

## Nuclear Magnetic Resonance Spectra of Anilides

### II. NMR Parameters and Rotational Barriers for Some *p*-Substituted Formanilides

ROBERT E. CARTER\*

*Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Gibraltargatan 5 A, Göteborg S, Sweden*

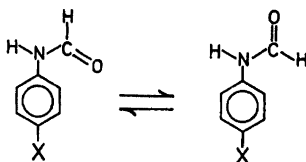
NMR parameters and rotational barriers ( $\Delta G^\ddagger$  at the coalescence temperature) in chloroform-*d* solutions are reported for some *p*-substituted formanilides ( $p\text{-X-C}_6\text{H}_4\text{NHCHO}$ , X=H, CH<sub>3</sub>, OCH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, F, Cl, Br). Data on the rate of isomer interconversion as a function of temperature could not be obtained due to concurrent intermolecular NH proton exchange. This work illustrates some of the difficulties involved in attempting to determine reliable values for rotational barriers in systems where temperature dependent solute-solute and/or solute-solvent interactions are likely to be significant.

Simple open-chain aromatic amides such as acetanilide and *N*-methylacetanilide, which lack substituents in the *ortho* positions, apparently exist predominantly (~99 %) in either the *endo*\*\* (acetanilide) or the *exo*\*\* (*N*-methylacetanilide) form,<sup>1,2</sup> and it is thus impossible to determine the size of the rotational barrier about the carbonyl-nitrogen bond with the NMR method in these cases. The NMR spectra of 2,6-disubstituted aromatic amides often demonstrate the presence of two stable isomers, which in some cases can even be isolated.<sup>5</sup> Compounds of this type have been investigated in some detail by Mannschreck and his co-workers.<sup>6</sup> Weil *et al.*<sup>7</sup> recently reported a careful NMR study of the energy barrier between the *endo* and *exo* isomers of 2,4,6-trinitro-*N*-methylacetanilide.

The original purpose of the present investigation was the determination of the barrier to rotation in a series of *p*-substituted formanilides in order to study the effect of the *para* substituent on the size of the barrier

\* Present address: Department of Organic Chemistry, Kemicentrum LTH, Box 740, S-220 07 Lund 7, Sweden.

\*\* The designations *endo* and *exo* refer, respectively, to the isomer in which the amide carbonyl group points towards the aromatic ring and to that in which it points in the opposite direction. These terms are unequivocal in the case of anilides and are thus preferable to *cis* and *trans*, which are used according to two different conventions.<sup>3,4</sup>



and thus gain some insight into the substituent effect on the double-bond character of the carbonyl-nitrogen bond. As will be discussed below, it soon became apparent that factors such as significant solute-solute interactions (intermolecular hydrogen bonds) and NH proton exchange would effectively thwart attempts to obtain enthalpies and reliable entropies of activation. Under these circumstances, a comparison of free energies of activation at the collapse temperature was considered the most adequate alternative. *Endo-exo* isomerism in formanilide itself has been investigated in some detail by Bourn, Gillies and Randall,<sup>3</sup> but they do not report a value for the barrier to isomer interconversion.

## RESULTS AND DISCUSSION

*NMR Parameters.* The assignment of specific peaks to the *endo* and *exo* isomers is straightforward, since for amides the larger coupling constant has been shown<sup>8</sup> to be associated with the isomer in which the NH and CH protons are *trans* to each other.

Chemical shifts and coupling constants for the protons in the amide group in the formanilides studied are presented in Table I for chloroform-*d* solutions at various temperatures below coalescence. Also included is the approximate ( $\pm 2$  %) percentage of *endo* isomer in each case, except those in which overlapping resonances made estimation of the isomer ratio very uncertain.

The NH and CH chemical shifts for the *exo* isomer were determined by AB analysis<sup>9</sup> of the low-temperature spectra. The *endo* coupling constant ( $\sim 2$  Hz) was unresolved in the NH peak due to quadrupole broadening and thus the AB analysis could not be applied. The chemical shift for *endo* NH was determined from the center of the NH band, and the *endo* CH chemical shift was taken to be halfway between the two peaks of the CH doublet. This is certainly justified at the lower temperatures listed in Table I since the ratio of the *endo* coupling constant to the internal chemical shift between *endo* NH and *endo* CH is in almost all cases rather small ( $\leq 0.06$ ). The chloro and bromo compounds seem to be exceptions to this rule.

