

The conformation of some disubstituted anilides

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The influence of substituents on the out of plane rotation of the acylamino group of anilides relative to the aromatic ring has been examined by X-ray crystallography

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The steric crowding by adjacent substituents on an aromatic ring may be reduced by the rotation of one of the substituents around its bond to the aromatic ring. In the case of 2,6-dimethylacetanilide this leads to the steric inhibition of resonance between the aromatic ring and the amide group thus diminishing the influence of the amide on the orientation of aromatic substitution.^{1,2} Consequently the electrophilic aromatic substitution of 2,6-dimethylacetanilide occurs predominantly at the C-3 position under the influence of the methyl groups rather than at C-4 *para* to the acylamino group. The original suggestion³ for the influence of the methyl groups on the rotation of the acylamino group was based on dipole moment measurements. Since then there have been some X-ray measurements on the conformation of aromatic amides. X-ray crystallographic studies have shown^{4,5} that the planes of the aromatic ring and the CH₃CONH group of acetanilide are at 17.5° to each other. On the other hand in lidocaine [2-(diethylamino)-*N*-(2',6'-dimethylphenyl)acetamide] salts as a result of steric crowding by the methyl groups, the amide and the phenyl ring are rotated to between 66° and 71° to each other depending on the salt.⁶ We now report a systematic study by X-ray crystallography of the rotation of the acylamino group relative to the aromatic ring in a series of disubstituted anilides.

We have examined 2,4-dimethyl and 2,6-dimethylacetanilides, 2,6-dimethylformanilide, 2,6-difluoro- and 2,6-dichloro-acetanilides, 2,6-dimethyl-3-nitro- and 2,6-dimethyl-4-nitro-acetanilides (see Figs 1–7). These compounds were

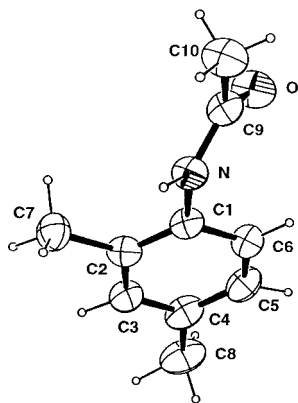


Fig. 1 X-Ray crystal structure of 2,4-dimethylacetanilide.

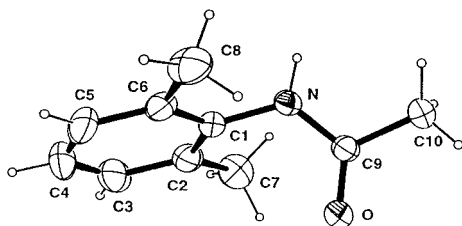


Fig. 2 X-Ray crystal structure of 2,6-dimethylacetanilide.

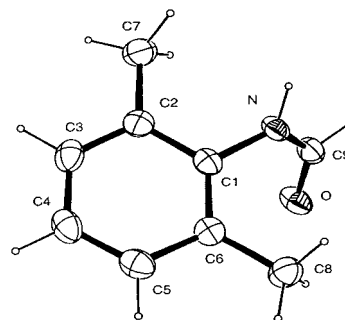


Fig. 3 X-Ray crystal structure of 2,6-dimethylformanilide.

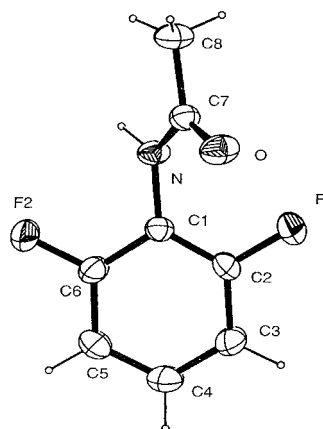


Fig. 4 X-Ray crystal structure of 2,6-difluoroacetanilide.

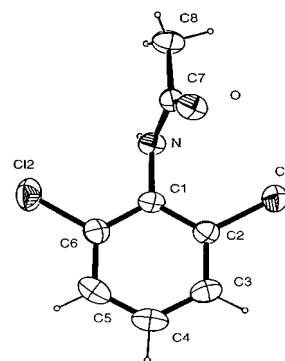


Fig. 5 X-Ray crystal structure of 2,6-dichloroacetanilide.

