119.6	-	-
2a	$(CD_3)_2CO$	170.9	159.5	149.8-120.6	-	-
	$C_2D_2Cl_4$	172.4	157.5	147.1-117.4	17.3, 18.2 (o-CH_3)	18.5 (o-CH_3)
2b	$(CD_3)_2CO$	172.9	158.5	148.6-118.3	17.5, 18.4 (o-CH_3)	18.7 (o-CH_3)
	$(CD_3)_2CO$	173.1	156.8	146.9-123.4	19.2 (2 o-CH_3)	19.8 (2 o-CH_3)
2c	$(CD_3)_2SO$	172.0	155.4	145.3-122.5	18.4 (2 o-CH_3)	18.9 (2 o-CH_3)
	$(CD_3)_2CO$	173.3	157.0	144.5-126.5	20.6 (p-CH_3),[a] 19.2 (2 o-CH_3)	20.9 (p-CH_3),[a] 19.7 (2 o-CH_3)
2d	$(CD_3)_2SO$	172.1	155.6	142.9-125.1	20.1 (p-CH_3),[a] 18.3 (2 o-CH_3)	20.3 (p-CH_3),[a] 18.8 (2 o-CH_3)
	$C_2D_2Cl_4$	172.8	155.3	144.8-123.2	24.5 ($2CH_2$), 13.2 ($2CH_3$)	24.7 ($2CH_2$), 13.5 ($2CH_3$)
2e	$(CD_3)_2CO$	173.3	156.4	145.6-123.8	25.3 ($2CH_2$), 13.9 ($2CH_3$)	25.5 ($2CH_2$), 14.1 ($2CH_3$)
	$C_2D_2Cl_4$	173.4	155.4	146.6-123.0	27.6 (2CH), 24.7, 22.6 ($4CH_3$)	29.3 (2CH), 25.0, 23.2 ($4CH_3$)
2f	$(CD_3)_2CO$	174.2	157.0	147.8-124.0	28.5 (2CH), 25.2, 22.9 ($4CH_3$)	30.0 (2CH), 25.5, 23.5 ($4CH_3$)
	$C_2D_2Cl_4$	170.4	157.3	135.8-114.0	55.4 (o-OCH_3)[a]	55.5 (o-OCH_3)[a]
2g	$(CD_3)_2CO$	170.7	158.5	138.2-114.8	55.6 (o-OCH_3)[a]	55.7 (o-OCH_3)[a]

[a] The assignment of signals to the amide or imine part of the molecule was tentative.

Table 2. Selected bond lengths [Å], bond angles and torsion angles [deg] for the substituted benzamidines 2b, d

2b		2d	
O1-C1	1.210(3)	O1-C1	1.220(3)
N1-C1	1.396(3)	N1-C1	1.397(3)
N1-C8	1.422(3)	N1-C8	1.460(3)
N1-C15	1.433(3)	N1-C17	1.416(3)
N2-C15	1.258(3)	N2-C17	1.279(3)
N2-C22	1.419(3)	N2-C18	1.424(3)
C1-C2	1.471(4)	C1-C2	1.491(4)
C15-C16	1.482(3)	C17-C27	1.493(4)
C1-N1-C8	118.9(2)	C1-N1-C8	115.7(2)
C1-N1-C8-C9	123.01(0.28)	C1-N1-C8-C9	83.63(0.32)
C1-N1-C8-C13	-60.00(0.34)	C1-N1-C8-C13	-95.02(0.31)
C15-N2-C22-C23	-51.18(0.41)	C17-N2-C18-C19	-107.47(0.32)
C15-N2-C22-C27	133.36(0.30)	C17-N2-C18-C23	81.05(0.36)
C1-N1-C15-N2	-37.25(0.40)	C1-N1-C17-N2	-153.83(0.27)
C1-N1-C15-C16	142.85(0.25)	C1-N1-C17-C27	29.94(0.39)
C8-N1-C15-N2	126.77(0.29)	C8-N1-C17-N2	23.10(0.36)
C8-N1-C15-C16	-53.13(0.31)	C8-N1-C17-C27	-153.14(0.24)
N1-C1-C2-C3	151.96(0.26)	N1-C1-C2-C3	-148.56(0.28)
N1-C1-C2-C7	-33.34(0.39)	N1-C1-C2-C7	36.24(0.42)

Table 3. Characteristic IR wavenumbers ν_{max}, cm^{-1} of benzanilides (1a-g) and N-substituted aroyl benzamidines (2a-g)

Compound	$\nu_{N-H\ str}$	Amide I[a] $\nu_{C=O\ str}$	$\nu_{C=N\ str}$	Amide II[b] $\nu_{N-H\ bend}$	Amide III[c] $\nu_{C-N\ str}$
1a	3343	1654	-	1531	1322
2a	-	1652	1626	-	1336
1b	3243	1648	-	1523	1309
2b	-	1675	1625	-	1286
1c	3272	1643	-	1519	1305
2c	-	1671	1646	-	1270 (t)[d]
1d	3270	1639	-	1517	1307
2d	-	1666	1621	-	1334
1e	3297	1641	-	1519	1290
2e	-	1668	1635	-	1295
1f	3276	1641	-	1521	1290
2f	-	1668	1619	-	1332

1g	3330	1646	-	1513	1249
2g	-	1648	1623	-	1344 (t)

[a] The amide-I band mainly involves C-O stretching, C[a]-C-N deformation, and CN stretching.[90] [b] The amide-II band arises from in-phase N-H in-plane bending (>50%) and C-N stretching.[89-91] [c] The amide-III band consists of C-N stretching (>50%) and out-of-phase N-H in-plane bending.[90, 91] [d] The assignment was tentative.

Stereochemistry of benzamidines. The symmetrically substituted bis(2,6-dimethylphenyl) (2c) and bis(2,4,6-trimethylphenyl) benzamidine (2d) showed separate ortho-methyl signals for the imide and amide N-aryl groups but no other non-equivalence, whereas the bis(2,6-diethylphenyl) (2e) and bis(2,6-di-isopropylphenyl) benzamidine (2f) exhibited additional non-equivalence of the methylene protons and the isopropyl methyl groups, respectively. The bis(2,6-diethylphenyl) benzamidine (2e) had the highfield methylene proton signal split into two equally intense signals at δ_H 2.2 and 2.4 ppm (Table 4). Whereas for the bis(2,6-di-isopropylphenyl) benzamidine (2f), the methyl signals (but not the methine signals) of the ortho orientated iso-propyl groups for both rings were split into two equally intense signals in the ^{1}H and ^{13}C NMR spectra. Similar spectra were obtained using several solvents. Splitting due to E and Z geometric isomers about the amide or imine group can be eliminated since the non equivalence was absent for the bis(dimethylphenyl) and bis(trimethylphenyl) benzamidines (2c) and (2d) and for the methine carbon of the isopropyl groups of (2f). Restricted rotation about the N-aryl rings would produce chiral molecules in an analogous way to biphenyls, the benzyolated amidine groups providing the necessary non-symmetry. Thus the prochiral nature of the groups and the equal intensity of the split signals provide convincing evidence that the benzamidines are chiral due to restricted rotation about the N-aryl rings and thus the origin of non equivalence of the prochiral groups.

