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ORTHO-SUBSTITUENT EFFECTS IN *N*-ARYLACETAMIDES. NMR AND MOLECULAR MECHANICS INVESTIGATION

ERKKI KOLEHMAINEN,* KATRI LAIHIA AND REIJO KAUPPINEN
Department of Chemistry, University of Jyväskylä, P.O. Box 35, FIN-40351 Jyväskylä, Finland

AND

DANUTA RASAŁA AND AGNIESZKA PUCHAŁA
Institute of Chemistry, Pedagogical University, Chęcińska 5, 25-020 Kielce, Poland

^{1}H, ^{13}C, ^{15}N and ^{17}O NMR spectra of *N*-phenylacetamide (acetanilide) and 21 *ortho*-substituted acetanilides were measured and assigned. The observed NMR parameters are related to the Hammett substituent parameters and conformational characteristics of the acetamido moiety estimated by molecular mechanics calculations. Significant relationships were found for the ^{13}C NMR chemical shifts of C-5 (*para* to substituent) and the direct spin–spin coupling constant, $^{1}J(C,H)$, of C-3 (*ortho* to substituent) with Hammett substituent parameters. For ^{15}N NMR chemical shifts of the amido nitrogen, no general correlation with the Hammett substituent parameters was found. The interactions between functionalities contiguous to the carbonyl group and the amino nitrogen in acetanilides are effectively hampered owing to the increased twist angle between the planes containing the phenyl ring and the H–N–C fragment in derivatives bearing bulky *ortho* substituents. Especially in *ortho*-halogen-substituted derivatives the ^{15}N NMR chemical shift of the amino nitrogen is very clearly related to the twist angle between the phenyl ring and H–N–C fragment. For ^{17}O NMR chemical shifts of the acetamido carbonyl, the observed variations can be related to the steric inhibition of resonance between the benzene ring and the acetamido group.

INTRODUCTION

Substituted phenylacetanilides are reported to possess physiological (anticonvulsant) activity.[1,2] In addition, their structure consists of a conformationally flexible fragment, $-C(sp^2)-NH-CO-C(sp^3)-$, serving as a useful model system for other biologically and biochemically important substances. The conformational difference between acetanilide and its *N*-substituted derivatives is interesting, the former existing almost entirely in an *endo* or *Z* and the latter in an *exo* or *E* form in the crystalline state, the difference being explained by steric crowding.[3–7] It is obvious that any *ortho* substituent in the ring will induce conformational changes at the acetamido moiety. They certainly will strongly affect the delocalization of the electron lone pair at the acetamido nitrogen between the aromatic π-system and C=O group of the side-chain. Unfortunately, in the literature there are no x-ray crystallographic data on *ortho*-substituted acetanilides.

Interactions between functionalities contiguous to the amino nitrogen atom and the substituents (mostly electron acceptors) in substituted anilines and *N*-methylanilines have been discussed by Bradamante and co-workers.[8] In particular, the ^{13}C NMR chemical shift of carbon in *para* positions with respect to the amino nitrogen atom has been used in probing the *N*-substituent induced changes.[8] For the majority of substituents directly attached to the nitrogen atom of *N*-methylaniline, partitioning of the nitrogen electron lone pair between the phenyl and the substituent is partially hampered because of the non-zero twist angle between the planes containing the phenyl ring and the Me–N–C fragment.[8c]

The nitrogen lone pair delocalization in *para*-substituted acetanilides have been utilized in explaining the H/D isotope shifts of ^{13}C NMR nuclear shielding.[9] These isotope effects are of great importance in struc-

* Author for correspondence.

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tural studies of a variety of biological compounds. Bennet *et al.*[10] investigated the influence of so-called amidic resonance on the infrared and the ^{13}C and ^{15}N NMR spectroscopic characteristics and on the barriers to rotation around the N–C(carbonyl) bond in some anilides and toluamides. Some *ortho*-methyl-substituted *N*-methylacetanilides and bicyclic anilides were included in that work, but the *ortho*-substituted acetanilides were not. Moreover, the significance of intermolecular hydrogen bonding on both the carbonyl carbon and nitrogen chemical shielding tensors of the amide fragment in acetanilide has been demonstrated by both solid-state ^{13}C and ^{15}N NMR spectroscopy and by theoretical (IGLO) calculations.[11]

According to Yamagami *et al.*,[1,2] the ^{15}N NMR chemical shift is a better indicator than the ^{13}C shift in estimating the transmission of electronic effects in the anilide moiety of phenylacetanilide derivatives. Westerman and Roberts[12] have shown that the ^{15}N NMR downfield shift of amide nitrogen in acetanilides induced by electron acceptors at the *para* position are attributed to a p–π interaction between the amide nitrogen lone pair and the aromatic ring. The origin of this phenomenon is explained by the decreased π-electron density at the nitrogen with concomitant deshielding.

Axenrod *et al.*[13] observed a linear relationship between the Hammett substituent constants and ^{15}N NMR chemical shifts and $^1J(N,H)$ spin–spin coupling constants in ring-substituted anilines. A similar dependence has been observed in ring-substituted benzamides and benzonitriles.[14] However, in *meta*- and *para*-substituted anilides serious difficulties have been encountered in attempts to relate the ^{15}N NMR chemical shifts with Hammett substituent parameters.[15] These anomalies have been explained by the differences in the conjugational or migration ability of the lone pair of electrons of the amido nitrogen.[16] Furthermore, intramolecular hydrogen bonding can influence the steric inhibition of conjugation between the amido group and benzene ring, as in the case of *ortho*-substituted benzoanilides.[16] The solvent effects on the ρ-values of the Hammett plots reveal that the local π-polarization of the amido group is strengthened in polar or hydrogen-donating solvents, as argued by Yuzuri *et al.*[17] Later, the same group reported[18] anomalous polar substituent effects on the ^{15}N NMR chemical shifts of *meta*- and *para*-substituted aniline derivatives. This phenomenon was ascribed to the very large contribution of a resonance effect.

