Substituent Effects in the Acid Solvolysis of *para*-Substituted Hippuric Acids in Acetic Acid at Low Water Concentrations. Neighbouring Group Participation by the Carboxy-group

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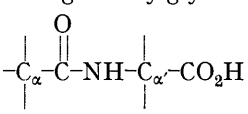
The rates of acid solvolysis of the *para*-substituted hippuric acids in acetic acid decrease with an increasing acid concentration for Cl, H, Me, and OMe indicating that the rate-controlling step is the ring closure reaction by the non-protonated amide to form an intermediate azlactone or its solvate. The acid–base equilibrium constants derived from the kinetic data vary in accordance with their substituent effects. Although the velocity constants show an irregular sequence, the products of the equilibrium and velocity constants vary as required by the substituent effects. This is in agreement with the reaction rate being dependent upon the zwitterion concentration through which the ring closure proceeds. The NO_2 group behaves differently from the other groups and gives only increasing rates with increasing acid concentrations and this behaviour is consistent with that of other strongly electronegative groups such as the trifluoroacetyl and the positive terminal amino-group of a dipeptide. These groups favour ring closure so that the acid catalysed ring fission of the azlactone solvate becomes the slow reaction.

In previous work [1-3] it was demonstrated that the reaction rate of acylamino-acids and dipeptides in acetic acid increases with increasing methylation at the carbon atoms adjacent to the amide bond. This type of behaviour is characteristic of a ring closure reaction and it has been suggested that at high acid concentrations the acylamino-acids form an azlactone solvate intermediate by ring closure in the rate-controlling step. This reaction proceeds simultaneously through the protonated amide and the zwitterion of the non-protonated amide with this latter reaction contributing the major part of the total reaction.

The methyl group repels or releases electrons by both inductive and hyperconjugative effects and direct substitution of this group, or more generally an alkyl group, at the seat of ring closure causes a reduction in rate as evidenced by the faster reaction of formylglycine compared with the homologous acylglycines.[3]



However at positions more remote from the point of ring closure, such as at C_α and $C_{\alpha'}$, increasing methylation produces increasing rates of reaction. It has now been recognised that this accelerating effect of the alkyl groups is due to more favourable entropy and enthalpy factors arising from better conformational preferences for ring closure.[4] Because of this dual role by the alkyl groups, the polar effects of methyl and other substituents were examined at a remote position where they will not exert steric or conformational effects on the ring closure. For this purpose the *para*-substituted hippuric acids were considered ideal and the results of the investigation are reported here.

EXPERIMENTAL

All compounds were prepared from the acid chlorides and glycine by the Schotten–Baumann reaction [5] and were crystallised from water.

The reaction rates were determined in acetic acid solution containing 0·25M-water at 95 °C. The initial rate method was used and all preparation of solutions and analytical and mathematical techniques have been described in detail previously.[3]

[1] R. J. L. Martin, *Austral. J. Chem.*, 1957, **10**, 268.
[2] R. J. L. Martin, *J. Chem. Soc.* (*B*), 1968, 1078.
[3] R. J. L. Martin, C. H. Skovron, and D. L. H. Yiu, preceding paper.
[4] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 196.
[5] A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 1957, p. 584.

RESULTS AND DISCUSSION

The results of the initial rate study are plotted in Figure 1 using total concentrations of acid and amide.

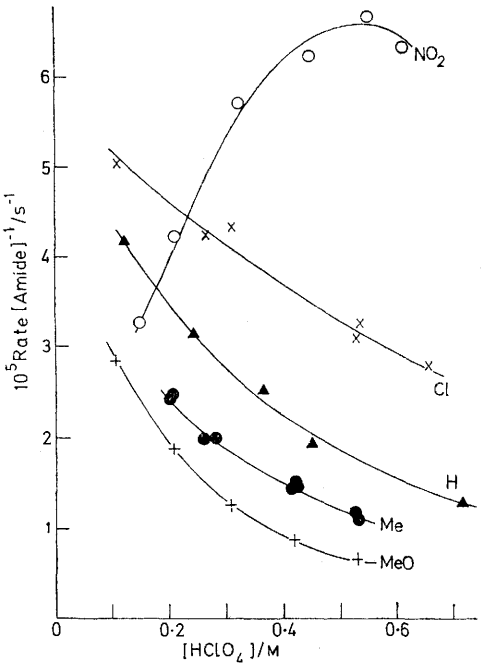
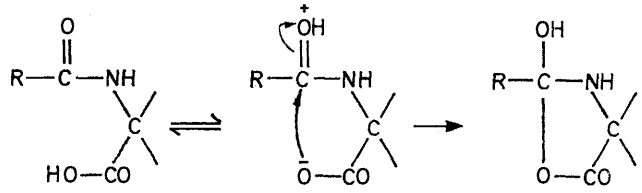