The unsymmetrically substituted bis(2-methylphenyl) benzamidine (2b) also showed additional splitting of the methyl signals in the ^{1}H and ^{13}C NMR spectra. In the absence of prochirality this non-equivalence clearly must have a different origin to the above. The possible causes of the additional splitting of the NMR methyl signals of (2b) were investigated by molecular modelling (see conformational analysis section below).

X-ray crystallography of the bis(2-methylphenyl) benzamidine (2b) and bis(2,4,6-trimethylphenyl) benzamidine (2d) (Figures 1 and 2 and Table 2) showed *trans* orientated aryl groups on the amide group for both structures. However, the orientation of the aryl groups on the imine group differed being *trans* for the 2-methylphenylbenzamidine (2b) and *cis* for the mesityl compound (2d). The mesityl rings were at approximately 80° angles to the amidine group supporting the concept of restricted rotation leading to a chiral molecule. This was reduced for the mono methyl compound (2b) the tolyl groups being about 60° and 50° out of the plane of the amide and imine groups respectively. In this structure the methyl groups have a *syn* relationship with respect to the bent amidine group, butthe most marked relationship was the juxtapositions of the amide tolylmethyl group and the amide carbonyl group (Figure 1).

Conformational analysis of benzamidines. The 270 MHz ^{1}H NMR spectrum of the bis(2,6-diethylphenyl) benzamidine (2e) in chloroform had three methylene signals at 3.03, 2.38 and 2.20 ppm in an intensity ratio of 2:1:1 (Table 4). The latter pair of signals were partially resolved two subsets of doublet of quartets ($^2J_{HH}$ 14.6 and $^3J_{HH}$.7.3 Hz) which coalesced to a singlet at 120°C. Application of the Eyring equation to the nmr data by treating the system as an uncoupled AB case with equal rotamer population gave an approximate barrier of 80 kJ mol^{-1}.
MM Molecular modelling was used to probe the stereochemistry of (2e) on the assumption that the amide group retains the *trans* aryl rings geometry as shown by the X-ray diffraction studies for amidines (2b) and (2d). While AM1 calculations indicated little difference in stability between the isomer with a *cis* imine group and that with the *trans* imine geometry, MM and HF STO-3G favoured the former by 20 kJ mol^{-1}. MM suggested that the most restricted N-aryl rotation was associated with the imine N-aryl group for both isomers.
Molecular modelling of the bis(2,6-di-isopropylphenyl) benzamidine (2f) indicated that the *cis* imine *trans* amide isomer is more stable than the *trans* imine *trans* amide structure by 10 to 40 kJ.mol^{-1} (AM1 and MM respectively). These results follow the trend shown by the solid state structures of amidines (2b) and (2d), i.e. the more hindered di-ortho substituted benzamidine favours a *cis* imine geometry. A variable temperature study of the 270 MHz ^{1}H NMR spectrum of the benzamidine (2f) in$C_2D_2Cl_4$ showed the upfield ortho-methyl signal pair of doublets at 0.95 and 0.81 ppm coalescing to a doublet at 90°C the other pair of doublets at 1.3 ppm being unchanged (Table 4). Calculation of the activation barrier from the nmr data, as above, gave a barrier of 76 kJ mol^{-1}. MM modelling predicted a lower rotational barrier about the amide aniline ring for both the trans(imine)-trans(amide) and cis(imine)-trans(amide) isomers thus indicating that for amidine (2f) the estimated energy barrier refers to restricted rotation about the N-aryl bond of the amide group.
Bis(2-methylphenyl) benzamidine (2b) also exhibits splitting of the methyl signals in the ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{3}C NMR spectra of a chloroform-*d* solution both contained three signals with an intensity ratio of 1:1:2 and the spectrum of a solution in 1,1,2,2-tetrachloroethane-d_2 exhibited four ^{1}H signals - the highest field signal at 1.35 ppm being broadened. As pointed out above, this non-equivalence must have a different origin to the chirality case. Variable temperature NMR experiments of a tetrachloroethane solution showed coalescence of the split ^{13}C signal at 65°C and coalescence of the two split ^{1}H nmr signals at 35°C (upfield pair) and 80°C (downfield pair) respectively, which together with the broadness of one signal, the similar intensity of the signals and the presence of only one carbonyl environment, make geometric isomerism most unlikely.

Table 4. ^{1}H NMR chemical shifts of the N-substituted aroyl benzamidines (2a-g)

		Chemical shift, ppm		
Compound	Solvent	Aromatic protons	Aliphatic substituents on the aniline rings	
			a	i
	$C_2D_2Cl_4$	8.1-6.6	-	-
2a	$(CD_3)_2CO$	8.2-6.5	-	-
	$C_2D_2Cl_4$	8.1-6.1	2.46, 2.18 (o-CH_3)	1.68, 1.35 (br) (o-CH_3)
2b	$(CD_3)_2CO$	7.9-6.8	2.46, 2.21 (o-CH_3)	1.58 (o-CH_3)
	$(CD_3)_2CO$	7.7-6.7	2.61 (2 o-CH_3)	1.97 (2 o-CH_3)
2c	$(CD_3)_2SO$	7.6-6.7	2.53 (2 o-CH_3)	1.89 (2 o-CH_3)
	$(CD_3)_2CO$	7.7-7.2 (m), 6.9, 6.7 (s)	2.19 (p-CH_3),[a] 2.56 (2 o-CH_3)	2.11 (p-CH_3),[a] 1.92 (2 o-CH_3)
2d	$(CD_3)_2SO$	7.6-7.2 (m), 6.9, 6.7 (s)	2.18 (p-CH_3),[a] 2.47 (2 o-CH_3)	2.10 (p-CH_3),[a] 1.83 (2 o-CH_3)
	$C_2D_2Cl_4$	7.5-7.0 (m), 6.9 (s)	2.38, 2.18 ($2CH_2$), 0.96 ($2CH_3$)[b]	3.02 ($2CH_2$), 1.34 ($2CH_3$)[c]
2e	$(CD_3)_2CO$	7.6-6.8	2.44, 2.23 ($2CH_2$), 0.95 ($2CH_3$)[b]	3.14, 3.04 ($2CH_2$), 1.34 ($2CH_3$)[b]
	$C_2D_2Cl_4$	7.6-6.9	2.84 (2CH), 0.95, 0.81 ($4CH_3$)[d]	3.63 (2CH), 1.34, 1.25 ($4CH_3$)[d]
2f	$(CD_3)_2CO$	7.7-6.9	2.98 (2CH), 0.95, 0.85 ($4CH_3$)[d]	3.79 (2CH), 1.40, 1.25 ($4CH_3$)[d]
	$C_2D_2Cl_4$	7.5-7.2 (m), 6.7 (s)	3.71 (p-OMe)[a]	3.74 (p-OMe)[a]
2g	$(CD_3)_2CO$	8.1-6.5	2.85 (br) (p-OMe)[a]	3.75 (p-OMe)[a]