Although there are very few data on the ^{17}O NMR spectroscopy of substituted acetanilides, the sensitivity of the ^{17}O NMR chemical shifts of the carbonyl oxygen to the twist angle between the acetamido moiety and phenyl ring was well established by Boykin and coworkers.[19] The most intriguing result, the decreased ^{17}O NMR chemical shifts jointly with increased steric hindrance in *ortho*-substituent-bearing derivatives, was explained by an increased contribution of a canonical form characterized by a partial double bond between the amido nitrogen and the carbonyl carbon.[19] In that study, however, the variety of *ortho* substituents was limited to only CH_3 and OCH_3 groups.

It is obvious that no systematic study has been made of the delocalization of the electron lone pair of the amino nitrogen atom in acetanilide derivatives carrying variable substituents in the *ortho* position with respect to the fixed $NHCOCH_3$ function. Hence it is a good reason to assume that multinuclear (^1H, ^{13}C, ^{15}N, ^{17}O) magnetic resonance spectroscopy would give additional information on the so-called amidic resonance due to the changes caused by the varying steric crowding in the comprehensive series of *ortho*-substituted acetanilides. These changes can be efficiently probed by NMR chemical shifts by nuclei located either in the aromatic ring or in the fixed side-chain also.

Molecular mechanics calculations using the MMP2 force field,[20] providing quantitative information on the conformational characteristics of the side-chain, are used as a basis of the interpretation of the spectral data. The present work is a continuation of our previous studies on *ortho*-substituted aromatics.[21]

EXPERIMENTAL

Compounds **1–22**. Acetanilide (**1**) and *ortho*-X-acetanilides, where X = F (**2**), Cl (**3**), Br (**4**), I (**5**), CH_3 (**6**), C_2H_5 (**7**), $CH(CH_3)_2$ (**8**), $C(CH_3)_3$ (**9**), C_6H_5 (**10**), CF_3 (**11**), OCH_3 (**12**), SCH_3 (**13**), $COCH_3$ (**14**), COC_6H_5 (**15**), $CONH_2$ (**16**), CO_2CH_3 (**17**), CN (**18**), $NHCOCH_3$ (**19**), NHC_6H_5 (**20**), $N(CH_3)_2$ (**21**) and NO_2 (**22**), were synthesized from the corresponding *ortho*-substituted anilines as reported in the literature.[22] The purities of the compounds were checked by thin-layer chromatography and by the ^1H and ^{13}C NMR spectra, which did not show any impurity signals. Analytical-grade nitromethane was used as a reference compound in ^{15}N NMR without further purification. Dimethyl-d_6 sulphoxide (DMSO-d_6) (Uvasol, 99%) from Merck was taken from the rubber-closed ampoules with a thoroughly dried syringe to prevent contamination by humidity.

NMR spectroscopy. All NMR spectra were measured with a Jeol JNM GSX-270 FT NMR spectrometer working at 270·17 in ^1H, 67·94 in ^{13}C, 27·38 in ^{15}N and 36·63 MHz in ^{17}O NMR experiments. The NMR samples were 0·5 M solutions in 99% DMSO-d_6. The ^1H and ^{13}C NMR measurements were carried out at 30 °C in 5 mm diameter NMR tubes and the ^{15}N and ^{17}O NMR experiments at 30 and 75 °C in 10 mm diameter NMR tubes. The ^1H and ^{13}C NMR chemical shifts were referenced to the centre peak of the solvent, DMSO-d_6, $\delta = 2{\cdot}60$ ppm in ^1H and $\delta = 39{\cdot}5$ ppm in ^{13}C measure-

ments from TMS, the ^{15}N chemical shifts to the signal of neat nitromethane, $\delta = 0$ ppm, measured at 30 °C in a 10 mm tube and the ^{17}O NMR chemical shifts to the signal of external H_2O, $\delta = 0$ ppm, in a 1 mm capillary tube inserted coaxially inside the 10 mm NMR tube.

In ^1H NMR measurements, the spectral width was 3500 Hz and the number of data points was 32K, giving a spectral resolution 0·21 Hz, using four scans with a pulse delay of 1 s and a flip angle of 90°. The FIDs were digitally filtered by using an exponential window function of the digital resolution prior to Fourier transformation (FT) to improve the signal-to-noise ratio (S/N) in the frequency spectra.

In ^{13}C NMR experiments, the spectral width was 15 kHz and number of data points 32K, giving a spectral resolution of 0·92 Hz. The number of scans in the proton broadband decoupled (BBD) spectra was 100 and in coupled spectra *ca* 8000 after overnight accumulation. The pulse delay was 3 s and the flip angle 90°. The FIDs were digitally filtered by using an exponential window function of the digital resolution prior to FT to improve the S/N in the frequency spectra.

The ^{13}C–^1H COSY experiments transmitted via $^1J(C,H)$ couplings were performed using a standard pulse sequence available in the spectrometer software. The spectral widths/data points were 1500 Hz/512 (^{13}C) and 500 Hz/128 (^1H). The FIDs of both directions were digitally filtered by the exponential window functions of the digital resolutions prior to FT to improve the S/N in the 2D contour map. The chemical shifts are referenced as in the 1D spectra.

