Tetrahedron, 1964, Vol. 20, pp. 1913 to 1919. Pergamon Press Ltd. Printed in Northern Ireland

THE TRANSMISSION OF ELECTRONIC EFFECTS

THE REACTION OF 5-SUBSTITUTED-2-FUROIC ACIDS WITH DIPHENYLDIAZOMETHANE[1]

Wo Kong Kwok, R. A. More O'Ferrall and S. I. Miller
Department of Chemistry, Illinois Institute of Technology,
Chicago 16, Illinois

(*Received* 18 *February* 1964; *in revised form* 30 *April* 1964)

Abstract—Rate data for the reactions of seven 2-furoic acids (H, 5-NO_2, 5-Br, 5-Cl, 5-$(CH_3)_3C$, 5-COOH, 5-CH_2OH) with diphenyldiazomethane (DDM) in ethanol have been obtained. The range of the activation parameters for $\Delta H^\ddagger$ is 13·6 to 16·1 kcal mole^{-1} and for $\Delta S^\ddagger$ -3 to -11 cal deg^{-1} mole^{-1}. Satisfactory Hammett lines have been calculated for k in l. mole^{-1} min.$^{-1}$: at 15·5°, $\log k = 1{\cdot}00\,\sigma + 0{\cdot}2406$ and at 24·9°, $\log k = 0{\cdot}975\,\sigma + 0{\cdot}6135$. The ρ values for nine families including the furoic acids follow the relation $\rho_{RGCOOH}/\rho_{RGCOS}$ = constant: within the limit of ±10–20% in ρ, the attenuation mechanisms by which electronic effects are changed by G are similar for acid dissociation or reaction with DDM. Based on three reactions, a fall off factor $\varepsilon = 1{\cdot}2 \pm 0{\cdot}2$ is calculated for G = 2,5-furyl compared with phenyl.

The furan nucleus appears to be highly efficient in relaying the electronic effects of a substituent to a reaction site. For example, the Hammett ρ for the dissociation of the 5-substituted-2-furoic acids in water is 1·4. This is higher than comparable ρ values for all alicylic and heterocyclic families of carboxylic acids to which the Hammett equation has been applied.[2] Basic to this work was the question whether this efficiency held up in still another process and what could thereby be learned about the transmission of electronic effects in general.

Recently, we have been interested in carboxyl reactions of compounds of the type R-G$_l$-COS where G$_l$ is the group through which a substituent R is electronically linked to a reaction site of a carbonyl function COS.[3–5] To see whether the attenuation of electronic effects through G$_l$ is predictable, we have been employing—really testing—two equivalent ρ-ρ relations

$$\rho_{RGCOOH}/\rho_{RGCOS} = \pi \qquad (1)$$

$$\rho_{RGCOS}/\rho_{RC_6H_4COS} = \varepsilon \qquad (2)$$

Each ρ derives from the Hammett equation and characterizes a family of compounds of the same G. π compares *various* reactions with a standard one, i.e. acid dissociations in water at 25°. For *one* given reaction, ε measures the relative efficiency of transmission through G as compared with —C_6H_4—. Apart from our series of papers, attenuation factors (ε) have been listed by Jaffé,[6] Charton[7] and Imoto *et al.*[2]

---

[1] Supported by the Office of Ordnance Research, U.S. Army and The Petroleum Research Fund of the American Chemical Society.

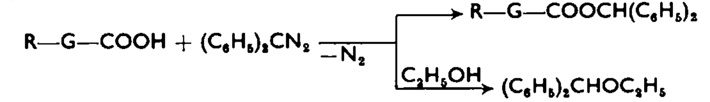
[2] E. Imoto and Y. Otsuji, *Bull. Osaka Prefect* **A6**, 115 (1958); Y. Otsugi, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori and T. Okawara, *Nippon Kagaku Zasshi* **80**, 1021 (1959) and succeeding papers.

[3] R. A. More O'Ferrall and S. I. Miller, *J. Amer. Chem. Soc.* **85**, 2440 (1963).

[4] J. D. S. Ritter and S. I. Miller, *J. Amer. Chem. Soc.* **86**, 1507 (1964).

[5] R. A. More O'Ferrall and S. I. Miller, to be published.