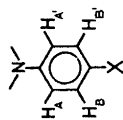
The parameter  $\delta\nu$  listed in Table I is the chemical shift (in Hz) between the *exo* and *endo* CH proton resonances. This parameter continues slowly increasing in magnitude with decreasing temperature even far below coalescence, where internal rotation is certainly extremely slow on the NMR time scale. This phenomenon has been shown to be fairly general for (aliphatic) amides<sup>10</sup> and has been attributed to solute-solute association. The choice of this parameter is not exceedingly critical for the calculation of  $\Delta G^\ddagger$  at the coalescence temperature, which will be used as a measure of the barrier height in this work.

Table 1. NMR parameters at 60 MHz for the amide group in some *p*-substituted formamides (*p*-X-C<sub>6</sub>H<sub>4</sub>NHCHO) in CDCl<sub>3</sub> solutions <sup>a</sup> at various temperatures below coalescence.

X	T, °C	% <i>endo</i> <sup>b</sup>	Chemical shifts, ppm from TMS				$\delta\nu$ (Hz)	$J_{\text{NHCH}}$ (Hz)	
			NH		CH			<i>exo</i>	<i>endo</i>
H	-39	52	10.14	9.33	8.73	8.29	26.4	11.2	1.9
	-20	51	9.88	9.08	8.72	8.30	25.2	11.4	2.0
	-8	51	9.73	8.95	8.72	8.31	24.6	11.4	2.0
	66	—	—	—	8.64	8.32	19.2	—	—
CH <sub>3</sub>	-42	51	10.18	9.35	8.68	8.27	24.6	11.3	~1
	-25	50	9.92	9.09	8.66	8.27	23.4	11.5	1.6
	-4	—	9.60	8.82	8.65	8.27	22.8	11.6	1.9
	56	—	—	—	8.60	8.27	19.8	—	—
OCH <sub>3</sub>	-33	59	9.78	9.09	8.58	8.27	18.6	11.7	2.1
	-23	56	9.60	8.93	8.56	8.26	18.0	11.5	2.1
	58	—	—	—	—	—	~13	~11	—
N(CH <sub>3</sub> ) <sub>2</sub>	-43	55	9.82	9.12	8.52	8.18	20.4	11.5	1.6
	-34	57	9.67	9.00	8.51	8.18	19.8	11.6	1.8
	-27	55	9.55	8.90	8.50	8.18	19.2	11.5	1.9
F	-21	63	9.78	9.12	8.63	8.31	19.2	11.6	2.2
	-10	66	9.55	8.93	8.61	8.30	18.6	11.5	2.0
	0	—	9.43	8.83	8.60	8.30	18.0	11.5	1.8
	36	64	—	—	8.60	8.33	~16	~11	1.5
Cl <sup>c</sup>	-20	ca. 60	9.60	8.58	8.69	8.35	20.4	11.5	1.8
	-10	—	9.42	8.37	8.70	8.37	19.8	11.8	—
Br <sup>c</sup>	-15	—	9.61	8.37	8.68	8.37	18.6	11	—
	54	—	—	—	8.60	8.35	15.0	—	—

<sup>a</sup> Mole fractions between 0.08–0.09 unless noted otherwise.<sup>b</sup>  $\pm 2$  %.<sup>c</sup> Mole fraction 0.03, due to poor solubility.