The ^{13}C–^{13}C INADEQUATE experiments were performed using a standard pulse sequence available in the spectrometer software. The spectral widths/data points were 1000–3000 Hz/512 (f_1-axis) (limited to aromatic area and cyano signal taken with **18**) and 2000–6000/128 (f_2-axis). Although saturated samples were used in these experiments, the number of scans had to be raised to 128 (256 for **12**) and the pulse delay increased to 6 s to ascertain sufficient relaxation of *ipso*-carbons. Under these conditions the total accumulation time was *ca* 13 h (26 h for **12**). The FIDs were digitally filtered by an exponential window function of the f_1-digital resolution prior to FT to improve the S/N in the symmetrized 2D contour map. The chemical shifts are fixed based on the proton BBD ^{13}C NMR spectrum.

In ^{15}N NMR experiments, the spectral width was 15 kHz and the number of data points was 64K, giving a spectral resolution of 0·5 Hz. In proton broadband decoupled (BBD) experiments the pulse delay was 7 s (giving a total repetition rate of 9·2 s) and the flip angle was 30°. The number of scans was set to 800 (corresponding to a total accumulation period of 2 h), which was sufficient for reliable detection of the ^{15}N NMR chemical shifts of the amido nitrogens (cyano and nitro groups characterized by unfavourable relaxation properties were not detected). The FIDs were digitally filtered by using an exponential window function of the digital resolution prior to FT to improve the S/N in the frequency spectra. In these proton BBD experiments, the intensities of the spectral lines were negative owing to the negative gyromagnetic ratio of nitrogen-15. In addition, inverse gated decoupling experiments with a long pulse delay (30 s) were performed for some compounds in order to check for the possible presence of unprotonated imido forms characterized by unfavourable relaxation properties. No additional ^{15}N NMR lines, however, were detected.

In ^{17}O NMR experiments, the spectral width was 36 kHz and the number of data points was 8K, giving a 9 Hz spectral resolution, the pulse delay was 0·1 s and the flip angle was 90°. The numberof scans was 100 000 (corresponding to a total accumulation period of 5·5 h per spectrum). The FIDs were digitally filtered by an exponential window function of 50 Hz to improve the S/N in the frequency spectra.

Computerized analyses of the ^1H NMR spectra were done with PERCH Software.[23]

RESULTS AND DISCUSSION

The structures and numbering of compounds **1–22** are given in Figure 1. The ^1H and ^{13}C NMR chemical shifts are given in Tables 1 and 2, $^1J(C,H)$ coupling constants in Table 3 and ^{15}N and ^{17}O NMR chemical shifts in Table 4. The minimum energies and the corresponding optimized structures and dihedral angles in degrees calculated by molecular mechanics[20] using the program PCMODEL (Serena Software)[24] are collected in Table 5.

Molecular mechanics calculations

In order to relate the observed NMR parameters with the conformational characteristics of *ortho*-substituted acetanilides, their energetically most stable structures have been calculated by molecular mechanics[20] (Table 5). As can be seen, a clear variation in dihedral angle between the benzene ring and the C–N–H fragment of the acetamido group occurs depending on the substituent, whilst the rest of the acetamido group is hardly affected by the substituent. The structures of compounds **14–17** and **22** are stabilized by an intramolecular hydrogen bond between the amido proton and the

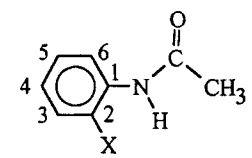


Figure 1. Structures and numbering of compounds **1–22**.

Table 1. ^{1}H NMR chemical shifts, δ (ppm), of compounds **1–22**

Compound	Substituent	H-3	H-4	H-5	H-6	NH	CH_3CO	CH_3	$CH_2/CH/NH_2$
1	—	7·38	7·11	7·38	7·68	9·99	2·14	—	—
2	F	7·29	7·22	7·22	7·95	9·79	2·19	—	—
3	Cl	7·57	7·27	7·41	7·82	9·57	2·20	—	—
4	Br	7·71	7·21	7·45	7·74	9·52	2·18	—	—
5	I	7·97	7·07	7·47	7·53	9·49	2·16	—	—
6	CH_3	7·29	7·16	7·24	7·50	9·35	2·16	2·30	—
7	CH_2CH_3	7·32	7·25	7·23	7·45	9·36	2·16	1·22	2·70
8	$CH(CH_3)_2$	7·35	7·24	7·27	7·40	9·41	2·15	1·25	3·44
9	$C(CH_3)_3$	7·49	7·30	7·29	7·14	9·28	2·14	1·43	—
10	Ph	—[a]	—[a]	—[a]	—[a]	9·33	2·00	—	—
11	CF_3	7·60	7·53	7·76	7·82	9·63	2·15	—	—
12	OCH_3	7·11	7·16	6·99	8·05	9·18	2·19	3·92	—
13	SCH_3	7·49	7·31	7·26	7·42	9·38	2·16	2·51	—
14	$COCH_3$	8·05	7·28	7·67	8·40	11·28	2·21	2·70	—
15	COPh	—[a]	—[a]	—[a]	—[a]	10·14	1·88	—	—
16	$CONH_2$	7·88	7·19	7·57	8·55	11·66	2·19	—	8·33, 7·78
17	$COOCH_3$	7·99	7·25	7·67	8·36	10·65	2·22	3·95	—
18	CN	7·88	7·42	7·77	7·69	10·23	2·21	—	—
19	$NHCOCH_3$	7·66	7·22	7·22	7·66	9·41	2·18	—	—
20	NHPh	7·64	7·18	7·05	7·36	9·45	2·16	—	—
21	$N(CH_3)_2$	7·22	7·14	7·08	7·99	9·09	2·22	2·71	—
22	NO_2	8·02	7·44	7·78	7·73	10·34	2·17	—	—

[a] Not analysed owing to overlapping patterns of two aromatic rings.