[a] The assignment of signals to the amide or imine part of the molecule was tentative. [b] 2 CH_2: two dq, J_{HH}=14.6 Hz, $^3J_{HH}$=7.3 Hz; $2CH_3$: t, $^3J_{HH}$=7.3 Hz. [c] $2CH_2$: q, $^3J_{HH}$=7.3 Hz; $2CH_3$: t, $^3J_{HH}$=7.3 Hz. [d] Splitting was not observed due to poor resolution

In the crystal the two methyl groups are approximately orthogonal and therefore the simpler explanation of *syn* and *anti* tolyl groups does not seem to apply and indeed there appears to be little hindrance to cause restricted rotation about the imino tolyl group which was confirmed by modelling studies. AM1 semi-empirical calculations and molecular mechanics (MM) modelling of the *trans-trans* compound (as established by X-ray crystallography) gave two global minima. As shown in Diagram 1, rotamer (2b-cisoid) (455 kJ mol^{-1}) resembled the crystal structure. It possessed a spiral *cisoid* chromophore* (N=C-N-C(O)) [*cisoid about the central C-N bond] with face-to-face stacking of the benzoyl ring with the imino N-tolyl ring and having the other two facing rings with their planes opened to about 80^o. The second global minimum corresponded to rotamer (2b-transoid) (455 kJ mol^{-1}). It possessed a *transoid* chromophore (N=C-N-C(O)) and had the two N-tolyl groups face to face with the two methyl groups *anti* and

the two C-phenyl rings face-to-face with the two pairs of rings approaching orthogonality. A large part of the stabilisation energy of these rotamers appears to arise from the favourable double set of aryl-aryl face-to-face interactions. The two rotamers are interconverted by rotation about the single C-N bond of the amidine group. Modelling indicated the barrier to be about 70 ±10 kJ mol^{-1}. The similar rotamer energies and unique environments for the methyl groups in the two rotamers account for the NMR four signals, with similar intensity. Modelling also identified four conformations contributing to the rotamer structures (2b-cisoid) andanother four to (2b-transoid), facile interconvertion of the conformers occurring by rotation about the N-tolyl groups.

Structure and stereochemistry of acetamidines. Key data from the NMR and IR spectra of the acetamidines (4a-f) are given in Tables 5 - 7 and were consistent with the acetamidine structures. The appearance of only one carbonyl signal in the ^{13}C NMR spectra at 172.3 - 172.8 ppm, one acetyl signal in the ^{1}H NMR spectra and one carbonyl band in the IR spectra showed that the amide group had only one geometry in all six acetamidines. The structure and stereochemistry of bis(2,6-diisopropylphenyl) acetamidine (4f) was established by X-ray diffraction analysis (Figure 3, Table 8). The consistency of the positions of the NMR signals and IR bands indicated that they all resemble (4f) having the methyl group *cis* to the amide N-aryl group which is in contrast to the benzamidines.

The ^{1}H and ^{13}C NMR spectra of *N*-acetyl-*N*,*N*′-bis(2,6-diisopropylphenyl)-acetamidine (4f) in tetrachloroethane exhibited similar non-equivalence of the isopropyl methyl groups to the corresponding benzamidine (2f). In this case the non-equivalence for both the carbon and proton signals persisted up to 130°C despite the smaller chemical shift differences between the split signals. Non equivalence of the methylene signals of *N*-acetyl-*N*,*N*′bis(2,6-diethylphenyl)acetamidine (4e) was also evident for solutions in chlorinated solvents but not in acetone. In contrast to the corresponding benzamidine the *N*-acetyl-*N*,*N*′-bis(2-methylphenyl)acetamidine does not exhibit non equivalence of the methyl signals in the NMR spectra. The absence of the benzoyl group removes the possibility of twin aryl-aryl interactions which lends support to this phenomenon being a stabilising effect on the rotamers for the benzamidine (2b) discussed above.

Table 5. ^{13}C NMR chemical shifts of the N-substituted acyl acetamidines (4c-f)

		Chemical shift, ppm						
Comp	Solvent	C=O	C=N	Aromatic carbons	CH_3-CO	CH_3-CN	Aliphatic substituents in the aniline rings	
							a	i
4c	$C_2D_2Cl_4$	172.3	156.8	145.8-122.8	24.3	19.4	18.1 (2 o-CH_3)[a]	18.2 (2 o-CH_3)[a]
	$(CD_3)_2CO$	172.2	158.0	147.2-123.4	24.8	19.6	18.3 (2 o-CH_3)[a]	18.4 (2 o-CH_3)[a]
4d	$C_2D_2Cl_4$	172.5	157.0	143.3-125.9	25.0	19.3	20.6 (p-CH_3),[a] 18.0 (2 o-CH_3)[a]	21.0 (p-CH_3),[a] 18.2 (2 o-CH_3)[a]
	$(CD_3)_2CO$	172.3	158.2	144.8-126.5	24.8	19.5	20.7 (p-CH_3),[a] 18.3 (2 o-CH_3)	21.0 (p-CH_3),[a] 18.3 (2 o-CH_3)
4e	$C_2D_2Cl_4$	172.6	156.9	144.9-123.0	25.0	19.9	23.6 (2 CH_2),[a] 13.4 (2 CH_3)[a]	24.3 (2 CH_2),[a] 13.7 (2 CH_3)[a]
	$(CD_3)_2CO$	172.6	158.4	146.0-123.9	24.9	20.2	24.4 (2 CH_2), 13.9 (2 CH_3)[a]	25.2 (2 CH_2), 14.3 (2 CH_3)[a]
4f	$C_2D_2Cl_4$	172.7	157.5	146.4-122.8	24.7	20.3	27.8 (2CH),[a] 24.0, 22.4 ($4CH_3$)[a]	28.9 (2CH),[a] 24.5, 23.3 ($4CH_3$)[a]
	$(CD_3)_2CO$	172.7	158.9	147.6-123.7	25.1	20.5	28.6 (2CH),[a] 24.4, 22.9 ($4CH_3$)[a]	29.8 (2CH),[a] 24.8, 23.9 ($4CH_3$)[a]

[a] The assignment of signals to the amide or imine part of the molecule was tentative.