Fig. 1 summarizes our tests of Eq. 1 to date for two important processes, the basic hydrolysis of esters (line A) and the reaction of diphenyldiazomethane (DDM) with acids (line B)



$$R\text{—}G\text{—}COOH + (C_6H_5)_2CN_2 \xrightarrow[-N_2]{} \begin{cases} \longrightarrow R\text{—}G\text{—}COOCH(C_6H_5)_2 \\ \xrightarrow{C_2H_5OH} (C_6H_5)_2CHOC_2H_5 \end{cases} \qquad (3)$$

Although most of the data on which this figure is based has been tabulated,[3] several

R—G—COOH
1. Ar
2. $ArCH_2$
3. $ArCH_2CH_2$
4. *trans*-ArCH=CH
5. *cis*-ArCH=CH
6. ArCH=CHCO
7. *p*-Ar—C_6H_4
8. *trans*-$\mathrm{ArCH\overset{CH_2}{\text{——}}CH}$
9. *cis*-$\mathrm{ArCH\overset{CH_2}{\text{——}}CH}$
10. ArC≡C
11. 2-furanyl
12. 2-thienyl
13. 2-$CH_3C_6H_3$
14. 2,6-$(CH_3)_2C_6H_2$
15. $ArOCH_2$
18. *trans*-CH=CH
19. C≡C
20. 3-or 4-R-1-naphthyl

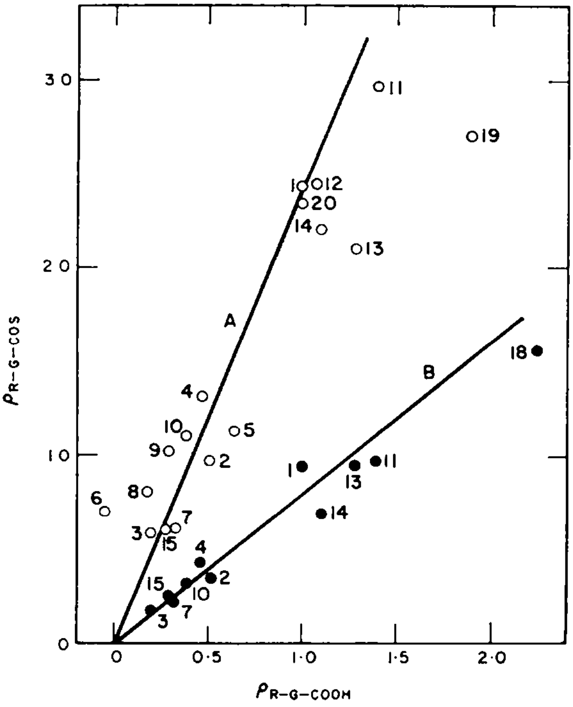


FIG. 1. ρ-ρ relation: A, the basic hydrolysis of R-G-$COOC_2H_5$ in 88% ethanol at 30°; B, the reaction of R-G-COOH with diphenyldiazomethane in ethanol at 30°.

new ρ values have since been added for G: *trans*-CH = CH—,[8] —C ≡ C—,[7] *trans*-C_6H_4CH = CH—,[4] $C_6H_4CH_2CH_2$—,[5] 2,6-$(CH_3)_2C_6H_2$—,[9,10] *p*-ArC_6H_4—,[10] 1-naphthyl,[11] and —$C_6H_4OCH_2$—.[10] In the present study, rate and product composition data are reported for a family of 2-furoic acids in Eq. 3 and the status of the ρ-ρ relations is reviewed.

[6a] H. H. Jaffé, *Chem. Rev.* **53,** 191 (1953); [b] S. Yeh and H. H. Jaffé, *J. Amer. Chem. Soc.* **81,** 3287 (1959).

[7] M. Charton, *J. Org. Chem.* **26,** 735 (1961).

[8] M. Charton and H. Meislich, *J. Amer. Chem. Soc.* **80,** 5940 (1958); J. Hine and W. C. Bailey, Jr., *Ibid.* **81,** 2075 (1959).

[9] J. F. J. Dippy and S. R. C. Hughes, *Tetrahedron* **19,** 1527 (1963).

[10] K. Bowden, *Canad. J. Chem.* **41,** 2781 (1963).

[11] L. K. Creamer, A. Fischer, B. R. Mann, J. Packer, R. B. Richards and J. Vaughan, *J. Org. Chem.* **26,** 3148 (1961); A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer and J. Vaughan, *J. Chem. Soc.* 1426 (1958).