Table 2. ^{13}C NMR chemical shifts, δ (ppm), of compounds **1–22**

Compound	Substituent	C-1	C-2	C-3	C-4	C-5	C-6	CO	CH_3	CH_3/CF_3	$CH_2/CH/C$
1	—	139·3	119·0	128·6	122·9	128·6	119·0	168·3	24·0	—	—
2	F	126·2	153·6	115·3	125·0	124·2	124·2	168·6	23·4	—	—
3	Cl	135·1	126·3	129·3	126·0	127·2	126·2	168·6	23·3	—	—
4	Br	136·4	117·8	132·5	126·8	127·8	127·1	168·4	23·2	—	—
5	I	139·7	96·5	138·8	127·5	128·6	127·4	168·3	23·2	—	—
6	CH_3	136·5	131·5	130·1	124·9	125·8	124·9	168·1	23·2	17·8	—
7	CH_2CH_3	137·7	135·8	128·3	125·7	125·4	126·0	168·4	23·1	14·1	23·7
8	$CH(CH_3)_2$	134·9	143·0	126·8	125·5	125·9	125·4	168·6	23·0	27·0	23·1
9	$C(CH_3)_3$	136·1	146·3	131·7	126·2	126·7	126·4	169·0	23·1	30·7	34·6
10	Ph[a]	136·6	134·9	130·2	125·9	127·6	127·3	168·6	22·9	—	—
11	CF_3	135·6	124·8	130·2	126·5	132·8	126·2	169·1	22·8	123·6	—
12	OCH_3	127·4	149·5	111·0	124·1	120·1	121·9	168·4	23·8	55·5	—
13	SCH_3	135·5	133·2	126·0	126·0	125·2	126·7	168·4	23·1	15·1	—
14	$COCH_3$[b]	124·3	139·0	131·3	122·8	133·9	120·5	168·6	24·7	28·6	—
15	COPh[c]	136·4	130·6	129·9	123·9	131·7	123·5	168·1	23·1	—	—
16	$CONH_2$[d]	139·6	119·8	128·5	122·2	132·0	120·2	168·1	24·9	—	—
17	$COOCH_3$[e]	139·8	117·4	130·3	122·9	133·8	120·9	168·4	24·5	52·3	—
18	CN[f]	140·3	107·2	133·1	125·5	133·7	125·4	168·7	23·1	—	—
19	$NHCOCH_3$[g]	130·5	130·5	124·7	124·6	124·6	124·7	168·6	23·7	23·7	—
20	NHPh[h]	129·4	135·8	125·1	125·1	121·4	119·7	168·7	23·5	—	—
21	$N(CH_3)_2$	132·1	144·3	119·0	124·0	122·8	122·1	168·2	23·9	43·6	—
22	NO_2	131·2	142·4	124·8	125·0	133·8	125·2	168·4	23·3	—	—

[a] X = Ph: 139·0 (C-1), 128·7 (C-2/6), 128·3 (C-3/5) and 127·1 ppm (C-4).
[b] X = $COCH_3$: 202·4 ppm (CO).
[c] X = COPh: 137·3 (C-1), 129·5 (C-2/6), 128·1 (C-3/5), 132·4 (C-4) and 195·2 ppm (CO).
[d] X = $CONH_2$: 170·7 ppm (CO).
[e] X = $COOCH_3$: 167·5 ppm (CO).
[f] X = CN: 116·9 ppm (CN).
[g] X = $NHCOCH_3$: 168·6 ppm (CO).
[h] X = 144·1 (C-1), 116·4 (C-2/6), 129·0 (C-3/5) and 119·4 ppm (C-4).

Table 3. ^1J(C, H) coupling constants (Hz) of compounds **1–22**

Compound	Substituent	C-3	C-4	C-5	C-6	CH_3	CH_3	CH_2/CH
1	—[a]	158·9	161·7	158·9	163·0	127·9	—	—
2	F[b]	165·1	164·6	162·3	162·3	128·0	—	—
3	Cl	168·5	162·6	162·3	163·9	127·8	—	—
4	Br	166·0	165·4	164·0	166·7	128·4	—	—
5	I	165·7	162·1	161·6	163·5	127·9	—	—
6	CH_3	158·6	160·3	162·0	160·3	127·7	126·7	—
7	CH_2CH_3	159·6	160·9	160·5	162·4	127·6	126·5	126·9
8	$CH(CH_3)_2$	160·0	160·7	160·0	156·2	127·6	126·0	128·9
9	$C(CH_3)_3$	160·7	161·3	160·7	156·8	127·4	125·7	—
10	Ph[c]	159·4	165·9	161·3	162·6	127·4	—	—
11	CF_3[d]	165·9	166·5	163·9	165·2	127·9	273·4	—
12	OCH_3	160·0	161·3	161·0	163·4	127·9	144·8	—
13	SCH_3	162·3	162·3	162·7	163·0	127·9	140·0	—
14	$COCH_3$	160·5	163·2	160·5	165·6	128·1	128·0	—
15	COPh[e]	161·7	166·1	160·6	163·5	128·0	—	—
16	$CONH_2$	159·3	162·3	160·0	166·0	128·1	—	—
17	$COOCH_3$	163·0	163·7	160·9	165·7	128·2	147·9	—
18	CN	166·2	164·3	163·0	166·2	128·3	—	—
19	$NHCOCH_3$	161·0	161·0	161·0	161·0	128·2	128·2	—
20	NHPh[f]	160·8	160·8	161·7	159·0	127·8	—	—
21	$N(CH_3)_2$	157·3	160·7	160·3	162·7	127·9	134·4	—
22	NO_2	167·4	165·4	163·3	166·4	128·4	—	—

[a] J(C-2, H-2) = 163·0 Hz.
[b] J(C-1, F) = 11·9 Hz, J(C-2, F) = 244·7 Hz, J(C-3, F) = 20·2 Hz, J(C-4, F) = 7·3 Hz, J(C-6, F) = 2·7 Hz.
[c] J(C-2, H-2) = J(C-6, H-6) = 159·4 Hz, J(C-3, H-3) = J(C-5, H-5) = 160·7 Hz, J(C-4, H-4) = 160·7 Hz.
[d] J(C-2, F) = 30·2 Hz.
[e] J(C-2, H-2) = J(C-6, H-6) = 162·5 Hz, J(C-3, H-3) = J(C-5, H-5) = 162·9 Hz, J(C-4, H-4) = 161·7 Hz.
[f] J(C-2, H-2) = J(C-6, H-6) = 159·0 Hz, J(C-3, H-3) = J(C-5, H-5) = 159·0 Hz, J(C-4, H-4) = 160·0 Hz.