The peaks in the aromatic proton region were interpretable as two overlapping AA'BB' systems, except of course in the case of formamide itself. In the case of *p*-fluoroformamide, two overlapping AA'BB' parts of two AA'BB'X spectra were observed. In all of the spectra, the aryl proton peaks that came furthest downfield were assigned to the protons *ortho* to the amide group in the *endo* isomer on the basis of comparisons with some of the corresponding acetanilides and *N*-methylacetanilides,<sup>2,11</sup> which were assumed to exist in known stable conformations.<sup>1,2</sup> A partial analysis<sup>12</sup> of the AA'BB' spectra yielded the internal chemical shifts  $\nu_A - \nu_B = \nu_{ortho} - \nu_{meta}$  and the values of the parameter  $N = J_{AB} + J_{A'B'}$  presented in Table 2. The data for formamide were obtained from the spectrum of the corresponding partially deuterated (ca. 80 % 2,4,6-*d*<sub>3</sub>) compound. The data for *p*-fluoroformamide

Table 2. NMR parameters at 60 MHz for aromatic protons in some *p*-substituted formamides from partial AA'BB' analysis.<sup>a</sup>

X	H <sup>b</sup>		CH <sub>3</sub>		OCH <sub>3</sub>		N(CH <sub>3</sub> ) <sub>2</sub>		F <sup>c</sup>		Cl		Br	
	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>
$N = J_{AB} + J_{AB'}$ (Hz)	8.7 <sub>1</sub>	8.7 <sub>1</sub>	8.2 <sub>5</sub>	8.2 <sub>5</sub>	9.0 <sub>8</sub>	9.0 <sub>0</sub>	8.9 <sub>9</sub>	9.0 <sub>1</sub>	9.0	9.0	9.1 <sub>5</sub>	9.0 <sub>8</sub>	—	8.2 <sub>7</sub>
$\nu_0\delta = \nu_{ortho} - \nu_{meta}$ (Hz)	16.8	-13.0	21.1	-6.6 <sup>d</sup>	38.8	10.9	44.4	19.4	32	5	14.7	-14.9	~0	-28.4
$(\nu_0\delta)_{endo} - (\nu_0\delta)_{exo}$	29.8 <sup>e</sup>		27.7		27.9		25.0		27		29.6		28.4	

<sup>a</sup> Spectra determined on chloroform-*d* solutions.

<sup>b</sup> Determined on the residual proton spectrum of formamide-2,4,6-*d*<sub>3</sub>; cf. Ref. 2.

<sup>c</sup> Data estimated by comparison with computer-calculated spectra; see text.

<sup>d</sup> Sign based on line width differences, on comparison with data for formamide, and on analogy with data in Ref. 2 for acetanilide and *N*-methylacetanilide.

<sup>e</sup> Assuming  $(\nu_{meta})_{exo} > (\nu_{meta})_{endo}$ ; cf. data for *N*-methylacetanilide and acetanilide in Ref. 2.

were estimated from a comparison of observed and computer-calculated spectra. However, since the primary goal of the analysis was to obtain a value for the difference  $(\nu_0\delta)_{endo} - (\nu_0\delta)_{exo}$  (see Table 2) for comparison with those from the partial AA'BB' analyses of the other formanilide spectra, no attempt was made to further refine the parameters for the fluoro compound. In all cases, the internal chemical shift in the *endo* isomer is greater (*i.e.* more positive) than that in the corresponding *exo* isomer. The difference between them is quite comparable to that found previously<sup>2</sup> for acetanilide and *N*-methylacetanilide (27.0 Hz), and ascribed primarily to the anisotropic effect of the carbonyl group.

A long-range anisotropic effect of the carbonyl group was noticeable in the methyl, methoxyl, and dimethylamino proton resonances of the *endo* and *exo* isomers, which were separated by 1.6<sub>3</sub>, 1.6<sub>8</sub> and 1.9<sub>6</sub> Hz, respectively, at low temperatures (*ca.* -20°C). This may be compared with the effect of the thiocarbonyl group in *p*-methyl- and *p*-methoxythioacetanilide, where Rae<sup>13</sup> reports a separation of 2 Hz, presumably at 30°C. From the relative heights of the peaks and the isomer populations it may be deduced that the resonance for the *endo* isomer occurs furthest downfield in the case of *p*-methylformanilide and furthest upfield for the *p*-methoxy compound. The situation with *p*-dimethylaminoformanilide is somewhat uncertain, as the relative heights of the two peaks change with temperature.