FIGURE 1 Effect of substituents and the acid concentration on the rate of solvolysis of *para*-substituted hippuric acids in acetic acid

It will be noticed that with the exception of the nitro-compound all rates decrease with an increasing acid concentration and the conditions used are therefore those for which the rate-controlling stage of the reaction



is ring closure. The relative order for reactivity is Cl > H > Me > OMe and is the order to be expected from the relative polar effects of these groups.

For the conditions used, the amides are extensively protonated and the equilibria in the system are (1) and

$$\text{Amide} + \Sigma H^+ \overset{K1}{\rightleftharpoons} \Sigma\text{AmideH}^+$$
$$K_1 = [\text{Amide}][\Sigma H^+]/[\Sigma\text{AmideH}^+] \quad (1)$$

$$H_2O + \Sigma H^+ \overset{K2}{\rightleftharpoons} \Sigma H_3O^+$$
$$K_2 = [H_2O][\Sigma H^+]/[\Sigma H_3O^+] \quad (2)$$

(2) where H^+ is the acetic acidium ion and Σ designates that the concentration includes the ions, ion pairs, and triple ions of that particular species.

[6] R. J. L. Martin and I. H. Reece, *Austral. J. Chem.*, 1959, **12**, 524.

The acetic acidium ion concentration was calculated from equation (3) which is derived from equations (1) and (2), where a is the concentration of amide, b perchloric acid, and c water. Previous work [3] on the acylamino-acids has shown that ring closure involved the non-protonated amide together with a small contribution from the protonated amide. Attempts were made to evaluate this data in the same manner but the values derived for ring closure by the protonated amide were an irregular series with respect to substituent effects and in some cases were negative. It was assumed that the contribution from this reaction was small so that Rate = k_1[Non-protonated amide]. ΣH^+ Was calculated from equation (3) using various values of K_1 and that value of K_1 was chosen where the slope of the graph Rate/[Non-protonated amide] against $[\Sigma H^+]$ was zero; K_2 was interpolated from data [6] for water and has a value of 0·10 at 95 °C. This mathematical analysis assumes that there are no salt or ionic strength effects for the ring closure reaction and that K_1 as defined is a constant for a wide range of salt concentrations. Both these conditions have been shown to apply for the acylamino-acids.[3] The data derived from the kinetic measurements are given in the Table.

$$\Sigma H^+ + a\Sigma H^+/(K_1 + \Sigma H^+) + c\Sigma H^+/(K_2 + \Sigma H^+) = b \quad (3)$$

Equilibrium and rate constants derived from the kinetic data for the *para*-substituted hippuric acids at 95 °C

Group	K_1/mol l^{-1}	$10^6 k_1$/s^{-1}
Cl	0·393	55·4
H	0·146	51·6
Me	0·114	38·9
OMe	0·050	41·7

The values of K_1 are in agreement with the known polar effects of these groups in that the electron-attracting chloro-group will decrease the stability of the protonated amide by an inductive effect and therefore increase the acidity of this ion. The electron-repelling methyl group and the electron-releasing methoxy-group will increase the stability of the protonated amide so that its acidity is reduced. The results plotted in Figure 2 show that there is a good correlation between pK_1 and the Hammett substituent constant σ_{para} particularly for Cl, H, and OMe.

A similar sort of relative order is to be expected for k_1 since the groups are positioned so that they would exert polar effects only, with no possibility of steric or conformational effects. The pattern of results is in agreement with the conclusion which has been derived for the acylamino-acids, *i.e.* electron-attracting groups such as chloro will favour ring closure and the electron-repelling methyl and the electron-releasing methoxy-group will retard ring closure. However in spite of the large difference in electronegativity between chlorine and hydrogen the difference in k_1 for these two groups is very small indeed. It would also appear that methyl is far more effective for releasing or repelling electrons than the methoxy-group.