Table 4. ^{15}N and ^{17}O NMR chemical shifts, δ (ppm) of compounds **1–22**

Compound	Substituent	$\delta(^{15}N)$	$\Delta\delta$	$\delta(^{17}O)$	$\Delta\delta$	C-2–C-1–N–H (°)
1	H	244·9	0·0	356·9	0·0	35·6
2	F	258·4	13·5	359·8	2·9	34·5
3	Cl	250·8	5·9	356·6	−0·3	38·8
4	Br	247·1	2·2	355·4	−1·5	41·0
5	I	240·2	−4·7	351·3	−5·6	42·4
6	CH_3	249·3	4·4	347·5	−9·4	39·2
7	CH_2CH_2	250·5	5·6	347·2	−9·7	43·1
8	$CH(CH_3)_2$	251·1	6·2	345·5	−11·4	52·1
9	$C(CH_3)_3$	246·6	1·7	344·6	−12·3	62·3
10	Ph	248·9	4·0	349·4	7·5	43·6
11	CF_3	253·9	9·0	352·3	−4·6	38·6
12	OCH_3	256·1	11·2	355·9[a]	−1·0	39·0
13	SCH_3	249·3	4·1	351·8	−5·1	42·0
14	$COCH_3$	251·1	6·2	369·9[b]	13·0	37·2
15	COPh	248·1	3·2	357·1[c]	0·2	42·1
16	$CONH_2$	251·0	6·1	366·5[d]	9·6	41·3
17	$COOCH_3$	251·8	6·9	368·5[e]	11·6	38·1
18	CN	250·6	5·7	363·2	6·3	42·0
19	$NHCOCH_3$	252·9	8·0	348·2	−8·7	42·0
20	NHPh	252·6	7·7	349·4	−7·5	40·3
21	$N(CH_3)_2$	253·3	8·4	356·6	−0·3	43·3
22	NO_2	254·1	9·2	361·7[f]	4·8	48·1

[a] $\delta(OCH_3)$ = 40·2 ppm.
[b] $\delta(COCH_3)$ = 541·4 ppm.
[c] δ(COPh) = 546 ppm (broad signal).
[d] $\delta(CONH_2)$ = 319·7 ppm.
[e] $\delta(COOCH_3)$ = 345·5 and 139·3 ppm.
[f] $\delta(NO_2)$ = 597·2 ppm.

Table 5. Minimum energies, MMXE (kcal mol^{-1}), and optimized dihedral angles (°) of **1–22**

Compound	Substituent	MMXE	C-2–C-1–N–H	C-2–C-1–N–C(O)	C-1–N–C(O)–CH_3	C-1–N–C=O
1	H	10·08	−18·5	159·8	175·3	−5·5
2	F	11·34	−21·7	155·8	175·4	−5·5
3	Cl	12·74	−26·9	151·0	175·2	−5·8
4	Br	13·20	−29·4	148·4	175·2	−5·7
5	I	13·08	−32·5	144·9	175·4	−5·6
6	CH_3	11·03	−28·6	148·8	175·6	−5·4
7	CH_2CH_3	13·41	−29·8	147·5	175·8	−5·2
8	$CH(CH_3)_2$	14·39	−31·5	146·8	175·4	−5·7
9	$C(CH_3)_3$	19·20	−39·9	137·1	176·4	−4·3
10	Ph	45·56	−54·4	125·4	177·3	−3·3
11	CF_3	42·04	−33·0	144·1	176·0	−4·9
12	OCH_3	16·12	−24·7	152·6	175·1	−5·8
13	SCH_3	14·49	−29·4	147·7	175·7	−5·3
14	$COCH_3$	15·60	−31·5	146·0	175·6	−5·4
15	COPh	32·19	−30·4	147·7	175·0	−6·1
16	$CONH_2$	8·22	−30·2	147·2	175·6	−5·4
17	$COOCH_3$	22·86	−30·3	147·9	175·1	−6·1
18	CN	14·73	−26·8	151·0	174·9	−6·2
19	$NHCOCH_3$	14·56	−31·5	146·0	175·3	−5·7
20	NHPh	28·54	−31·3	146·2	175·5	−5·4
21	$N(CH_3)_2$	19·99	−30·9	146·3	176·1	−4·8
22	NO_2	18·27	−37·8	140·2	175·9	−5·4

carbonyl or nitro group of the substituent at C-2. The other conformation of the acetamido group, where the acetyl group is twisted by 180° around the N–C bond, exhibits a 1·8 kcal mol^{-1} (1 kcal = 4·184 kJ) higher energy than the present one in the case of acetanilide (**1**) itself; for its derivatives these differences are even greater. Therefore, the relationships between the observed NMR parameters and the dihedral angles were calculated only for the preferred conformations and are given in Table 5.