Table 6. Characteristic IR wavenumbers ν_{max}, cm^{-1} of acetanilides (3a-f) and N-substituted acyl acetamidines (4a-f)

Compound	$\nu_{N-H\ str}$(Z)	Amide I $\nu_{C=O\ str}$	$\nu_{C=N\ str}$	Amide II $\nu_{N-H\ bend}$	Amide III $\nu_{C-N\ str}$
3a	3295	1665	-	1599	1323
4a	-	1687	1656	-	1295
3b	3222	1658	-	1537	1301
4b	-	1690	1657	-	1295
3c	3235	1650	-	1541	1303
4c	-	1686	1662	-	1280
3d	3237	1646	-	1542	1290
4d	-	1691	1656	-	1272 (t)
3e	3212	1637	-	1538	1294
4e	-	1689	1662	-	1274 (t)
3f	3272	1649	-	1520	1287
4f	-	1676(br)	1676(br)	-	1260 (t)

Table 7. ^{1}H NMR chemical shifts of the N-substituted acyl acetamidines (4c-f)

		Chemical shift, ppm				
Compd	Solvent	Aromatic protons	CH_3-CO	CH_3-CN	Aliphatic substituents in the aniline rings	
					a	i
4c	$C_2D_2Cl_4$	7.19-6.84	2.17	1.92	1.92 (2 o-CH_3)[a]	2.28 (2 o-CH_3)[a]
	$(CD_3)_2CO$	7.20-6.77	2.16	1.88	1.91 (2 o-CH_3)[a]	2.32 (2 o-CH_3)[a]
4d	$C_2D_2Cl_4$	6.97, 6.79 (s)	2.31	2.14	1.93 (p-CH_3),[a] 1.88 (2 o-CH_3)[a]	2.22 (2 o-CH_3, p-CH_3)[a]
	$(CD_3)_2CO$	6.99, 6.77 (s)	2.28	2.13	1.87 (2 o-CH_3, p-CH_3)[a]	2.27 (2 o-CH_3),[a] 2.17 (p-CH_3)[a]
4e	$C_2D_2Cl_4$	7.36-6.89	2.15	1.96	2.21 ($2CH_2$),[a] 1.00 ($2CH_3$)[a, b]	2.63 ($2CH_2$),[a] 1.28 ($2CH_3$)[a, b]
	$(CD_3)_2CO$	7.37-6.86	2.15	1.91	2.25 ($2CH_2$),[a] 0.95 ($2CH_3$)[a, c]	2.71 ($2CH_2$),[a] 1.29 ($2CH_3$)[a, c]
4f	$C_2D_2Cl_4$	7.42-6.99	2.08	2.05	2.56 (2CH),[a] 1.22 ($4CH_3$)[a, d]	3.09 (2CH),[a] 1.15, 0.84 ($4CH_3$)[a, d]
	$(CD_3)_2CO$	7.44-6.97	2.13	2.00	2.71 (2CH),[a] 1.28, 1.25 ($4CH_3$)[a, e]	3.19 (2CH),[a] 1.18, 0.89 ($4CH_3$)[a, e]

[a] The assignment of signals to the amide or imine part of the molecule was tentative. [b] $2CH_2$: m; $2CH_2$: q, $^3J_{HH}$= 7.3 Hz; $4CH_3$: two t, $^3J_{HH}$= 7.3 Hz [c] 4 CH_2: two q, $^3J_{HH}$= 7.3 Hz; $4CH_3$: two t, $^3J_{HH}$= 7.3 Hz [d] 4CH: two sept, $^3J_{HH}$= 6.6 Hz; $4CH_3$ (amide): two d, $^3J_{HH}$= 6.6 Hz; $4CH_3$ (imine): d, $^3J_{HH}$= 6.6 Hz [e] 4CH: two sept, $^3J_{HH}$= 6.7 Hz; $4CH_3$ (amide): two d, $^3J_{HH}$= 6.7 Hz; $4CH_3$ (imine): d, $^3J_{HH}$= 7.3 Hz

Table 8. Selected bond lengths [Å], bond angles and torsion angles [deg] for N-acetyl-N,N'-bis(2,6-diisopropylphenyl)-acetamidine 4f

O3-C27	1.221(2)	C27-N1-C2-C7	-73.40(0.27)
N1-C27	1.387(3)	C1-N2-C15-C14	84.31(0.28)
N1-C1	1.436(3)	C1-N2-C15-C16	-102.10(0.25)
N1-C2	1.449(2)	C2-N1-C27-C28	-14.50(0.30)
N2-C1	1.261(3)	C15-N2-C1-C26	0.27(0.34)
N2-C15	1.430(3)	C2-N1-C1-N2	-30.79(0.27)
C27-C28	1.503(3)	C2-N1-C1-C26	144.35(0.19)
C1-C26	1.509(3)	C27-N1-C1-N2	136.48(0.21)
C27-N1-C2	122.0(2)	C27-N1-C1-C26	-48.38(0.27)
C27-N1-C2-C3	107.15(0.24)		

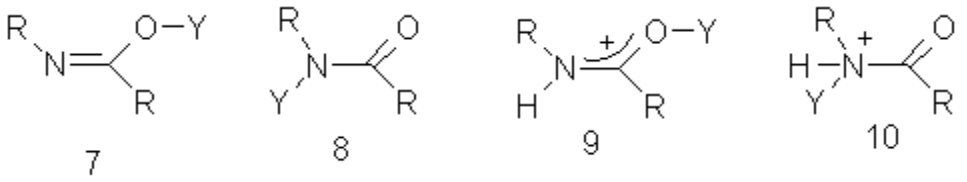
Table 9. Selected bond lengths [Å], bond angles and torsion angles [deg] for the N-isobutyldibenzamide 6