RESULTS AND DISCUSSION

Data for the reactions of the 5-substituted-2-furoic acids with DDM are given in Table 1. The ester to ether ratio in Eq. 3 is ca. 59–66% for the seven acids. This is close to the value reported for the great majority of acids studied in ethanol. The near constancy of this product ratio has recently been taken as compelling evidence for a single rate-determining step in Eq. 3 followed by rapid steps in which partitioning occurs.[12] It was of interest to us here that the product ratio fell in a narrow range and was essentially independent of the fact that the 2-furoic acids were ca. ten times stronger than the benzoic acids.[13]

TABLE 1. RATE AND PRODUCT COMPOSITION DATA FOR THE REACTION OF SOME 5-SUBSTITUTED-2-FUROIC ACIDS WITH DIPHENYLDIAZOMETHANE IN ETHANOL

5-Substituent	k l $mole^{-1}$ min^{-1}[a]		α, Ester fraction[b]		$\Delta H^{\ddagger}$[c] Kcal $mole^{-1}$	$-\Delta S^{\ddagger}$[c] cal deg^{-1} $mole^{-1}$ 24·9°
	24·85 ± 0·1°	15·5 ± 0·1°	24·85 ± 0·1°	15·5 ± 0·1°		
NO_2	24·9 ± 0·5	11·4 ± 0·2	0·61 ± 0·02	0·67 ± 0·02	13·6	9·5
Br	7·17 ± 0·2	3·09 ± 0·08	0·57 ± 0·01	0·69 ± 0·03	14·7	7·0
Cl	7·16 ± 0·18	2·95 ± 0·02	0·57 ± 0·03	0·60 ± 0·02	15·6	4·0
$C(CH_3)_3$	2·78 ± 0·07	1·25 ± 0·03	0·66 ± 0·04	0·70 ± 0·03	14·0	11
H	4·22 ± 0·12	1·69 ± 0·05	0·57 ± 0·01	0·68 ± 0·02	16·1	3·4
COOH	9·65 ± 0·40[d]	4·12 ± 0·05[d]	0·57 ± 0·03	0·63 ± 0·07	14·9	5·7
CH_2OH	3·85 ± 0·15	1·65 ± 0·05	0·60 ± 0·02	0·68 ± 0·02	14·8	7·9

[a] Average deviation is based on 4–9 runs.

[b] The fraction of the benzhydryl furoate in the product is usually based on two or three determinations.

[c] Based on two temperatures. The uncertainty in $\Delta H^{\ddagger}$ is probably no more than ±1 kcal $mole^{-1}$ and in $\Delta S^{\ddagger}$ ± 3 e.u.

[d] Calculated with twice the stoichiometric acid concentration.

In applying the Hammett equation to the DDM rate data in Table 1 it seemed appropriate that *para* substituent constants (σ) should be used.[2] When this work was started, there was no reported σ value for *p*-$HOCH_2$—. We therefore determined the thermodynamic p*K* values of furoic and 5-hydroxymethyl-2-furoic acids to be 3·19 and 3·18 respectively in water at 28°. Then, using the reported Hammett correlation of 2-furoic acids ($\rho = 1{\cdot}4$) as a standard,[2] we found $\sigma_{HOCH_2} = 0{\cdot}007$. This agrees nicely with the recently reported value of $\sigma_{HOCH_2} = -0{\cdot}01$ determined on *p*-hydroxymethylbenzoic acid.[14] Thus, $\sigma_{p-HOCH_2} = 0{\cdot}00 \pm 0{\cdot}01$. In passing, it might be noted that para σ values for the pairs $\sigma_{Cl} = 0{\cdot}23$,[15] $\sigma_{ClCH_2} = 0{\cdot}12$[15] and $\sigma_{NC} = 0{\cdot}66$,[15] $\sigma_{NCCH_2} = 0{\cdot}17$[14] and now $\sigma_{OH} = -0{\cdot}37$,[15] $\sigma_{CH_2OH} = 0{\cdot}00 \pm 0{\cdot}01$: evidently it is hazardous to estimate σ_{XCH_2} from σ_X with the fall-off factor of ca. $\frac{1}{2}$ which is often used for an interposed methylene group.

There were also some special points of interest in connection with the 2,5-furan dicarboxylic acid. Over a range of acid to DDM concentrations $\frac{11}{1}$ to $\frac{1}{3}$ we found

---

[12] R. A. More O'Ferrall, W. K. Kwok and S. I. Miller, to be published.

[13] W. E. Catlin, *Iowa State Coll. J. Sci.* **10**, 65 (1935); A. P. Dunlop and F. N. Peters, *The Furans* p. 492. Reinhold, New York, N.Y. (1953).