^{1}H NMR assignments

The assignment of the ^{1}H NMR chemical shifts (Table 1) is based on the characteristic intra-ring couplings and ^{13}C–^{1}H COSY correlation maps (all samples) as well as on ^{13}C–^{13}C INADEQUATE experiments for four samples (**6**, **12**, **18** and **21**). Measuring the INADEQUATE correlation maps for all samples would be very time consuming and not necessary in view of the reliability of the spectral assignments. Calculation of the ^{1}H NMR chemical shifts as a 'simple sum' of single substituent effects did not show any satisfactory prediction properties owing to variations in steric compression and conformational preferences of the acetamido moiety with respect to the benzene ring exhibiting a strong anisotropy effect.

Additional difficulties in explaining the observed chemical shifts are encountered with compounds **10**, **15** and **20**, characterized by a phenyl containing substituent at C-2. In **15** the intramolecular hydrogen bond NH···CO forming a six-membered ring structure can fix the conformation of the acetamido group. Consequently, the acetamido methyl cannot be in the vicinity of the aromatic moiety in **15**. In **10** and **20**, where intramolecular hydrogen bonding is not possible, the conformational freedom of the acetamido group is higher than in **15**, allowing the acetyl methyl to 'feel' the anisotropic effect of the phenyl-containing substituent at C-2. However, one should remember that protons are affected also by intermolecular and solvent effects. Therefore, too far reaching conclusions should be avoided in interpreting of the ^{1}H NMR data of these complex systems.

^{13}C NMR assignments

Th assignment of the ^{13}C NMR chemical shifts (Table 2) is based on characteristic substituent chemical shifts (SCS), the ^nJ(C, H) and ^nJ(C, F) coupling constants, ^{13}C–^{1}H COSY (all samples) and ^{13}C–^{13}C INADEQUATE correlation maps (**6**, **12**, **18** and **21**; see Figure 2). For the alkyl-substituted derivatives **7–9**, the assignments of the *ipso*-carbons 1 and 2 (both characterized by poorly resolved complex coupling patterns in proton-coupled ^{13}C NMR spectra) are based on a monotonous increase in the ^{13}C NMR chemical shift of the C-2 with increasing number of β-carbons.[25]

The suitability of trifluoroacetic acid as a solvent was

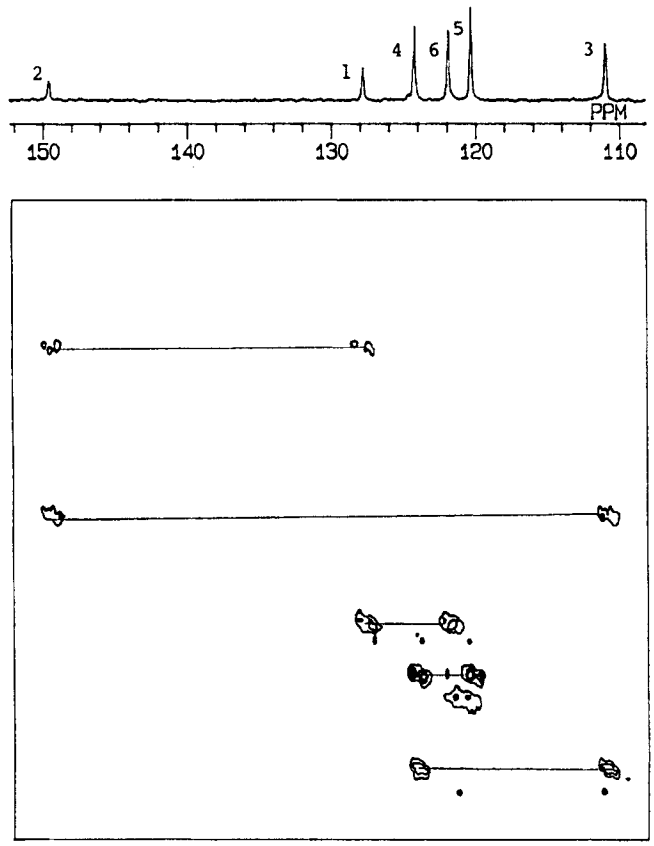


Figure 2. $^{13}C-^{13}C$ INADEQUATE correlation map of *ortho*-methoxyacetanilide (**12**)

also checked in hope that it would induce systematic changes in the ^{13}C NMR chemical shifts of C-1 via the formation of a hydrogen bond with the amido proton, thus helping in the assignment of the *ipso*-carbons. No clear trends were found, however. A serious drawback in using trifluoroacetic acid was that some congeners decomposed rapidly, preventing reliable NMR measurements.

The variation of the ^{13}C NMR chemical shifts of C-4 ($\Delta\delta = 5{\cdot}3$ ppm) *para* to the $NHCOCH_3$-substituted carbon and C-5 ($\Delta\delta = 13{\cdot}8$ ppm) *para* to C-2 suggests that the properties of the varying substituent X at C-2 are responsible for the different behaviours of these ^{13}C NMR chemical shifts. One way to estimate these effects is to correlate the observed chemical shifts with the Hammett substituent constants catalogued by Hansch *et al.*[26] A multiple linear regression analysis using field (F) and resonance (R) parameters derived by Swain and Lupton[27] (using the equation $\sigma_p = \alpha F + R$, where σ_p is the Hammett constant for a *para* substituent and α is a constant) gave a relationship for the ^{13}C NMR chemical shift of C-5 (ppm) *para* to the substituent X:

$$\delta(\text{C-5}) = (5{\cdot}2 \pm 2{\cdot}2)F + (11{\cdot}5 \pm 1{\cdot}4)R + (128{\cdot}5 \pm 0{\cdot}8)$$

(statistical coefficients: $r = 0{\cdot}91$, $n = 22$, standard deviation$s = 1{\cdot}82$ and $F = 47$).

