First Thermodynamic Dissociation Constants of Barbituric Acid Derivatives in Water at 25 °C. Part 3.[1,2] 5,5-Alkylenebarbituric Acid Derivatives. A Comparison with 5,5-Dialkylbarbituric Acids, and with Mono- and Di-carboxylic Acids

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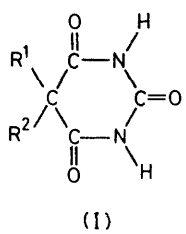
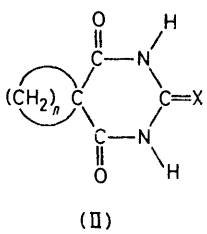
The synthesis and determination of the first thermodynamic dissociation constants for three 5,5-alkylenebarbituric acid derivatives (II; n = 2—4) is described. A pK_1 value for a fourth derivative (II; n = 5) is also reported. In a previous study the steric effect of the 5-substituents in 5,5-disubstituted barbituric acids, *e.g.* (I; $R^1 = R^2$; Me to Et), was found to be acid strengthening. This acid strengthening effect has been attributed to solvent exclusion in the undissociated molecule. In the derivatives (II) steric effects of the 5-substituents are minimized and remain essentially constant. These derivatives all have high pK_1 values (8.73—8.88), similar to that, 8.51, of (I; $R^1 = R^2$ = Me). Polar effects of the 5-substituents in the derivatives (II) were small but in keeping with those expected for 5,5-alkylene groups and pK_1 values followed the expected inductive order for electron release in derivatives (II) (n = 5 > n = 4 > n = 3 > n = 2). Comparison of the pK_1 values for the barbituric acid derivatives with those for certain mono- and di-carboxylic acids reveal similarities in substituent effects which are very pronounced in the barbituric acid reaction series, although not as pronounced as in the malonic acid series.

ATTENTION has previously been drawn to the desirability of a more critical assessment when multi-independent-variable linear free energy relationships (l.f.e.r.) are involved, as against single-independent-variable relationships.[3] In addition to the empirical evidence previously found in the l.f.e.r.[1] for the steric acid-strengthening effect of 5-substituents in barbituric acid derivatives, independent evidence is provided in this paper which supports the previous conclusion. This evidence was gained from pK_1 values for barbituric acid derivatives in which the 5-alkyl substituents were ' tied back ' into a second ring to give the derivatives (II). Steric effects in these structures (II) would be expected, in the absence of perturbations due to additional factors, to be no greater than in (I; $R^1 = R^2$ = Me). An increase in the 5,5-alkylene ring size from (II; n = 2) to (II; n = 4) wil produce a structure analogous to (I; $R^1 = R^2$ = Et), except that the 5,5-alkylene substituent would not be able to adopt orientations with alkyl groups over the heterocyclic nucleus. Acid strengths in the derivatives (II) would therefore be expected to be similar to that for (I; $R^1 = R^2$ = Me). In addition, as ring size increases from n = 2 to n = 5 they would be expected to become weaker acids, following the polar effects of the substituents.



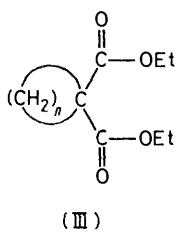
(I)

a; $R^1 = R^2$ = Me
b; $R^1 = R^2$ = Et



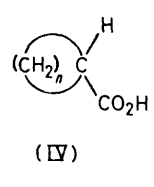
(II)

a; n = 2
b; n = 3
c; n = 4
d; n = 5
X = O or NH

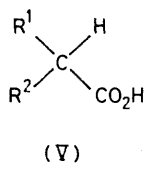


(III)

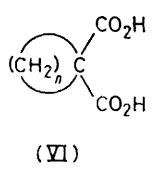
a; n = 2
b; n = 3
c; n = 4



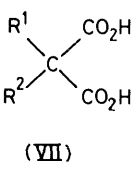
(IV)



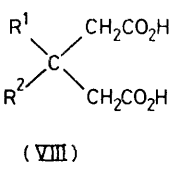
(V)



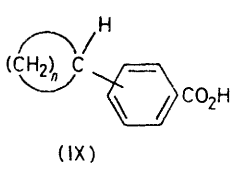
(VI)



(VII)



(VIII)



(IX)

EXPERIMENTAL

Procedures were mainly the same as those given in Part 1.[2] I.r. spectra were recorded for solids in potassium bromide discs and for liquids as films between sodium chloride windows using a Unicam SP200G grating spectrophotometer. N.m.r. spectra were recorded for solutions in $CDCl_3$ or $CDCl_3$–$(CD_3)_2SO$ (1 : 1) with tetramethylsilane as internal standard, using a Varian T60 or HA100 spectrometer. Mass spectra were obtained at low and high resolution by using a Varian CH7 or an AEI MS9 spectrometer respectively. For t.l.c., chloroform–butan-1-ol–ammonium hydroxide (*d* 0.880) (14 : 8 : 1) and benzene–methanol–glacial acetic acid (90 : 16 : 8) were used as developing solvents. Also used were chloroform–acetone (90 : 10) and chloroform–propan-2-ol–aqueous ammonia (7.5% w/w) (45 : 45 : 10).