[14] O. Exner and J. Jonas, *Coll. Czech. Chem. Commun.* **27**, 2296 (1962).

[15] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

no significant trends in the rate constants as the reaction approached completion. This suggested that the rate constant for a carboxyl group whether in the diacid or the monoester was effectively constant. This is in accordance with identical substituent effects ($\sigma = 0{\cdot}45 \pm 0{\cdot}1$) derived from the dissociation of *p*-benzoic acids with either HOOC— or C_2H_5OOC— as substituents.[15] In this particular case we used a rate law derived from the expression

$$\frac{dx}{dt} = k(2a - \alpha x)(d - x) \tag{4}$$

where a is the initial diacid concentration, d is the initial DDM concentration and α is the fraction of acid consumed as ester. A test of Eq. 4 is given in the experimental section. To a first approximation, say 10%, the rate constants and activation parameters for the 2,5-furan dicarboxylic acid and its monobenzhydryl ester may be taken as identical.

Though we used $\sigma = 0{\cdot}45$ for the diacid,[15] the figure $\sigma = 0{\cdot}36$, given by Hine,[16] is based on data[17,18] which appears to be more accurate. The use of the lower value does not alter ρ significantly, although the Hammett correlation is improved slightly.

The parameters of the Hammett plots for the p*K* values and the DDM rates of the furoic acids are given in Table 2. The correlations are satisfactory. These will be discussed first with emphasis on furan then in the general context of the ρ-ρ relation.

TABLE 2. HAMMETT CORRELATIONS FOR THE REACTION OF 5-SUBSTITUTED-2-FUROIC ACIDS WITH DIPHENYLDIAZOMETHANE

°C	ρ	log k^a	r^b	s^c	n^d
15·5	1·00	0·2406	0·991	0·010	7
24·85	0·975	0·6135	0·994	0·008	7

[a] Intercept of the Hammett equation; k has the units l. mole.$^{-1}$ min.$^{-1}$.
[b] Correlation coefficient.
[c] Standard deviation.
[d] Number of compounds used.

As a transmitter of electronic effects, the furan nucleus is interesting in several respects. Judging from the Hammett ρ values for acid dissociation,[2] the basic hydrolysis rates of the ethyl esters[2] and the DDM rates,[3] the attenuation factors ε of Eq. 2 of 5-furyl relative to phenyl are 1·4, 1·2 and 1·0 respectively or $\varepsilon = 1{\cdot}2 \pm 0{\cdot}2$. Such an $\varepsilon > 1$ means of course that the relay is enhanced rather than attenuated.

The origins of this factor are fairly straightforward. In chemical reactions, the diene and ether character of furan is well known;[19] this also shows up as a field–inductive effect in the enhanced acidity of the 2-furoic acids e.g. 2-furoic, p*K* 3·1; cyclopentane carboxylic, p*K* 5·0; benzoic, p*K* 4·2; acetic, p*K* 4·8; ethoxyacetic,

---

[16] J. Hine, *J. Amer. Chem. Soc.* **81**, 1126 (1959).
[17] B. J. Thamer and A. F. Voigt, *J. Phys. Chem.* **56**, 225 (1952).
[18] G. Kortum, W. Vogel and K. Andrussow, *Dissociation of Organic Acids in Aqueous Solution.* Butterworths, London (1961).
[19] R. C. Elderfield and T. N. Dodd, Jr., *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. I; chap. 4. J. Wiley, New York, N.Y. A. Albert, *Heterocyclic Chemistry* Chap. VI. Athlone Press, University of London (1959).

pK 3·6; vinylacetic, pK 4·3.[18] The diminished aromatic character of furan shows up in a calculated atom localization energy of 2·4 β compared with 3·5 β for thiophen and 4 β for benzene (for a simple alkene, the figure is 2 β).[20] Hammett correlations of acid dissociation for the 2-thienyl ($\rho = 1{\cdot}1$),[2] 2-furoic ($\rho = 1.4$)[2] and *trans*-vinyl carboxylic ($\rho = 2{\cdot}2$) acids[8] seem to reflect this order for ρ appears to increase with electron availability. The same order presumably holds for the reactions of these acid families with DDM—see Fig. 1.