In two cases the calculated and observed values differ markedly: in **12** ($X = OCH_3$) $\Delta\delta = -3{\cdot}5$ ppm and in **21** [$X = N(CH_3)_2$] $\Delta\delta = 4{\cdot}8$ ppm (the 2D ^{13}C-INADEQUATE correlation maps for **12** and **21** ascertained their correct ^{13}C NMR spectral assignments).

The δ(C-5/ppm) values related to the σ_p^+ and σ_p^- constants[26] gave a slightly improved equation:

$$\delta(\text{C-5}) = (3{\cdot}0 \pm 0{\cdot}8)\sigma_p^+ + (4{\cdot}4 \pm 1{\cdot}1)\sigma_p^- + (127{\cdot}1 \pm 0{\cdot}5)$$

($r = 0{\cdot}94$, $n = 20$, $s = 1{\cdot}44$ and $F = 67$).

The origin of the large deviations between the experimental and calculated ^{13}C NMR chemical shifts may be the variable interaction between the contiguous substituents caused by the alterations in the conformational preferences of the $NHCOCH_3$ group and/or by

intramolecular hydrogen bonding between the amido proton and the heteroatom of the *ortho* substituent.[21b]

The significance of this steric interaction can be estimated by relating the ^{13}C NMR chemical shift of C-1 (bearing an acetamido group) with the variable *ortho*-substituent chemical shift (SCS) of monosubstituted benzene, as done previously for *para*-substituted acetanilides by O'Connor *et al.*[28] They found excellent linearity (slope 0·86 and $r = 0·999$)[28] whereas for *ortho*-substituted isomers a relationship characterized by slope of 0·50 and a poor $r = 0·70$ was obtained. This different behaviour shows that in the case of *ortho*-substituted acetanilides the additivity rule of the substituent effects is far from valid.

Furthermore, the similarity of the *ortho*- and *para*-substituent effects on the ^{13}C NMR chemical shift of the *ipso*-carbon of substituted nitrobenzenes[21b] is by no means true for the present series of compounds, as was found after comparison of the present values with those for *para*-substituted acetanilides.[28] This means that the *ortho*-substituted acetanilides did not show any strong tendency to be planar, thus differing from *ortho*-substituted nitrobenzenes but in agreement with the present molecular mechanics calculation.

Coupling constants

$^1J(C,H)$ coupling constants (Table 3) show clear variations, the ranges being 11·2 (C-3) > 10·5 (C-6) > 6·2 (C-4) > 5·1 (C-5) > 1·0 Hz (2-$NHCOCH_3$). As in the case of the ^{13}C NMR chemical shifts, these values are related to the Hammett[26] and Swain–Lupton[27] substituent parameters. For ^1J(C-3, H-3) a relationship

$$^1J(\text{C-3, H-3}) = (14·5 \pm 2·2)F + 158·3 \pm 0·7 \text{ Hz}$$

($r = 0·82$, $n = 22$, $s = 1·9$ and $F = 42$) can be obtained. The inclusion of R term in the model did not improve the result significantly. In the case of ^1J(C-5, H-5), the multiple linear regression analysis did not give any reasonable result, because the correlation coefficient, r, remained at 0·65. Similarly, ^1J(C-6, H-6), showing a 10·5 Hz total variation, cannot be related reliably with F and R terms, the multiple r remaining at 0·75. This is understandable since C-6 located at an *ortho* position to the acetamido group is also strongly affected by its conformational changes.

^{15}N NMR spectra (Table 4)

Generally, ^{15}N NMR chemical shifts are sensitive to intermolecular interactions.[29] The total variation of the ^{15}N NMR chemical shifts of the amido nitrogen in *ortho*-substituted acetanilides is 13·5 ppm. This is a much greater variation than that observed for the ^{13}C NMR chemical shifts of acetamido methyl (1·9 ppm) or carbonyl (1·0 ppm), supporting the hypothesis on the usefulness of ^{15}N NMR chemical shifts as an indicator of electronic effects in the acetamido moiety.[1,2]

Previously, Axenrod *et al.*[13] have shown for ^{15}N-enriched *meta*- and *para*-substituted anilines that $^1J(N,H)$ and ^{15}N NMR chemical shifts are linearly related with the Hammett substituent constants. The explanation for these findings can be understood by the resonance structures in Scheme 1, in which the hybridization of the aniline nitrogen and consequently the s character of the N–H bond are affected by the electronegativity of the ring substituent. Since the substituent is attached to the benzene ring further from the nitrogen atom as in the systems studied by Bradamante and co-workers[8] effects such as anisotropy or field cannot be expected to influence the ^{15}N NMR chemical shifts significantly. Therefore, they can be assumed to be sensitive mostly to the electronic (inductive and resonance) and steric substituent effects.

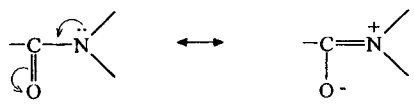
A multiple linear regression analysis performed for the whole ^{15}N NMR data set observed did not, however, reveal any significant relationship between the ^{15}N NMR chemical shifts and Hammett substituent parameters, thus being in agreement with the results for the *meta*- and *para*-substituted anilides.[15] As stated in the case of the ^{13}C NMR data, this must be due to the interaction between the contiguous substituents and the varying conformational preferences of the acetamido moiety.