Materials.[2]—Guanidine carbonate was dried for 10 h at 105 °C and stored in a desiccator over silica gel.

5,5-*Ethylenebarbituric Acid* (IIa).[4,5]—Compound (IIIa) (47 g, 0.25 mol; Fluka) and urea (18 g, 0.30 mol) in ethanol

TABLE 1

Properties of synthesized barbituric acid derivatives and their malonic ester intermediates

Compound		M.p. (°C)	Lit. M.p. (°C)	Yield [a] (%)	$\nu_{max.}$/cm^{-1} N–H stretching region	$\nu_{max.}$/cm^{-1} C=O stretching region
(IIa)		320—325 (decomp.)	330 (decomp.) [5]	10.1	3 195 (sh), 3 155, 3 060	1 795, 1 755, 1 722, 1 670
(IIb)	(i)	252—256	258 [6]	4.5	3 200, 3 080	1 760, 1 709, 1 681
	(ii)	256—259	258 [6]	43	3 200, 3 080	1 759, 1 710, 1 680
(IIc)		270—273	269—269.5 [7] 272—274 [8]	53	3 200, 3 080	1 754, 1 735, 1 692
		η_D^{20}	Lit. η_D^{20}			
(IIIa)		1.4330	1.4331 *			1 730
(IIIb)		1.4354	1.4359 *			1 732
(IIIc)		1.4405	1.4435 † 1.4387 [8]			1 732

[a] Yields are of the recrystallized material.

* G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1948, 804.
† V. P. Gol'mov, *Russ. J. Chem.*, 1952, **22**, 1944.

(150 ml) were mixed in a flask immersed in ice. Sodium ethoxide (0.74 mol) in ethanol (300 ml) was added dropwise with shaking over 30 min and the mixture was allowed to reach room temperature and to stand for 3.5 h. The resultant gel was added to hydrochloric acid–ice (1 : 1; 200 ml) and the precipitated solid was filtered off and extracted with acetone for 24 h in a Soxhlet apparatus. Removal of the solvent left a residue which was recrystallized from ethanol as fine plates (Table 1).

5,5-*Trimethylenebarbituric Acid* (IIb).[6]—(i) Compound (IIIb) (50.0 g, 0.25 mol) in ethanol (150 ml) was condensed with guanidine carbonate (38.5 g, 0.21 mol) in the presence of sodium ethoxide (0.74 mol) in ethanol (300 ml). The product (IIb; X = NH; sodium salt) was filtered off, washed with cold ethanol and vacuum dried (20 mmHg; 60 °C) over silica gel. The solid was dissolved in an excess of hydrochloric acid (5M), the solution was refluxed for 1 h, and cooled, whereupon (IIb) crystallized and was finally recrystallized from acetone–water (3 : 1) as faintly green needles (Table 1).

(ii) Compound (IIIb) (50.6 g, 0.25 mol) and urea (17 g, 0.28 mol) were dissolved in ethanol (150 ml). Sodium ethoxide solution [as in (i)] was added dropwise over 1 h and the mixture was maintained at 83° for 2 h. The sodium salt of (IIb) was precipitated from the reaction mixture, and was filtered off, washed with ethanol, and dried by suction. The solid was added to hydrochloric acid–ice (1 : 1; 200 ml) to precipitate (IIb) which was filtered off, washed free of hydrochloric acid with ice-cold distilled water, and recrystallized thrice from distilled water as needles (Table 1).

5,5-*Tetramethylenebarbituric Acid* (IIc).[7,8]—Compound (IIIc) (53.3 g, 0.25 mol) was condensed with urea (18 g, 0.30 mol) in the presence of sodium ethoxide as for (IIb). The same procedure as for (IIb), method (ii), was employed. The reflux temperature was 80°. (IIc) was recrystallized twice from distilled water as needles (Table 1).

5,5-Dimethyl- (I; $R^1 = R^2 = Me$) and 5,5-diethylbarbituric acid (I; $R^1 = R^2 = Et$) were available from previous work.[2]

Results of synthetic and spectroscopic work are presented in Tables 1 and 2.

