Tetrahedron Letters No.45, pp. 3953-3956, 1970. Pergamon Press. Printed in Great Britain.

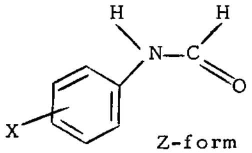
ELECTRONIC INFLUENCES ON ROTAMERISM IN FORMANILIDES

A. F. Cockerill and D. M. Rackham

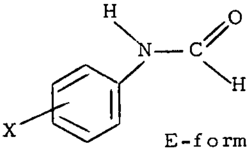
Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey.

(Received in UK 13 July 1970; accepted for publication 27 August 1970)

The partial double-bond character of amides leads to hindered rotation about the N-C bond.[1] LaPlanche and Rogers[2] have demonstrated that in simple formamides the larger group prefers to occupy the anti-position to the carbonyl group. Steric interactions are usually invoked to explain this observation. However, in formanilide the predominant form in concentrated solution is the Z-form (w.r.t. the positions of the hydrogens), but in dilute solution, cyclic dimer formation, in preferentially stabilising the E-form, gives rise to it becoming the major isomer.[3,4] It is obvious that factors other than steric are operative. We, therefore, decided to investigate, by proton magnetic resonance spectroscopy, the influence of electronic factors on the position of the equilibrium in a series of formanilides substituted in the meta- and para- positions.



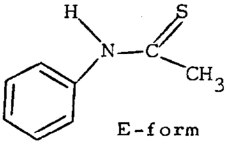
Z-form

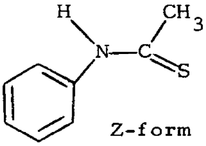


E-form

All measurements were made on a Varian A-60A spectrometer at normal probe temperature. Dimethyl sulphoxide was selected as the solvent and the same concentration (0.5M) of substrate was used throughout. The aldehydic protons in the two forms are readily distinguished since the chemical shift difference between the two forms is about 25 Hz and the coupling constant for the Z-form is only 2 Hz whereas it is 11 Hz in the E-form.[3,5] The results are listed in the Table and the variations in the Z/E ratio with the electronic properties of the substituent as measured by its Hammett substituent constant, σ,[6] are illustrated in the Figure.

Very recently, Walter and Kubersky[7] have shown that the logarithm of the ratio of the Z to the E form of p-substituted thioacetanilides increases in a linear fashion with the Hammett substituent constant, σ, the reaction constant, ρ, being 0.76 in CCl_4 and 0.57 in $CHCl_3$. Steric interaction between


E-form


Z-form

the thioacyl group and the ortho-hydrogen of the phenyl ring favours the E-form, but electrostatic considerations, namely interaction between the dipole moment of the phenyl ring and the induced dipole of the thioamide group*, favour the Z-form. As the substituent becomes more electron-withdrawing, the extent of double bond character of the C-N bond of the thioamide decreases and the angle between the planes of the thioamide and phenyl groups increases. Thus, the separation between the thioacyl group and the ortho-hydrogen of the phenyl ring increases and the proportion of the Z-form rises as the electrostatic factor gains in importance to steric considerations.

We find that the formanilides show a similar increase in the Z/E ratio with increasing electron-withdrawing power of the substituent, but there is a distinct discontinuity near the $\sigma = 0$ region (see Figure). These observations can be rationalised in terms of the above electrostatic-steric theory coupled with variations in the importance of the cyclic dimer structure, which stabilises the E-isomer. This latter factor is more important in amides than thioamides due to the greater electronegativity of oxygen than sulphur. The stability of the cyclic dimer structure is dependent on the strengths of the hydrogen bonds, which will be related to both the acidity of the N-H bond and the nucleophilicity of the carbonyl group. As the substituent X becomes less electron releasing, the system becomes less planar and the electrostatic factor competes more effectively with the steric effect, causing the Z-form to become more favourable. Eventually the acidity of the N-H bond increases, and cyclic dimer formation becomes more important, leading to an increase in the proportion of the E-isomer, and thus the discontinuity near $\sigma = 0$. Further increases in the electron-withdrawing power of the substituent enhance N-H acidity but decrease carbonyl nucleophilicity. Consequently, the stability of the cyclic dimer decreases and the Z/E ratio increases as the electrostatic effect becomes the major influence.

Footnote: * An alternative way of explaining the "electrostatic effect" is in terms of an attractive force between the negative pole of the (thio) carbonyl group and the electrophilic C-1 atom of the benzene ring.

In an earlier publication, Carter[8] attempted to measure the differences in free energies of activation by measuring the coalescence temperature for a number of *p*-substituted formanilides in $CDCl_3$. Problems in assessing hydrogen-bonding and other association effects led to uncertainties in the $\Delta G_c^{\ddagger}$ values and no significant correlation was obtained with the Hammett equation. We found that certain formanilides were insufficiently soluble in $CDCl_3$ and the aldehydic and aromatic protons were not clearly resolved.

It is interesting to note that the chemical shift of the amide proton only correlates with the Hammett equation if the exalted substituent constants σ^- are used for the powerful electron-withdrawing groups. Possibly the Z/E ratios of the formanilides should be subjected to this correlation rather than the simple Hammett equation. A linear correlation would still not arise, but as on this scale the nitro group is much more electron-withdrawing than the other substituents, the marked difference between the value of the ratio for *p*-nitroformanilide and the other substrates is more easily understood.

We thank Dr. N. J. A. Gutteridge for suggestions which led to the initiation of this work. We also acknowledge helpful comments from the referee.

Table Proportions of Z and E forms of substituted formanilides in dimethyl sulphoxide at 37°

substituent	*p*-NMe$_2$	*p*-OMe	*p*-Me	*m*-Me
$\sigma(\sigma^-)$[6]	-0.83	-0.27	-0.17	-0.07
Z/E	3.00 ± 0.12	3.33 ± 0.18	3.24 ± 0.08	2.70 ± 0.09
substituent	H	*m*-OMe	*p*-Br	*m*-CF$_3$
$\sigma(\sigma^-)$[6]	0.00	0.11	0.23	0.43
Z/E	2.47 ± 0.09	2.58 ± 0.10	3.30 ± 0.15	3.57 ± 0.12
substituent	3,5-Cl$_2$	*p*-CN	*p*-NO$_2$	
$\sigma(\sigma^-)$[6]	0.74*	0.66(0.90)	0.78(1.24)	
Z/E	3.61 ± 0.10	3.70 ± 0.06	> 8	

The Z/E ratio was determined by comparison of the integrated areas of the two forms of the aldehydic proton. Between 6 to 11 integrations were employed and the average deviation from the mean is listed. Most compounds were run in duplicate.

* 2 x σ_m

References

1. H. Kessler, Angew. Chem. Intern. Edit., 1970, 9, 219.

2. L. A. LaPlanche and M. T. Rogers, J. Amer. Chem. Soc., 1963, 85, 3728; 1964, 86, 337.
3. A. J. R. Bourn, D. G. Gillies and E. W. Randall, Tetrahedron, 1964, 20, 1811.
4. I. Suzuki, M. Tsuboi, T. Shimanouchi and S. Mizushima, Spectrochim Acta, 1960, 16, 471.
5. I. D. Rae, Canad. J. Chem., 1966, 44, 1334.
6. H. H. Jaffé, Chem. Rev., 1953, 53, 191.
7. W. Walter and H. P. Kubersky, Spectrochim Acta, 1970, 26A, 1155.
8. R. E. Carter, Acta Chem. Scand., 1968, 22, 2643.

Figure Graph of log (Z/E ratio) against Hammett substituent constant for a series of substituted formanilides in dimethyl sulphoxide at 37°