*Rotational barriers.* Estimates of the rotational barriers at the coalescence temperature ( $T_c$ ) were obtained by the use of the approximate Gutowsky-Holm<sup>14</sup> formula

$$k_c = \frac{\pi}{\sqrt{2}} (\delta\nu_{\infty}) \quad (1)$$

for the rate constant at  $T_c$ , in conjunction with the Eyring rate equation,<sup>15</sup> and incorporating a transmission coefficient ( $\kappa$ ) of unity. As pointed out

$$k_c = \kappa \frac{kT_c}{h} \exp(-\Delta G_c^\ddagger/RT_c) \quad (2)$$

above, the chemical shift in the absence of exchange ( $\delta\nu_{\infty}$ ) was found to be somewhat temperature dependent, but as the calculated  $\Delta G_c^\ddagger$  values (see Table 3) are not very sensitive to the choice of this parameter, no attempt was made to extrapolate a  $\delta\nu_{\infty}$  value for the coalescence temperature. When preliminary results were in hand it became apparent that in view of the narrow range of  $\Delta G_c^\ddagger$  values and the interference of NH proton exchange, it would be virtually impossible to unequivocally distinguish the effect of the *para* substituent on the rotational barrier from its effect on, for example, hydrogen bond equilibria or the proton exchange process. Thus it was felt that a complete line shape analysis at various temperatures was not warranted for this system, and it was decided to use  $\Delta G_c^\ddagger$  as a measure of the barrier height, at least for purposes of comparison within the group of formanilides studied.

Table 3. Coalescence temperatures and free energies of activation ( $\Delta G_c^\ddagger$ ) for isomer interconversion in some *p*-substituted formamides (*p*-X-C<sub>6</sub>H<sub>4</sub>NHCHO) in CDCl<sub>3</sub> solutions.<sup>a</sup>

X	$T_c$ , °K ( $\pm 2^\circ$ )	$\delta\nu_\infty$ , <sup>b</sup> Hz	$\Delta G_c^\ddagger$ ( $\pm 0.2$ ), kcal/mole
H	349	25	17.7
CH <sub>3</sub>	352	24	17.9
OCH <sub>3</sub>	351	18	18.1
N(CH <sub>3</sub> ) <sub>2</sub>	356	19	18.3
F	348	19	17.8
Cl	347	20	17.8
Br	344	~19	17.7

<sup>a</sup> For concentrations, see Table 1 (footnotes).

<sup>b</sup> From the data in Table 1.

The line shape equation as derived by McConnell<sup>16</sup> and modified to include the NH—CH coupling<sup>17</sup> was used with the aid of a computer\* to generate spectra corresponding to that observed at the coalescence temperature. The relaxation time  $T_2$  was estimated from the line width at low temperatures (−20 to −40°C) and it was assumed that this parameter is the same for *endo* and *exo* CH protons. No attempt was made to take into account the temperature dependence of this parameter, but this is not expected to significantly affect the calculated line shape at the coalescence point. It is known that a temperature dependent  $\delta\nu_\infty$  value may have an important effect on the calculated line shape,<sup>18</sup> and for this reason  $\delta\nu_\infty$  was varied in an attempt to obtain better agreement between the observed and the calculated spectra. However, apparently due to the contribution of NH proton exchange, it was not possible to secure an exact fit. Surprisingly enough, it was found that the best agreement was obtained when the parameter  $\tau_c = 1/2k_c$  derived from the approximate Gutowsky-Holm formula (eqn. 1) was used in the line shape equation. The  $\Delta G_c^\ddagger$  values derived in this manner are satisfactory for comparison purposes since they were all determined under very similar conditions. The data in Table 3 show that for all of the compounds studied, the total variation in  $\Delta G_c^\ddagger$  is only 0.6 kcal/mole, which may be compared with the estimated experimental error of  $\pm 0.2$  kcal/mole. Of interest in this connection is the work of Korver,<sup>19</sup> who measured the barrier to internal rotation in a series of *p*-substituted *N,N*-dimethylbenzamides. In terms of  $\Delta G_{25}^\ddagger$ , the total variation in barrier height was found to be 1 kcal/mole.