Physical Measurements.—pK_1 Values were determined as described in Part 1.[2] The results obtained are presented in Table 3.

DISCUSSION

Syntheses.—The reactions employed for the synthesis of the three derivatives (IIa—c) follow those previously described [5-8] with some minor modifications [2,9] to the procedures, giving improved yields.[7] Thus, these modifications appear to have reduced side-reactions of the ester intermediates. The coloured product (IIb) [method (i)] did not give the expected percentage of carbon, on microanalysis, despite repeated recrystallization in three different solvents and was not used for physical measurements. The tenacity of the contaminating substance has yet to be explained, although studies on the synthesis of guanidine salts have been reported in which coloured impurities were formed.[10]

Acid Strengths.—The first thermodynamic dissociation constants for the three derivatives (IIa—c) together with an additional derivative (IId),[11] are compared with those of 5,5-dimethyl- and 5,5-diethyl-barbituric acid (I; $R^1 = R^2 = Me$) and (I; $R^1 = R^2 = Et$), respectively, in Table 3. The pK value for benzoic acid was determined at the same time and is in good agreement with literature values.[2,12]

In the previous report,[1] the significance of steric effects of 5-substituents in determining acid strengths in 5,5-disubstituted barbituric acid derivatives was demonstrated through an empirical l.f.e.r. (Table 4 of ref. 1, and the equation given therein). This l.f.e.r. has provided

TABLE 2

^{1}H N.m.r. data for barbituric acid derivatives and intermediates (δ values downfield from Me_4Si; J/Hz)

Compound	Solvent	δ			
(IIa)	$CDCl_3$–$(CD_3)_2SO$	11.23 (2 H, s, D_2O exchanged, NH)	1.72 (4 H, s, CH_2CH_2)		
(IIb) (ii)	$CDCl_3$–$(CD_3)_2SO$	11.02 (2 H, s, D_2O exchanged, NH)	2.48 (4 H, t, J 7.5, $CH_2CH_2CH_2$)	2.08 (2 H, quint., J 7.5, $CH_2CH_2CH_2$)	
(IIc)	$CDCl_3$–$(CD_3)_2SO$	11.04 (2 H, s, D_2O exchanged, NH)	2.07 [4 H, m, $CH_2(CH_2)_2CH_2$]	1.79 [4 H, m, $CH_2(CH_2)_2CH_2$]	
(IIIa)	$CDCl_3$	4.20 (4 H, q, J 7, CH_3CH_2O)	1.40 (4 H, s, CH_2CH_2)	1.27 (6 H, t, J 7, CH_3CH_2O)	
(IIIb)	$CDCl_3$	4.20 (4 H, q, J 7, CH_3CH_2O)	2.55 (4 H, t, J 7.5, $CH_2CH_2CH_2$)	1.98 (2 H, quint, J 7.5, $CH_2CH_2CH_2$)	1.25 (6 H, t, J 7, CH_3CH_2O)
(IIIc)	$CDCl_3$	4.15 (4 H, q, J 7, CH_3CH_2O)	2.17 [4 H, t, J 6.5, $CH_2(CH_2)_2CH_2$)]	1.67 [4 H, m, $CH_2(CH_2)_2CH_2$]	1.22 (6 H, t, J 7, CH_3CH_2O)

TABLE 3

pK_1 Values for barbituric acid derivatives and benzoic acid in water at 25 °C

Compound	pK_1 (mean)	Set number	Number of titrations in set	pK_1 (lit.) [a]
(Ia)	8.50 ± 0.03	73	3	7.14(C)*; 8.51(P) [2]
(Ib)	8.00 ± 0.02	40	1	7.980(P) [2,†]
(IIa)	8.73 ± 0.03	57	3	
(IIb)	8.82 ± 0.02	60	3	
(IIc)	8.83 ± 0.03	108	2	
(IId) [b]	8.88 ± 0.03	103	4	
Benzoic acid	4.21 ± 0.02	73	2	4.190—4.203(C) ‡ 4.204— 4.218(P) [12b,‡] 4.203—4.216(S) ‡

[a] (C) Conductance method; (P) potentiometric method; (S) spectrophotometric method. [b] This derivative was prepared by Baird,[11] who also determined the pK_1 value. We are indebted to him for the use of this information.