O1-C1	1.222(3)	C8-C9	1.491(3)
O2-C8	1.220(2)	C8-N1-C1	114.5(2)
N1-C1	1.407(3)	C1-N1-C15	116.2(2)
N1-C8	1.403(3)	C8-N1-C15	119.0(2)
C1-C2	1.491(3)		

Structure of *N*-isobutyldibenzamide - The ^{1}H, ^{13}C NMR and infra red spectra were consistent with the structure, N-isobutyldibenzamide (6) and was confirmed by X-ray diffraction analysis (Figure 4, Table 9).Notable for all the products (2), (4) and (6) was the typical carbonyl bond lengths 1.22 - 1.23 Å but low field position of the ^{13}C NMR signals for the amide carbonyl groups i.e. 170.4 - 174.4 ppm c.f. 165.2 for benzanilide. On the other hand, the imide groups which have slightly shorter bond lengths (1.26 - 1.28 Å) than normal (1.29 - 1.33 Å), had ^{13}C NMR signals 156 - 158 ppm close to those of the imine groups in Schiff's bases c.f. 158 ppm for PhCH=NPh.

Reaction mechanism. Amides are important functional groups in living systems and an improved understanding of their reactivity would be invaluable.Thus, the site of phosphorylation and potential for phosphorotropy, the diverging reaction pathways depending on the nitrogen substituents, together with possible involvement of amide tautomers (imidols) in the condensation process, promised that a study of the reaction pathway might provide useful mechanistic information.

NMR spectroscopic monitoring of the phosphorylation of N-benzoyl-2-methylaniline showed after 15 minutes the appearance and increase in intensity of transitory NMR signals at δ_H 1.98 ppm and δ_C 18.79 and 170.8 ppm corresponding to an ortho methyl group and a sp^2 carbon atom of an intermediate.After 10 days the spectra contained signals corresponding to the presence of starting material, benzamidine (2b) and intermediate in approximate ratio of 2:3:7,respectively.It was anticipated that this intermediate may be either the O-phosphorylated imidate (7; Y = $P(O)X_2$) or the phosphorylated amide (8; Y = $P(O)X_2$).A ^{13}C NMR chemical shift prediction programme gave very similar parameters for the signals of the carbonyl group and imine group of each of these structures. Thus a larger deshielding effect expected by introducing a directly bound O-phosphate group on an imine carbon, normally at 158 ppm, could bring its chemical shift to a similar position to that caused by a smaller deshielding effect caused by phosphorylation of an amide nitrogen atom normally at 165 ppm.



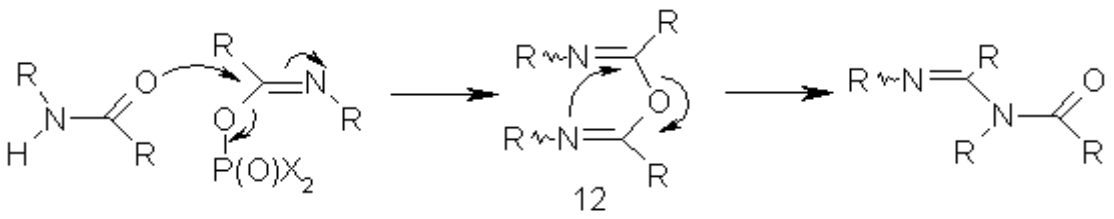
While MO calculations give larger partial negative charges on the amide N atoms and give larger coefficients for N compared to O in their HOMO's,[11] it has been established experimentally that amides, which include benzamide, are O-protonated in strong acids, such as trifluoroacetic acid, to give delocalised cations (9; Y = H)[12b] and there is strong evidence that alkylation and acylation also occurs initially on oxygen with potential to rearrange to N-alkylated and N-acylated products when they are thermodynamically favoured.[12c]In addition, phosphorylation of tertiary amides, such as DMF, readily forms O-phosphorylated Vilsmeier reagents.[13]

MM and MO studies indicated that these observed trends may be assigned to the greater stability of the intermediates. Thus semi empirical AM1 calculations on the non solvated molecules were consistent with experimental results showing the cation from O protonation of formamide and benzanilide (9; Y = H) to be 40 kJ·mol^{-1} and 80 kJ·mol^{-1}, respectively, more stable than the cations such as (10; Y = H) from N-protonation.The difference was even greater for phosphorylation.The cation formed upon phosphorylation at oxygen (9; Y = P(O)(OH)$_2$) was favoured over that from phosphorylation at nitrogen (10;Y = P(O)(OH)$_2$)) by nearly 200 kJ·mol^{-1}.The extra stabilisation can be attributed to the formation of a very strong P-O bond.It seems unlikely that solvation by chloroform would reverse these trends.

The possibility of amides reacting as nucleophiles via their iminol tautomers (11) has long been recognised[14] despite the extensive predominance of the amide form.[15]Phosphorylation of very low concentrations of the iminol tautomer would be a plausible route to the phosphorylated amide (8).Since prototropy is subject to acid catalysis, the phosphorylation of benzanilide was carried out in the presence of additional phosphoric acid.No rate enhancement was observed.[16]

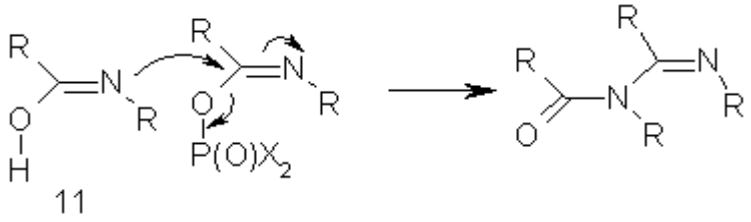
Following the above additional studies we have revised the tentative conclusion made in our preliminary communication[1] and now prefer to assign the O-phosphorylated imidate structure (7) to the initially formed intermediate rather than the phosphorylated amide structure (8) for the following reasons:- 1) the less hindered position of the carbonyl oxygen to attack by phosphoric anhydride, 2) consistency with other studies showing electrophilic attack at amide oxygen in solution, 3) the calculated greater stability of the initial O-phosphorylated cation (9; Y = P(O)X$_2$) and 4) the absence of phosphoric acid catalysed formation of an imidol tautomer.