No significant correlation was obtained between the  $\Delta G_c^\ddagger$  values for the formamides and Hammett's  $\sigma_p$  constants. A similar lack of correlation was observed by Korver<sup>19</sup> in the case of the *p*-substituted benzamides. This is in contrast to the reasonable correlation obtained by Sandström and Isaksson<sup>20</sup> in their recent study of the barrier to internal rotation about the thiocarbonyl-

\* The author is grateful to Mr. Kjell-Ivar Dahlqvist of the Royal Institute of Technology in Stockholm for making the computer program available and for carrying out the computer calculations.



temperature dependent solute-solute and/or solute-solvent interactions are likely to be significant.

*Line shapes above coalescence.* At temperatures far above coalescence, the appearance of two relatively sharp peaks separated by a weighted-average coupling constant

$$J' = p_{endo}J_{endo} + p_{exo}J_{exo} \quad (3)$$

would be expected. The value of  $J'$  will depend on the value of the *endo/exo* ratio at a given temperature, but it must fall within the approximate limits  $2 < J' < 11$  Hz. However, in the spectra of all of the formanilides studied in the present work, the line width at half-height steadily decreased above the coalescence temperature and in the case of formanilide itself reached a value of *ca.* 4.6 Hz at 100°C in chloroform-*d* solution. In the case of *p*-methyl-formanilide, the line width decreased to 2.2 Hz at 150°C in 1,1,2,2-tetra-chloroethane solution. These results are understandable in terms of the intermolecular NH proton exchange process, which becomes fast at high temperatures and thus in effect destroys the coupling between the NH and CH protons. One would certainly expect to be able to resolve even a 2 Hz coupling in the absence of exchange. Sunners, Piette and Schneider<sup>21</sup> found a similar exchange process taking place in neat formamide, but they were able to eliminate this complication by using acetone as a diluent in order to isolate the formamide molecules from each other and thus prevent exchange. In the present work, the use of acetone as solvent apparently did not prevent NH proton exchange in formanilide in view of the fact that between 100 and 130°C the CH peak remained unsplit with a half-width of 4–5 Hz.

## EXPERIMENTAL

*Materials.* All of the formanilides used in this work, with the exception of formanilide itself, which was a commercial product (Eastman White Label), were synthesized \* by reaction of the corresponding aniline derivative with formic acid in toluene solution. Melting points and yields of pure material after several recrystallizations are summarized in Table 4.

*NMR spectra* were determined on a Varian A-60 spectrometer \*\* equipped with a V-6031 variable temperature probe. Calibration of spectra and sweep was performed using sidebands from internal TMS generated by a Hewlett-Packard model 200 CD wide range oscillator. The sideband frequency was measured with a Hewlett-Packard model 3734A frequency counter. The temperature of the sample was varied by means of a Varian V-6040 variable temperature controller and was measured by the concentric capillary technique,<sup>22</sup> using a methanol/aq.HCl mixture for temperatures below that of the probe and ethylene glycol for higher temperatures. Temperatures could be determined to about  $\pm 0.2^\circ$  by this method. The difference in temperature before and after a series of spectra was recorded at a given temperature was often of the order of  $\pm 1^\circ$ .

*Temperature calibration.* The capillaries were calibrated with a copper-constantan thermocouple inserted into a spinning NMR tube containing chloroform or *ortho*-dichloro-

\* The preparation of these compounds by Mr. Lars-Håkan Wieck is gratefully acknowledged.

\*\* Some of the spectra were run on a Varian A-60A spectrometer at the Institute of Technology in Lund. The author is indebted to Profs. Sture Forsén and Börje Wickberg for permission to use this instrument.



Table 4. Melting points and yields of *p*-substituted formamides (*p*-X-C<sub>6</sub>H<sub>4</sub>NHCHO)<sup>a</sup>.

X	M.p., °C	Lit. m.p., °C	Solvent for recryst.	Yield, <sup>b</sup> %
CH <sub>3</sub>	49 — 53	53 <sup>24</sup>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	28
F	66 — 68	—	H <sub>2</sub> O	—
Cl	102 — 103	102 <sup>25</sup>	CCl <sub>4</sub> ; H <sub>2</sub> O	76
Br	116.5 — 118	119 <sup>26</sup>	CH <sub>3</sub> CH <sub>2</sub> OH/H <sub>2</sub> O	71
OCH <sub>3</sub>	80 — 81	80 — 81 <sup>27</sup>	CH <sub>3</sub> CH <sub>2</sub> OH	44
N(CH <sub>3</sub> ) <sub>2</sub>	107 — 108	108 <sup>28</sup>	H <sub>2</sub> O; CH <sub>3</sub> CH <sub>2</sub> OH/H <sub>2</sub> O	20