* J. K. Wood, *J. Chem. Soc.*, 1906, 1831. † G. G. Manov, K. E. Schuette, and F. S. Kirk, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 84. ‡ Ref. 12*a*, p. 522.

the foundation from which a number of critical tests have been devised. These tests have been directed at examining the adequacy of the initial treatment of the data for the 14 derivatives in the original reaction series in accounting for reactivity and the soundness of the conclusions drawn from the l.f.e.r.

ca. 0.3. For derivatives (II), increasing the ring size from $n = 2$ to $n = 4$ gives an increase in p.c. to *ca.* 1.4, still only a fraction of the p.c. for (I; $R^1 = R^2 = Et$) (4.6).[13] Hence, the three lines of evidence: (i) the l.f.e.r. with a significant correlation for steric effects; [1] (ii) the weakened acid-strength of derivatives (II); and (iii) the low partition coefficients, all support the solvation hypothesis as a significant cause of acid weakening.

In series (II), with the substituent steric effects minimized or essentially constant, it has been concluded, therefore, that the order for acid strengths is predominantly determined by the polar effects of the 5,5-alkylene groups. The polar effect of the substituents is considered to operate by electron release [(IId) > (IIc) > (IIb) > (IIa)] from the carbocyclic ring to the electronegative reaction centre [1] for the barbituric acid molecule. The extent to which electron release can occur increases with ring size but the electronegative reaction centre is regarded as the primary source, constant in effect, for electron withdrawal from the carbocyclic substituents. The magnitude of this effect is believed to relate to the bifunctional nature of the reaction centre (malonyl) and will be referred to again for the malonic acids where it is even greater.

The effect of cycloalkyl ring size on the dissociation constants of *meta*-substituted benzoic acids and the rates

TABLE 4

pK Values for cycloalkane-substituted barbituric and carboxylic acids at 25 °C

	Compound						
	(II)	(IV)		(VI)		(IX)	
n	pK_1 (From Table 3)	pK [a]	pK [b]	pK_1 [12a]	pK_2 [12a]	pK (*meta*) [c]	pK (*para*) [c]
2	8.73	5.53	4.83	1.824	7.431	5.85 (5.80)	5.91 (5.96, 5.94)
3	8.82	6.20	4.79	3.127	5.879	5.89	5.89
4	8.83	6.20	4.99	3.230	6.081	5.93	5.89
5	8.88	6.48	4.90	3.451	6.108	5.93	5.89
6		6.49					

[a] Solvent, aqueous ethanol (50%, v/v).[20] [b] Solvent, water.[21a] [c] Solvent, aqueous ethanol (50% v/v).[14] For series (VI) the solvent was water.[21b]

Relative to the original reaction series,[1] it may be seen in Table 3 that the derivatives (IIa—d) have lowered acid strengths as for (I; $R^1 = R^2 = Me$). This is in accord with the much reduced steric effects and small polar effects anticipated for the carbocyclic substituents in compounds (II). It has been concluded, therefore, that steric effects remain small and essentially constant and this accounts for the low acid strengths in series (II) in general. This, we consider, provides independent evidence for the steric effects established for series (I) in the l.f.e.r.[1] The low acid-strengths in series (II) is attributed to increased solvation in the undissociated molecules relative to derivatives where steric effects can reduce solvation, *e.g.* (I; $R^1 = R^2 = Et$).

Further evidence for the variation in hydration of undissociated molecules is given by their partition coefficients (p.c.) (octan-1-ol–0.1M-hydrochloric acid),* measured at 25 °C.† We find, for (I; $R^1 = R^2 = Me$) and (II; $n = 2$), the partition coefficient is very small, of hydrolysis of a series of carbinyl chlorides have been investigated. Reactivities in these reaction series were interpreted on the basis of electron release by the substituents in the order: cyclohexyl > cyclopentyl > cyclobutyl > cyclopropyl.[14] This supports the conclusions reached for derivatives (II) (Table 4). It was also suggested that ' the increase in acid strength of *m*-cycloalkylbenzoic acids with decreasing ring size could be rationalized on the basis of decreasing steric interference to solvation with decreasing ring size '.[14-16] However, while there may be some basis to the solvation effects proposed (as an alternative to hyperconjugative effect arguments) to account for the reactivity in the examples cited,[15,16] in support of the *m*-cycloalkylbenzoic acid case, it is doubtful, in our view, whether the explanation given applies to these acids.

* The aqueous phase was made 0.1M in HCl to suppress dissociation of the barbituric acid.

† The measurements will be presented in full in a later paper.