These anomalies are eliminated if it is assumed that there exists equilibrium (4) between the non-protonated

$$RCO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H \rightleftharpoons RC(OH)^{+}{=}NH{\cdot}CH_2{\cdot}CO_2^{-} \quad (4)$$

amide and its zwitterion which is postulated to be the active species. The magnitude of this equilibrium constant is not known but as a first approximation it may be assumed that it is directly proportional to the acid–base equilibrium constant since the zwitterion equilibrium involves an intramolecular rather than an

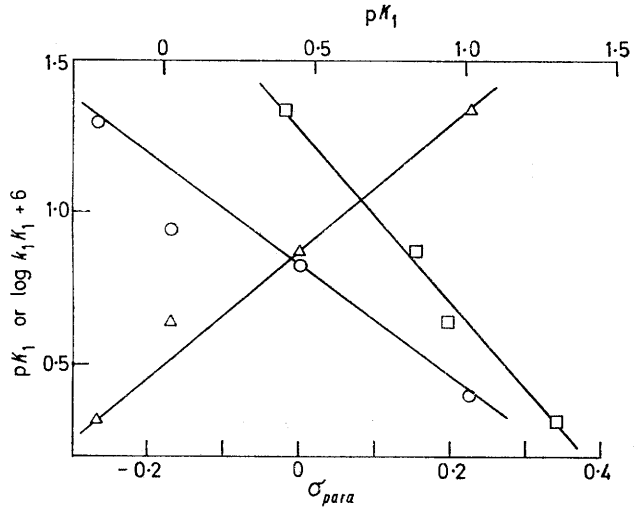


FIGURE 2 Variation of pK_1 and $\log k_1K_1$ with σ_{para}: ○ pK_1 *vs.* σ_{para}; △ $\log k_1K_1$ *vs.* σ_{para}; □ $\log k_1K_1$ *vs.* pK

intermolecular proton transfer as in the case of the acid–base equilibrium.

Since $K_1 = [\text{Amide}][\Sigma H^+]/[\Sigma\text{AmideH}^+]$, for a constant acid concentration $[\text{Amide}] \propto K_1[\Sigma\text{AmideH}^+]$ and $[\text{Amide}] \propto K_1[\text{Zwitterion}]$. The specific rate constant k_1^1 for the zwitterion reaction is $k_1^1 = \text{Rate}/[\text{Zwitterion}]$ which is proportional to $K_1\text{Rate}/[\text{Amide}] \propto K_1k_1$ since $k_1 = \text{Rate}/[\text{Amide}]$.

In Figure 2, $\log K_1k_1$ is plotted against the Hammett substituent constant σ_{para} or more strictly it may be better to use pK_1 instead of σ and in both cases a good correlation is obtained so that the polar effects of the substituents occur in the sequence usually expected for these groups. Deviations however are to be expected for the following reasons. It is assumed that the concentration of the zwitterion is dependent only on the basicity of the amide centre and that the acidity of the terminal carboxy-group or its ability to release a proton to form the zwitterion is unaffected by the nature of the *para*-substituent. This assumption is probably reasonably correct because the group is located some distance from the terminal carboxy-group. The other assumption that the zwitterion concentration is directly proportional to the total amide concentration may not be valid and may be the reason for deviations.

Strong electron-attracting groups such as chloro give increasing rates because they increase the magnitude of the positive charge induced at the point of ring closure. Electron-repelling or -releasing groups such as methyl or methoxy reduce the rate of reaction because of a reduction in the positive charge induced at the region of ring closure. This behaviour of the methyl group agrees with that already noted for acetylglycine and its homologues which react more slowly than formylglycine.[3]

The very strongly electron-attracting nitro-group behaves entirely differently from the other groups, Cl, H, Me, and OMe. The nitro-compound appears to be passing through a rate maximum at acid concentrations considerably in excess of those required for the other compounds. By extrapolation it would appear that the rate of ring closure for the nitro-compound is greater than that for the chloro-compound which is in agreement with the expected order of electron attraction by the groups.

The nitro-compound behaves very similarly to other compounds containing strongly electron-attracting groups such as trifluoro- and trichloro-acetylglycine[3] and the positive terminal amino-group of the dipeptides.[7] In all these cases the characteristic behaviour of ring closure being a rate-controlling step where the rate decreases with increasing acid concentration is either not observed or apparently begins to appear at very high acid concentrations. Clearly then, strong electron-attracting groups accelerate ring closure making it impossible or difficult to observe this reaction as the rate-controlling stage.

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[3/886 *Received*, 26*th April*, 1973]

[7] R. J. L. Martin, unpublished work.