The transmission of electrical effects from a substituent through the furan nucleus can be treated quantitatively according to the method of Dewar and Grisdale[21] This has been carried out for the dissociation of the 2-furoic acids with satisfactory results[4] and there is every reason to suppose that the method will hold for the DDM reaction. What is of interest here is that the theory requires that *the substituent exerts its effect at the remote carboxylic acid site both through a coulombic or field effect and by a perturbation of the π-electrons, i.e. by mesomeric induction.* It is probable that this dual approach to substituent effects is applicable to heterocyclic systems other than furan.

The DDM reaction contributes point 11 to line B of Fig. 1. Apart from points 14 and 18 for the 2,6-dimethylbenzoic and *trans*-acrylic acids respectively, the ρ-ρ relation Eq. 1 seems to be a useful correlation. The maximum allowable deviation in ρ has been set arbitrarily at 10–20% or essentially the mean deviation of the parent Hammett equation.[6a] For this group of families the ρ values form a consistent set. Electronic effects are relayed from substituent to site in much the same fashion for the two reactions being compared. Large variable solvation or specific steric effects appear to be absent: the prediction of *some* ρ values now seems possible for several families of compounds involved in the same process. Conversely, the relay of electronic effects in families whose ρ values deviate from Eq. 1 may be regarded as unsystematic and subject to specific effects: certainly the prediction of the reactivities in such families would be hazardous. It remains to be seen whether the ρ-ρ relation will hold up in still other reactions at the carboxyl site and whether it will apply to reactions at other sites.

EXPERIMENTAL

The furoic acids used in this study were purchased or prepared by standard methods; the 5-hydroxymethyl-2-furoic acid was a gift of the Quaker Oats Co. The properties of the acids are given in Table 3. The kinetics of the DDM reaction with the acids were followed spectrophotometrically and the data treated as described previously.[8] Reactions were generally carried out under pseudo first order conditions, that is, ca. 0·02–0·06M acid and ca. 0·002M DDM. To obtain the ester to ether product ratio of Eq. 3, the reaction had to be carried out at comparable concentrations of reactants, ca. 0·001–0·003M and the data were analysed by a method described elsewhere.[12] The rate constants obtained from these runs checked those obtained under pseudo first order conditions. The fraction of ester in the product or α showed some scatter. All of the rate and product composition data as well as their precision are given in Table 1.

The kinetic data were taken at two temperatures so that an estimate of ρ at 30° would be possible. Although activation parameters are given in Table 1, it need hardly be emphasized that they are based on two temperatures ca. 10° apart. As in previous work[4] a compensation law plot, $\Delta S^\ddagger$ *vs.* $\Delta H^\ddagger$, was made but in this case the scatter was too great to yield a satisfactory straight line.

Because of the special interest in the 2,5-furandicarboxylic acid, we have given some rate data in Table 4. Even in the runs containing comparable concentrations of acid and DDM, the changes in

[20] F. L. Pilar and J. R. Morris, *J. Chem. Phys.* **34**, 389 (1961).

[21] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.* **84**, 3548 (1962).

TABLE 3. PROPERTIES OF THE 5-SUBSTITUTED-2-FUROIC ACIDS

5-Substituent	Equiv. wt. calc.	 found	M.p., °C lit.	 found	pK^a	σ^b
NO_2	157·1	157·4	185–185·5[c]	188–189	2·061	0·778
Br	190·9	190·7	190–191[d]	190	2·841	0·232
Cl	146·5	146·4	176–177[e]	183–184	2·832	0·227
$C(CH_3)_3$	168·1	167·6	105–105·5[f]	103–105	—	−0·197
H	112·1	111·9	131·5[g]	132–133	3·128[j]	0·00
COOH	78·0	77·9	365[h]	366	2·60[h]	0·45[l]
CH_2OH	142·1	141·4	164–165[i]	167–168	3·116[j]	0·00[k]
I					2·936	0·18
CH_3					3·419	−0·17

[a] Ref. 13; ambient temp.

[b] Ref. 15.

[c] B. T. Freure and J. R. Johnson, *J. Amer. Chem. Soc.* **53**, 1142 (1931).

[d] L. C. Raiford and W. G. Huey, *J. Org. Chem.* **6**, 858 (1941).

[e] H. B. Hill and L. L. Jackson, *Amer. Chem. J.* **12**, 22 (1890).

[f] J. H. Simons and H. J. Passino, *J. Amer. Chem. Soc.* **60**, 2956 (1938).

[g] C. D. Hurd, J. W. Garrett and E. N. Osborne, *J. Amer. Chem. Soc.* **55**, 1082 (1933).