In order to relate the observed ^{15}N NMR chemical shifts with the structural parameters, dihedral angles of the energetically most stable structures of the side-chain were also calculated by molecular mechanics[20] with the program PCMODEL[24] and are collected in Table 5. Torsion angles of 18·5° obtained for the parent compound and 28·6° for $X = CH_3$ are in reasonable agreement with the values obtained by Boykin *et al.*[19a] and those obtained by x-ray analysis for acetanilide itself.[3b] Although the clear trends exist in the subgroups of the compounds such as in *ortho*-halogenated acetanilides, in which the shielding is increased with increasing C-2–C-1–N–H dihedral angle,

$$\delta(^{15}N) = (1·9 \pm 0·1)\theta(\text{C-2–C-1–N–H}) + (294·7 \pm 3·6)$$

($r = 0·99$, $n = 4$, $s = 1·0$ and $F = 164$), no general relationship between the ^{15}N NMR chemical shifts and conformational characteristics of the acetamido moiety was observed. One improvement would be that intra- and intermolecular hydrogen bonding could also be taken into account in these considerations. Hence the next attempt to find an improved model was to include the ^1H NMR chemical shifts of amido protons serving as a probe for the hydrogen bonding. This approach, however, did not improve the situation.

Scheme 1



Scheme 2

The variation of the ^{15}N NMR chemical shifts of *ortho*-X-acetanilides (Table 4) is much smaller than that of *ortho*-X-anilines (X = F, Cl, Br and I) (ref. 29, p. 54), where the $\delta(^{15}N_{anil.}) - \delta(^{15}N_{2\text{-}X\text{-}anil.})$ values are 11·8 (F), 0·6 (Cl), −4·2 (Br) and −11·9 ppm (I). This means that the CO group is influencing the ^{15}N NMR chemical shifts of the neighbouring amido nitrogen. The delocalization of the nitrogen lone pair in the –NH–CO– fragment (so-called amidic resonance[10,17,29]) can be described by the canonical structures given in Scheme 2.

Since the influence of the methyl group in the $NHCOCH_3$ function on the CO group is small, the reduction of the N–aromatic ring orbital overlap could cause the dominance of the contribution of structure B (Scheme 3), which was observed in the ^{13}C NMR chemical shift variations at the *para* positions in *N*-functionalized anilines and *N*-methylanilines.[8] In our case, however, the set of substituents is much more comprehensive, varying in their electronic and steric requirements,[30] than those included in the previous studies.[2,8]

^{17}O NMR spectra

^{17}O NMR chemical shifts (Table 5) obtained in this work are comparable to those available in the literature measured in acetonitrile at 75 °C,[19] viz. acetanilide itself (355·3 ppm) and 2-CH_3 (349·0 ppm) and 2-OCH_3 derivatives (359·1 ppm). The greatest difference is found for the 2-OCH_3 derivative, 3·2 ppm. The contribution of the carbonyl group in the corresponding mesomeric structures is also visible in the ^{17}O NMR chemical shift of the carbonyl oxygen, showing a 25·3 ppm total variation. Generally, the observed variations in the ^{17}O NMR chemical shifts can be rationalized via the structures given in Scheme 3 as follows: (a) in those derivatives where the form A is predominant, the ^{17}O NMR chemical shifts are deshielded, steric effects are negligible and hydrogen bonding may rise as an important factor; and (b) when the B form is the most favoured structure, steric effects contribute strongly to the observed changes, as in the case of halogen- or alkyl-substituted derivatives. Although no general relationships exist for the whole set of compounds, some clear trends within the subgroups of compounds are obvious. Thus, the dihedral angle C-2–C-1–N–H is related significantly with the ^{17}O NMR chemical shifts in halogenated **2–5** congeners:

$$\delta(^{17}O) = (-0{\cdot}75 \pm 0{\cdot}12)\theta(\text{C-2–C1–N–H}) + (376{\cdot}5 \pm 3{\cdot}4)$$

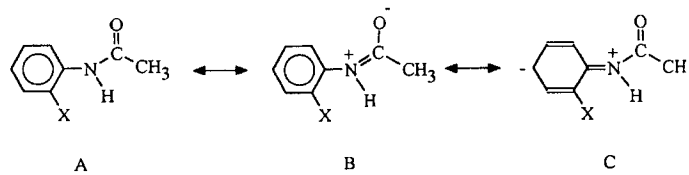
($r = 0{\cdot}97$, $n = 4$, $s = 0{\cdot}96$ and $F = 38$) and in alkylated **6–9** congeners:

$$\delta(^{17}O) = (-0{\cdot}24 \pm 0{\cdot}09)\theta(\text{C-2–C1–N–H}) + (354{\cdot}0 \pm 2{\cdot}8)$$

($r = 0{\cdot}89$, $n = 4$, $s = 0{\cdot}76$ and $F = 8$).

CONCLUSION

Ortho-substituted acetanilides form an interesting series owing to (a) the four useful NMR nuclei in their structures, (b) the presence of the conformationally flexible acetamido moiety and (c) the variable steric interaction depending on the size and electronic characteristics of the *ortho* substituents. Owing to the varying steric crowding between the *ortho* substituent and acetamido group, the interaction of the contiguous amido nitrogen and carbonyl carbon is more or less hampered. Consequently, no simple sum rules of single substituent effects are valid in predicting the experimental chemical shifts. Regarding ^{13}C NMR, the chemical shifts of C-5 at the *para* position to the *ortho* substituent can be related to the Hammett substituent parameters. Among the direct spin–spin coupling constants, ^1J(C-3, H-3) also showed a similar kind of dependence. For ^{17}O NMR chemical shifts of the side-chain carbonyl, resonance structures with varying double bond character between the C(aryl)–N(amido) and N(amido)–C(carbonyl) bonds can explain the observed variations as mostly due to steric effects and intramolecular hydrogen bonding than to electronic effects alone. Especially in the case of halogen- and alkyl-substituted derivatives the observed ^{17}O NMR chemical shifts of the carbonyl group are related to the torsional characteristics of the side-chain revealing the



A B C

Scheme 3

significance of the steric effects in these subgroups of compounds.

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