<sup>a</sup> Prepared by Mr. L.-H. Wieck.<sup>b</sup> After several recrystallizations.

benzene. The thermocouple itself had been previously calibrated against a standard thermometer for the range 0–100°C, and at the vaporization point of solid CO<sub>2</sub><sup>28</sup> for the range 0 to –90°C. Voltages were measured with a Croydon type P3 potentiometer.

*Acknowledgement.* The author wishes to thank Prof. Lars Melander for his interest in this work, and for reading the manuscript prior to publication.

## REFERENCES

- Pedersen, B. F. and Pedersen, B. *Tetrahedron Letters* **1965** 2995.
- Carter, R. E. *Acta Chem. Scand.* **21** (1967) 75, and references cited therein.
- Bourn, A. J. R., Gillies, D. G. and Randall, E. W. *Tetrahedron* **20** (1964) 1811.
- LaPlanche, L. and Rogers, M. T. *J. Am. Chem. Soc.* **86** (1964) 337.
- See, for example, Walter, W., Maerten, G. and Rose, H. *Ann.* **691** (1966) 25; Mannschreck, A. *Tetrahedron Letters* **1965** 1341; *Angew. Chem.* **77** (1965) 1032; Staab, H. A. and Lauer, D. *Tetrahedron Letters* **1966** 4593.
- Mannschreck, A., Mattheus, A. and Rissman, G. *J. Mol. Spectry.* **23** (1967) 15.
- Weil, J. A., Blum, A., Heiss, A. H. and Kinnaird, J. K. *J. Chem. Phys.* **46** (1967) 3132.
- Randall, E. W. and Baldeschwieler, J. D. *J. Mol. Spectry.* **8** (1962) 365.
- Pople, J. A., Schneider, W. G. and Bernstein, H. J. *High-resolution Nuclear Magnetic Resonance*, McGraw, New York 1959, p. 119.
- Whittaker, A. G. and Siegel, S. *J. Chem. Phys.* **42** (1965) 3320; **43** (1965) 1575.
- Wieck, L.-H. and Carter, R. E. *Unpublished results*.
- Emsley, J. W., Feeney, J. and Sutcliffe, L. H. *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon, London 1965, p. 399 ff.
- Rae, I. D. *Can. J. Chem.* **45** (1967) 1.
- Gutowsky, H. S. and Holm, C. H. *J. Chem. Phys.* **25** (1956) 1228.
- Glasstone, S., Laidler, K. J. and Eyring, H. *The Theory of Rate Processes*, McGraw, New York 1941, p. 190 f.
- McConnell, H. M. *J. Chem. Phys.* **28** (1958) 430.
- Cf. Dahlqvist, K.-I. and Forsén, S. *J. Phys. Chem.* **69** (1965) 4062.
- See, for example, Gutowsky, H. S., Jonas, J. and Siddall, III, T. H. *J. Am. Chem. Soc.* **89** (1967) 4300.
- Korver, P. K. *Thesis*, Amsterdam 1966.
- Isaksson, G. and Sandström, J. *To be published*.

21. Sunners, B., Piette, L. H. and Schneider, W. G. *Can. J. Chem.* **38** (1960) 681.
22. Cf. Duerst, R. and Merbach, A. *Rev. Sci. Instr.* **36** (1965) 1896.
23. Scott, R. B. In *Temperature: Its Measurement and Control in Science and Industry*, Reinhold, New York 1941, p. 206.
24. Bamberger, E. and Wulz, P. *Ber.* **24** (1891) 2080.
25. Chattaway, F. D., Orton, K. J. P. and Hurlley, W. H. *Ber.* **32** (1899) 3636.
26. Dennstedt, N. *Ber.* **13** (1880) 234.
27. Frölich, E. and Wedekind, E. *Ber.* **40** (1907) 1009.
28. Pinnow, J. and Pistor, G. *Ber.* **26** (1893) 1314.

Received April 1, 1968.