[h] S. Oae, M. Hamada, Y. Otsuji and N. Furukawa, *Ann. Rept. Radiation Center Osaka Prefect.* **2**, 106 (1961). *Chem. Abstr.* **57**, 9281 (1962). This pK of 2·6 does not appear to fall on or near a Hammett plot for the 5-substituted-2-furoic acids. From the cited work it is clear that the first and second ionization constants of the diacid are sufficiently close so that an accurate determination may be difficult.

[i] A. L. Mndzhoyan, A. A. Aroyan, *Dokl. Akad. Nauk. Armyan, S.S.R.* **27**, 101 (1958); *Chem. Abstr.* **53**, 18934 (1959).

[j] This study.

[k] This study and Ref. 14.

[l] See text and Refs. 15, 16.

TABLE 4. RATE AND COMPOSITION DATA FOR THE REACTION OF 2,5-FURANDICARBOXYLIC ACID WITH DIPHENYLDIAZOMETHANE

Temp °C	2,5-Diacid mole $l^{-1} \times 10^{3}$	DDM mole $l^{-1} \times 10^{3}$	k^a l $mole^{-1}$ min^{-1}	α, ester fraction[b]
24·85	22·30	2·011	8·92	
	20·44	2·681	9·37	
	18·58	3·352	9·95	
	3·227	3·352	9·44	0·51
	3·227	3·352	9·99	0·58
	2·904	4·022	10·22	0·60
			Mean[c] 9·65 ± 0·4	0·57 ± 0·03
15·5	16·69	3·16	4·16	
	18·08	2·107	4·06	
	10·85	2·107	4·07	
	1·002	3·16	3·96[d]	0·55
	1·669	3·16	4·38[d]	0·70
			Mean 4·12 ± 0·05	0·63 ± 0·07

[a] The statistical factor of two has been used. Conversions were ca. 95% based on the DDM, except as indicated.

[b] The fraction of ester in the product.

[c] Three more runs included in the mean.

[d] Run to ca. 50% completion based on the DDM.

k were close to experimental uncertainty. A typical second order run is in part given in Table 5. As the optical density of DDM was used ($\varepsilon_{525\ m\mu} = 99{\cdot}5$), the expression derived from Eq. 4

$$kt = \frac{1}{(2a - \alpha d)} \ln \frac{d}{2a} \frac{(2a - \alpha x)}{(d - x)} \tag{5}$$

was recast in terms of the optical density of DDM. Under pseudo first order conditions the statistical factor of two was also applied to observed rate constants.

TABLE 5. A KINETIC RUN OF 2,5-FURANDICARBOXYLIC ACID (0·001599M) WITH DIPHENYLDIAZOMETHANE (0·004022M) AT 25·85° IN ETHANOL

Time, min	Optical density of DDM	k, l mole^{-1} min^{-1}
0	1·71	
8	1·354	10·5
16	1·096	10·3
24	0·900	10·4
36	0·693	10·4
56	0·478	10·3
80	0·320	10·3
100	0·250	9·9

pK determinations on two of the acids were made on a Beckman Model G pH meter—a glass *vs.* saturated calomel electrode is involved. Ionization constants were calculated from the pH of the half-neutralized acid at 28° from

$$\mathrm{p}K = \mathrm{pH} + \log\,[\mathrm{HA}]/[\mathrm{A}^-] \tag{6}$$

to give for 2-furoic acid pK = 3·128 and for 5-hydroxymethyl-2-furoic acid pK = 3·116. The activity coefficient correction $-\log f_{A^-}$, to Eq. 6 for the ionic strength $\mu = 0{\cdot}015 - 0{\cdot}02$ at the half-neutral point gave thermodynamic values of 3·19 and 3·18 respectively for these two acids. Our pK values from Eq. 6 for 2-furoic acid at 28° may be compared with the reported 3·12[18] or the thermodynamic pK values of 3·179[22] and 3·272[23] at 25°.

Acknowledgment—We wish to thank J. Belluzi for preparing several of the acids and Dr. A. P. Dunlop of the Quaker Oats Company for samples of 5-hydroxymethyl-2-furoic acid and ethyl 5-chloromethyl-2-furoate. The manuscript was written by S. I. M. during his tenure as a National Science Foundation Senior Post Doctoral Fellow at University College, London.

[22] W. L. German, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.* 1604 (1937).

[23] D. S. Klett and B. F. Freasier, *J. Chem. Soc.* 4741 (1962).