Table 1 Angles (°) between the planes of the acylamino group and the phenyl ring (ESD)

	Angles (°)
Acetanilide	17.5
2,4-Dimethylacetanilide	49.28 (0.38)
2,6-Dimethylacetanilide	62.50 (0.09)
2,6-Dimethylformanilide	66.95 (0.16)
2,6-Difluoroacetanilide	54.00 (0.2)
2,6-Dichloroacetanilide	70.03 (0.1)
3-Nitro-2,6-dimethylacetanilide	62.67 (0.14)
4-Nitro-2,6-dimethylacetanilide	62.1 (0.1)

* Correspondence.

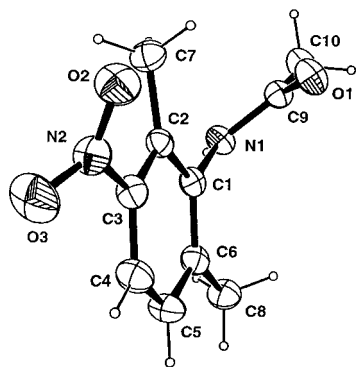


Fig. 6 X-Ray crystal structure of 2,6-dimethyl-3-nitroacetanilide.

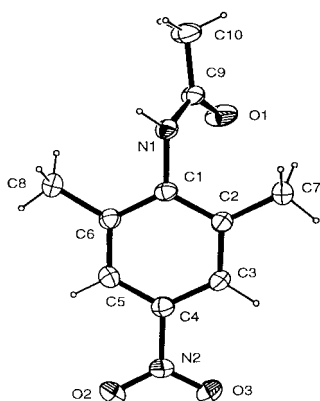


Fig. 7 X-Ray crystal structure of 2,6-dimethyl-4-nitroacetanilide.

chosen to reveal the influence of the number of alkyl groups adjacent to the acylamino group, the size of the acylamino group, the effect of adjacent halogen substituents and the influence of the electron-withdrawing nitro group at C-3 and C-4.

The angles between the planes through the acylamino group and the aromatic ring are given in Table 1. These reflect the rotation of the acylamino grouping. The bond lengths between the amide nitrogen and the aromatic ring and between the amide nitrogen and the carbonyl group are given in Table 2. These may reflect changes in conjugation.

Although the conformation of the acylamino group relative to the aromatic ring may be influenced by intermolecular hydrogen bonding and crystal packing,⁷ nevertheless, some trends are apparent. Firstly, as expected, the adjacent methyl groups induce a rotation which increases with the number of alkyl groups. The formylanilide showed a comparable rotation to acetanilide. Not only does an adjacent chlorine have a substantial effect but a fluorine does as well. This suggests that there may be more than a steric effect on the rotation. The 3- and 4-nitro groups have no effect on the rotation of the acylamino group brought about by methyl groups. However, the bond lengths reflect the change in conjugation between the aromatic ring and the amide. As the steric hindrance increases

and the plane of the acylamino group rotates, the C(1)-nitrogen bond becomes longer and the amide carbonyl-nitrogen bond becomes shorter. However, these effects are quite small.

In conclusion we have provided X-ray crystallographic evidence for the rotation of the acylamino group in sterically hindered acetanilides.