The next step of the pathway is a condensation reaction involving the formation of a new C-N bond. Thus O-phosphorylated imidate appears to be reacting as an electrophile.If it has sufficient reactivity, presumably attack would again occur at the amide oxygen to give bis imidate (12) and intramolecular rearrangement would then be necessary to generate the amidine as shown in Scheme 1.However this mechanism could only explain the formation of dibenzamide (6) from the N-alkylbenzamide if the amide reacted as a nitrogen nucleophile.



Scheme 1

Since the formation of amidine was accelerated by the addition of protic media at the end of the reaction, it is envisaged that the careful work up with a protic solvent could be responsible for converting a proportion of the O-phosphorylated imidate (7) to the imidol tautomer (11).The lifetime of the imidol should be increased by hydrogen bonding of the imidol proton to a phosphoryl group which might also assist the association of thereacting intermediates.The imidol, like enols, would be expected to be more reactive towards electrophiles with much better potential for reacting at its N atom with O-phosphorylated imidate as shown in Scheme 2. This was supported by *ab initio* calculations which estimated the N-protonated benzimidol cation, $[PhNH{=}COHPh]^+$, to be over 220 $kJ{\cdot}mol^{-1}$ more stable than the O protonated cation $[PhN{=}COH_2Ph]^+$.



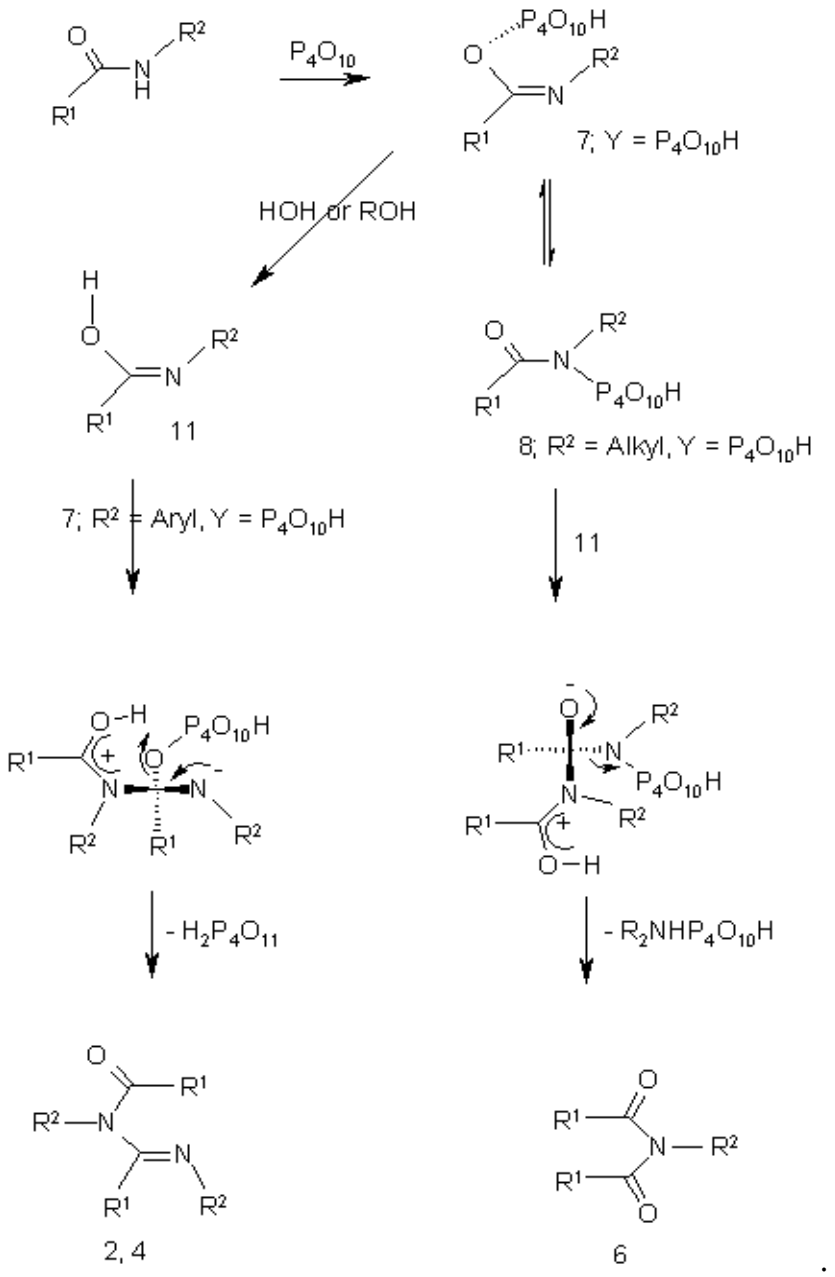
Scheme 2

AM1 and PM3 calculations indicated that after proton loss by the cations the phosphorylated amide and imidate have similar stabilities.Thus phosphorotropy leading to an equilibrium mixture of N and O phosphorylated intermediates seems quite feasible and has been previously invoked.[17]Indeed, the formation of dibenzamide (6) in the reaction of N-isobutylbenzamide with phosphoric anhydride supports for the formation of N-phosphorylated amide (8) by phosphorotropyof the O-phosphorylated imidate (7).The detection of only one transitory set of NMR signals indicates that the equilibrium strongly favours the imidate in the case of the phosphorylated benzanilides. The lower yield of dibenzamide may be due to a poorer match of the rate of conversion of imidate to imidol to the rate of phosphorotropy.

Thus the proposed reaction mechanism for the phosphorylation of the benzamides is summarised in Scheme 3. The first step is envisaged as involving O-phosphorylation of the amide with phosphorotropy leading to the formation of an equilibrium mixture of O-phosphorylated imidate (7) and N-phosphorylated amide (8), the former predominating. It is

postulated that the action of a protic solvent or atmospheric moisture on the O-phosphorylated imidate (7) produces the iminol tautomer (11), which attacks the imino carbon of the O-phosphorylated intermediate to give a reactive intermediate possessing a nitrogen anion stabilised by the N-aryl ring.Elimination of phosphate produces the amidine.When the N-aryl group is replaced by an N-alkyl group the developing nitrogen anion is not delocalised and thus the reactive intermediate is less stable and instead attack by iminol at the carbonyl group of the tautomeric N-phosphorylated amide is faster leading to imide (6) after elimination of phosphate as shown in Scheme 3.

In conclusion, our evidence indicates that both steps in the reaction pathway are controlled by the stabilities of the first transitory intermediate, i.e. that there are late transition states, and thus the reactions do not involve concerted delivery of a proton to the phosphoric anhydride during its electrophilic attack of the substrate. This was also supported by an ab initio calculation of a high barrier to rotation about the amide C-N of benzanilide (~40 $kJ \cdot mol^{-1}$) to convert the trans amide to a *cis* amide which would be necessary for a six membered concerted mechanism to occur.The barrier was estimated to be ~270 $kJ \cdot mol^{-1}$ for the imine C=N bond of the corresponding iminol tautomer.



Scheme 3

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded using a Jeol JNM-FX270 spectrometer. Chloroform-*d*, 1,1,2,2-tetrachloroethane-d_2, methanol-*d* or methanol-d_4, acetone-d_6 and dimethylsulfoxide-d_6 were used as solvents and TMS was used as internal reference standard.^{31}P NMR spectra were obtained on a Jeol FX90Q spectrometer operating at 90 MHz with 85% phosphoric acid as the external reference standard. IR spectra (KBr discs) were

recorded on a ATI Mattson Genesis Series FTIR™ spectrometer.Melting points were measured using a Gallenkamp manual operation apparatus and are uncorrected.

Benzanilides (1a-h) were prepared by the Schotten-Baumann reaction from the appropriate anilines and benzoyl chloride, purified by recrystallisation from hot ethanol and dried *in vacuo* at 60°C for 12 h before use.

Acetanilides (3a-h) were synthesised from the corresponding anilines and acetic anhydride, purified by recrystallisation from hot ethanol and dried *in vacuo* at 60°C for 12 h prior to use.

***N*-Isobutylbenzamide (5a)** was prepared under the conditions of the Schotten-Baumann reaction from N-isobutylamine and benzoyl chloride followed by recrystallisation from ethanol and drying in vacuo at 45°C for 12 h before use.

***N*-Isobutylacetamide (5b)** was prepared by reacting N-isobutyl amine with acetic anhydride.The liquid compound was purified by extraction with dichloromethane and dried by sodium sulphate.

General procedure for preparation of N-substituted aroyl benzamidines (2a-h)

The reactions involved the addition of dry powdered benzanilide to phosphoric anhydride suspended in chloroform (freshly distilled over P_4O_{10}) in the amide to anhydride ratio of 3:1.The reaction mixture was stirred at room temperature until the anhydride was consumed.The removal of the solvent gave a viscous residue which was taken up in a minimum of ethanol. Slow addition of water precipitated a mixture of the product and starting benzanilide.After filtration the crude benzamidine was extracted by carbon tetrachloride and purified by recrystallisation from ethanol.The ^{1}H and ^{13}C NMR data of the products are summarised in Tables 1 and 4.The IR data are listed in Table 3.

***N*-Benzoyl-*N,N′*-diphenyl-benzamidine (2a).** was prepared as outlined above from benzanilide (4.1 g, 0.021 mol) and phosphoric anhydride (1.99 g, 0.007 mol) in dry chloroform (15 mL) as a pale yellow solid (2.53 g, 64 %), m. p. 173-174°C (173-174°C)[18]Anal. Calc. for $C_{26}H_{20}N_2O$: C, 82.95; H, 5.35; N, 7.44. . Found: C, 82.71; H, 5.33; N, 7.42.

***N*-Benzoyl-*N,N′*-bis(2-methylphenyl)-benzamidine (2b).** N-Benzoyl-2-methylaniline (2.7 g, 0.013 mol) and phosphoric anhydride (1.22 g, 0.004 mol) were reacted in dry chloroform (15 mL) using the method described above, yielding the yellow crystalline product (2.15 g, 83 %), m. p. 144-146°C.The reaction in chloroform-*d* (15 mL) was monitored using ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Anal. Calc. for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.12; H, 5.98; N, 6.95.

***N*-Benzoyl-*N,N′*-bis(2,6-dimethylphenyl)-benzamidine (2c).** *N*-Benzoyl-2,6-dimethylaniline (2.6 g, 0.012 mol) was reacted with phosphoric anhydride (1.11g, 0.004 mol) in dry chloroform (15 mL) as outlined above and gave a pale brown powder (2.10 g, 84 %), m. p. 162-164°C. Anal. Calc. for $C_{30}H_{28}N_2O$: C, 83.30; H, 6.52; N, 6.48. Found: C, 83.06; H, 6.49; N, 6.47.

***N*-Benzoyl-*N,N′*-bis(2,4,6-trimethylphenyl)-benzamidine (2d).** was prepared as described in the general method from N-benzoyl-2,4,6-trimethylaniline (2.9 g, 0.012 mol) and phosphoric

anhydride (1.16 g, 0.004 mol) in dry chloroform (15 mL) as a yellow solid (1.70 g, 61 %), m. p. 188-189ºC. Anal. Calc. for $C_{32}H_{32}N_2O$: C, 83.44; H, 7.00; N, 6.08. Found: C, 82.47; H, 7.00; N, 5.94.

***N*-Benzoyl-*N,N′*-bis(2,6-diethylphenyl)-benzamidine (2e).** was prepared as outlined above from N-benzoyl-2,6-diethylaniline (3.7 g, 0.015 mol) and phosphoric anhydride (1.39 g, 0.005 mol) in dry chloroform (25 mL) as a yellow solid (2.09 g, 59 %), m. p. 100-102ºCAnal. Calc. for $C_{34}H_{36}N_2O$ C, 83.57; H, 7.43; N, 5.73. Found: C, 83.27; H, 7.51; N, 5.74.

***N*-Benzoyl-*N,N′*-bis(2,6-diisopropylphenyl)-benzamidine (2f).** was prepared as described above from N-benzoyl-2,6-diisopropylaniline (3.53 g, 0.013 mol) and phosphoric anhydride (1.19 g, 0.004 mol) in dry chloroform (15 mL) as a dark yellow solid (1.40 g, 41 %), m. p. 170-172ºC. Anal. Calc. for $C_{38}H_{44}N_2O$ C, 83.78; H, 8.14; N, 5.14. Found: C, 83.86; H, 8.33; N, 5.25.

***N*-Benzoyl-*N,N′*-bis(p-anisidine)-benzamidine (2g).** N-Benzoyl-p-anisidine (3.21 g, 0.014 mol) and phosphoric anhydride (1.34 g, 0.005 mol) in dry chloroform (15 mL) were reacted as above and gave a yellow powder (1.91 g, 62 %), m. p. 144-147ºC (149-150ºC).[18] Anal. Calc. for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42. Found: C, 76.88; H, 5.56; N, 6.41.