Experimental

X-ray crystallographic data and structure determinations

(a) 2,4-dimethylacetanilide $C_{10}H_{13}NO$, M_r 163.21, triclinic, space group $P\bar{1}$ (No.2), $a = 4.790(2)$, $b = 7.667(3)$, $c = 12.957(5)$ Å, $\alpha = 102.13(2)^\circ$, $\beta = 98.09(2)^\circ$, $\gamma = 91.98(2)^\circ$, $V = 459.6(3)$ Å³, $Z = 2$, $D_{calc} = 1.18$ g cm⁻³, $\mu = 0.08$ mm⁻¹, $F(000) = 176$. Data were collected using a crystal of size $1.00 \times 0.05 \times 0.02$ mm³ on a KappaCCD diffractometer. A total of 2476 reflections were collected for $4.68^\circ < \theta < 22.03^\circ$ and $-4 \leq h \leq 5$, $-7 \leq k \leq 8$, $-13 \leq l \leq 13$. There were 1099 independent reflections and 746 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.066$, $wR_2 = 0.163$ and (all data) $R_1 = 0.097$ and $wR_2 = 0.191$. The largest difference peak and hole was 0.19 and -0.21 e Å⁻³.

(b) 2,6-dimethylacetanilide $C_{10}H_{13}NO$, M_r 163.21, monoclinic, space group $P2_1/n$ (No.14), $a = 7.6836(6)$, $b = 16.0769(11)$, $c = 8.1209(4)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 111.881(4)^\circ$, $V = 930.89(11)$ Å³, $Z = 4$, $D_{calc} = 1.17$ g cm⁻³, $\mu = 0.08$ mm⁻¹, $F(000) = 352$. Data were collected using a crystal of size $0.4 \times 0.4 \times 0.1$ mm³ on a KappaCCD diffractometer. A total of 6750 reflections were collected for $4.67^\circ < \theta < 25.02^\circ$ and $-9 \leq h \leq 7$, $-19 \leq k \leq 18$, $-8 \leq l \leq 9$. There were 1625 independent reflections and 1373 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.050$, $wR_2 = 0.129$ and (all data) $R_1 = 0.060$, $wR_2 = 0.137$. The largest difference peak and hole was 0.20 and -0.21 e Å⁻³.

(c) 2,6-dimethylformanilide $C_9H_{11}NO$, M_r 149.19, orthorhombic space group $P2_12_12_1$ (No.19), $a = 4.5031(2)$, $b = 8.5372(4)$, $c = 20.8505(9)$ Å, $\alpha = \beta = \gamma = 90^\circ$, $V = 801.57(6)$ Å³, $Z = 4$, $D_{calc} = 1.24$ g cm⁻³, $\mu = 0.08$ mm⁻¹, $F(000) = 320$. Data were collected using a crystal of size $0.30 \times 0.05 \times 0.05$ mm³ on a KappaCCD diffractometer. A total of 5070 reflections were collected for $3.78^\circ < \theta < 25.00^\circ$ and $-5 \leq h \leq 5$, $-9 \leq k \leq 10$, $-24 \leq l \leq 24$. There were 1370 independent reflections and 1214 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.037$, $wR_2 = 0.088$ and (all data) $R_1 = 0.046$, $wR_2 = 0.093$. The largest difference peak and hole was 0.14 and -0.22 e Å⁻³. There was an intermolecular N-H...O hydrogen bond.

(d) 2,6-difluoroacetanilide $C_8H_7F_2NO$, M_r 171.15, monoclinic, space group $P2_1/n$ (No.14), $a = 4.7569(3)$, $b = 9.9932(7)$, $c = 16.4089(13)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 95.249(3)^\circ$, $V = 776.75(10)$ Å³, $Z = 4$, $D_{calc} = 1.60$ g cm⁻³, $\mu = 0.15$ mm⁻¹, $F(000) = 384$. Data were collected using a crystal of size $0.10 \times 0.05 \times 0.05$ mm³ on a KappaCCD diffractometer. A total of 5943 reflections were collected for $4.08^\circ < \theta < 25.03^\circ$ and $-5 \leq h \leq 4$, $-11 \leq k \leq 11$, $-19 \leq l \leq 19$. There were 1357 independent reflections and 879 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.075$, $wR_2 = 0.171$ and (all data) $R_1 = 0.125$, $wR_2 = 0.196$. The largest difference peak and hole was 0.28 and -0.35 e Å⁻³.