General procedure for preparation of N-substituted acetamidines (4a-f)

Dry and powdered acetanilide was added to a heterogeneous chloroform solution of phosphoric anhydride (chloroform was freshly distilled over P_4O_{10}) and was stirred at room temperature until the mixture became homogeneous.Evaporation of the solvent under reduced pressure gave viscous residue which was dissolved in a minimum of ethanol.The mixture of acyl acetamidine and a parent acetanilide was precipitated then by addition of water.After filtration the crude acetamidine was extracted from the mixture by diethyl ether (unless otherwise stated) and purified by recrystallisation from ethanol.The ^1H and ^{13}C NMR data of N-substituted acetamidines studied are given in Tables 2 and 3 respectively.The IR characteristic data are listed in Table 4.

***N*-Acetyl-*N,N′*-diphenyl-acetamidine (4a).** Prepared from acetanilide (1.17 g, 0.009 mol) and phosphoric anhydride (2.4 g, 0.008 mol) in dry chloroform (25 mL) heated under reflux for 3 h. After cooling, the top transparent layer was separated and triturated with ethanol.Evaporation and extraction by diethyl ether gave a white solid (0.023 g, 2 %).

***N*-Acetyl-*N,N′*-bis(2-methylphenyl)-acetamidine (4b).** was prepared from 2-methylacetanilide (2.3 g, 0.015 mol) and phosphoric anhydride (2.22 g, 0.008 mol) in dry chloroform (25 mL).After cooling trituration of the bottom yellow with acetone gave a white solid (0.11 g, 5 %), m. p. 122-124ºC.

***N*-Acetyl-*N,N′*-bis(2,6-dimethylphenyl)-acetamidine (4c).** was prepared using the general procedure from 2,6-dimethylacetanilide (2.03 g, 0.012 mol) and phosphoric anhydride (1.18 g, 0.004 mol) in dry chloroform (15 mL) as a white solid (0.40 g, 21 %), m. p. 112-113ºC. Anal. Calc. for$C_{20}H_{24}N_2O$ C, 77.89; H, 7.84; N, 9.08. Found: C, 78.00; H, 8.02; N, 9.03.

***N*-Acetyl-*N,N′*-bis(2,4,6-trimethylphenyl)-acetamidines (4d).** was prepared by reacting 2,4,6-trimethylacetanilide (2.22 g, 0.013 mol) with phosphoric anhydride (1.19 g, 0.004 mol) in dry

chloroform (15 mL), using the general method described above, as a white solid (1.3 g, 62 %), m. p. 129-130ºC. Anal. Calc. for $C_{22}H_{28}N_2O$ C, 78.53; H, 8.39; N, 8.33. Found: C, 78.47; H, 8.52; N, 8.17.

***N*-Acetyl-*N,N′*-bis(2,6-diethylphenyl)-acetamidine (4e).** 2,6-Diethylacetanilide (2.80 g, 0.015 mol) and phosphoric anhydride (1.39 g, 0.005 mol) reacted exothermically.Extraction of product by dry toluene gave a colourless solid (0.61 g, 23 %), m. p. 62-64ºC. Anal. Calc. for $C_{24}H_{32}N_2O$ C, 79.08; H, 8.85; N, 7.68. Found: C, 79.31; H, 8.99; N, 7.75.

***N*-Acetyl-*N,N′*-bis(2,6-diisopropylphenyl)-acetamidine (4f).** was prepared, following the general procedure. 2,6-Diisopropylacetanilide (2.85 g, 0.013 mol) and phosphoric anhydride (1.23 g, 0.004 mol) in dry chloroform (15 mL) reacted exothermically to give, after workup, a white solid (2.0 g, 74 %), m. p. 135-137ºC. Anal. Calc. for $C_{28}H_{40}N_2O$ C, 79.95; H, 9.58; N, 6.66. Found: C, 79.80; H, 9.76; N, 6.67.

Preparation of *N*-Isobutyldibenzamide (6a)

Phosphoric anhydride (1.20 g, 0.004 mol) was stirred in dry chloroform (15 mL), and dry and powdered *N*-isobutylbenzamide (5a) (2.24 g, 0.013 mol) was added.The mixture was stirred at the room temperature for 41 h until phosphoric anhydride was completely consumed.Removal of the solvent under reduced pressure gave a pale yellow oil.Column chromatography (silica gel - Sorbsil C60 (60-210 um) A, chloroform) gave a white solid (0.42 g, 24 %), m. p. 89-91ºC. Anal. Calc. for $C_{18}H_{19}NO_2$ C, 76.84; H, 6.81; N, 4.98. Found: C, 77.08; H, 6.86; N, 6.15.

Molecular modelling

Calculations were performed on a Silicon Graphics O2 workstation using a Spartan 5.0 program.

MM and semi-empirical MO studies of benzamidine (2b). - Based on the retention of the trans-trans geometries for the imine and amide groups, a molecular mechanics conformational search gave eight conformers whose structures were optimised by AM1 calculations.Four conformers had spiral cisoid amidine groups (A-D-cisoid) with close phenyl-tolyl interactions and four had a transoid amidine group (A-D-transoid) with close phenyl-phenyl and tolyl-tolyl interactions as shown in Diagram 1. The energy of the most stable cisoid conformer (A-cisoid) and the energy of the most stable transoid conformer (A-transoid) were the same.Rotational barriers were estimated using MM coordinate driving and AM1 calculations of conformer transition state energies.

Energy barriers between the appropriate pairs of (2b-cisoid) and (2b-transoid) rotamers were calculated by MM and AM1 and found to be approximately 75 to 65 $kJ \cdot mol^{-1}$ respectively whereas the barriers between the four cisoid and between the four transoid conformers were in the range 2 - 20 $kJ \cdot mol^{-1}$.

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11. MO calculations on simple amides, e.g. formamide, gives a non-bonding HOMO consisting of nearly equal amounts of 2pp atomic orbital (AO) on O and ν with a node at the amide carbon atom.HOMO -1 is mainly the lone pair on oxygen and HOMO-2 has three amide AO's in phase with the maximum density on ν - this latter MO being held responsible for the restricted rotation about the amide bond.[11a]Benzanilide has its HOMO and HOMO-1 similar to formamide but its HOMO -2 has the electron density on the amide group restricted to the carbonyl p-bond. HOMO -5 has delocalisation across all three atoms of the amide group.The partial charge on ν was slightly larger for formamide (-0.45) than for benzanilide (-0.37) the charges on O being the same (-0.30) [HF STO-3G).Electrostatic potentials although considerably higher in magnitude followed the same trends.

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