(e) 2,6-dichloroacetanilide $C_8H_7Cl_2NO$, M_r 204.05, monoclinic, space group $P2_1/n$ (No.14), $a = 7.7889(2)$, $b = 15.2657(4)$, $c = 8.2059(2)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 112.010(1)^\circ$, $V = 904.59(4)$ Å³, $Z = 4$, $D_{calc} = 1.50$ g cm⁻³, $\mu = 0.67$ mm⁻¹, $F(000) = 416$. Data were collected using a crystal of size $0.40 \times 0.15 \times 0.10$ mm³ on a KappaCCD diffractometer. A total of 7579 reflections were collected for $3.78^\circ < \theta < 25.37^\circ$ and $-8 \leq h \leq 9$, $-16 \leq k \leq 17$, $-9 \leq l \leq 9$. There were 1607 independent reflections and 1388 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.033$, $wR_2 = 0.078$ and (all data) $R_1 = 0.041$, $wR_2 = 0.083$. The largest difference peak and hole was 0.19 and -0.27 e Å⁻³. There are N-H...O hydrogen-bonded chains along the n glide.

Table 2 Bond lengths involving the amide (Å)(ESD)

	ArC ₁ -N	HN-C(O)
Acetanilide	1.413	1.354
2,4-Dimethylacetanilide	1.426(5)	1.354(5)
2,6-Dimethylacetanilide	1.435(2)	1.342(2)
2,6-Dimethylformanilide	1.431(2)	1.338(3)
2,6-Difluoroacetanilide	1.427(5)	1.349(5)
2,6-Dichloroacetanilide	1.419(2)	1.345(2)
2,6-Dimethyl-3-nitroacetanilide	1.425(2)	1.355(2)
2,6-Dimethyl-4-nitroacetanilide	1.430(3)	1.360(3)

(f) 2,6-dimethyl-3-nitroacetanilide $C_{10}H_{12}N_2O_3$, M_r 208.22, monoclinic, space group $P2_1/n$ (No.14), $a = 4.7679(3)$, $b = 19.6379(11)$, $c = 11.1048(5)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 94.993(3)^\circ$, $V = 1035.8(1)$ Å³, $Z = 4$, $D_{\text{calc}} = 1.34$ g cm⁻³, $\mu = 0.10$ mm⁻¹, $F(000) = 440$. Data were collected using a crystal of size $0.20 \times 0.05 \times 0.05$ mm³ on a KappaCCD diffractometer. A total of 6349 reflections were collected for $4.28^\circ < \theta < 25.04^\circ$ and $-5 \leq h \leq 5$, $-22 \leq k \leq 23$, $-10 \leq l \leq 13$. There were 1825 independent reflections and 1435 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were $[I > 2\sigma(I)] R_1 = 0.042$, $wR_2 = 0.103$ and (all data) $R_1 = 0.058$, $wR_2 = 0.114$. The largest difference peak and hole was 0.18 and -0.23 e Å⁻³.

(g) 2,6-dimethyl-4-nitroacetanilide $C_{10}H_{12}N_2O_3$, M_r 208.22, triclinic, space group $P\bar{1}$ (No.2), $a = 4.7659(2)$, $b = 8.4244(4)$, $c = 13.5506(6)$ Å, $\alpha = 76.656(2)^\circ$, $\beta = 80.528(2)^\circ$, $\gamma = 760.384(2)$, $V = 510.98(4)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.35$ g cm⁻³, $\mu = 0.10$ mm⁻¹, $F(000) = 220$. Data were collected using a crystal of size $0.10 \times 0.02 \times 0.02$ mm³ on a KappaCCD diffractometer. A total of 5381 reflections were collected for $4.39^\circ < \theta < 24.96^\circ$ and $-4 \leq h \leq 5$, $-9 \leq k \leq 9$, $-15 \leq l \leq 16$. There were 1760 independent reflections and 1291 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final

R indices were $[I > 2\sigma(I)] R_1 = 0.051$, $wR_2 = 0.107$ and (all data) $R_1 = 0.081$, $wR_2 = 0.120$. The largest difference peak and hole was 0.20 and -0.21 e. Å⁻³.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 225985 – 225992)

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