Comparisons with Some Mono- and Di-carboxylic Acids.—Certain similarities between substituent effects on acid strength in other acids (the malonic acids in particular) and those observed for the barbituric acid derivatives caused us to examine this question more widely. It was thought that explanations developed for the barbituric acids so far described should have general application for acids and bases in aqueous solutions, but only when a certain combination of structural circumstances arises do the superimposed steric effects discussed become significant enough to cause substituent effects which do not follow the usual order for electron release ($Bu^t > Pr^i > Et > Me$) for alkyl groups.*

These circumstances, for the carboxylic acids, relate to (i) the number of carboxy-groups present in the molecule, (ii) the number, (iii) the size, and (iv) the proximity to the reaction centre (CO_2H) of the substituents in the molecule. In going from the mono- to the di-carboxylic acids an increase in solvation (dipole–dipole interaction) in the undissociated molecule could be anticipated in addition to the more obvious increase that would be present in the bivalent anion (ion–dipole interactions). The former we see as the main factor responsible for the acid strengthening steric effects, as in the barbituric acid derivatives. Also, there will be a certain minimum size or chain length for a substituent at which the onset of solvent exclusion in the undissociated molecule will produce an acid strengthening effect. In the n-aliphatic acids this is seen to occur when butanoic acid is reached, although this has been attributed to the other causes in the past [17] and some consider propanoic acid as the anomaly in the homologous series, but on grounds † other than those discussed here.[18]

The converse, long proposed for sterically hindered carboxylic acids,[19] where the stronger ion–dipole solvation in the anion is hindered, has been detailed in Part 2.[1] For anions of both mono- and di-carboxylic acids a certain minimum size and chain length of substituents is necessary before the onset of an acid-weakening steric solvent exclusion effect becomes evident.

This steric acid-weakening effect [19] is in opposition to the steric acid-strengthening effect already proposed (for the undissociated molecules) and leads to a smaller overall change in the pK_1 value, since both the initial and final states in the dissociation reaction are thermodynamically less stable than for a derivative which is not sterically hindered. This hindrance to solvation, of steric origin, in both the initial and final states for the dissociation reactions would explain the unexpected substituent effects noted in a number of acids, some of which will be discussed here.

(a) *Cycloalkanecarboxylic and cycloalkane-1,1-dicarboxylic acids.* Reported pK values for the cycloalkanecarboxylic acids increase with ring enlargement (IV; $n = 2$—6) in ethanol–water (1 : 1, v/v),[20] but with water alone as solvent, there are discontinuities in the order for acid strengths.[21a] For the cycloalkane-1,1-dicarboxylic acids (cycloalkylmalonic acids) (VI; $n = 2$—5) the pK_1 values (Table 4) [21b] show very clearly that ring enlargement is acid weakening. The largest difference in pK_1 values is observed on going from the cyclopropane to the cyclobutane ring (VI; $n = 2$ to $n = 3$) as was also found in derivatives (II; $n = 2$ to $n = 3$), although the magnitude of the change was less for these derivatives.‡ Nevertheless, the remaining changes in pK_1 values continue the trend in the expected acid-weakening direction, commensurate with the order for electron release from the cycloalkyl rings. This, we again believe, is due to the minimization, if not the complete removal, of substituent steric effects in (VI; $n = 2$—5) which then show acid strengths following substituent electronic effects alone. Also, it may be seen that with the exception of (VI; $n = 2$),‡ the lowered acid strengths in the cycloalkyl series more closely resemble that of dimethylmalonic acid (VII; $R^1 = R^2 = Me$), where steric effects are least rather than derivatives whose larger substituents can exert significant steric effects, *e.g.* (VII; $R^1 = R^2 = Et$).

(b) *Alkyl-substituted mono- and di-carboxylic acids.* The pK_1 values for the acyclic dialkylmalonic acids (VII) (Table 5) decrease in going from methyl to larger substituents.[22-27] This follows the pattern found in the barbituric acid series.

TABLE 5

pK_1 Values for substituted barbituric and carboxylic acids in water at 25 °C

R^1	R^2	(I)	(V)	(VII)	(VIII)
Me	Me	8.51 [1]	4.848 *	3.151 †	3.85 ‡
Et	Et	7.98 [1]	4.734 *	2.151 [27]	3.67 ‡
Pr^n	Pr^n			2.037 ¶	3.65 ‡
Pr^i	Pr^i			2.124 [27]	3.63 ‡
Me	H		4.874 *	3.072 †	4.35 ‡
Et	H		4.820 *	2.961 †	
Pr^n	H		4.842 *	2.989 †	4.32 ‡
Pr^i	H		4.780 *	2.94 §	4.28 ‡
Bu^t	H			2.92 §	
Me	Ph	7.78 [1]			4.12 ‡
Et	Ph	7.45 [1]			3.89 ‡
Me	Pr^n				3.626 †
Et	Pr^n				3.510 †

* Ref. 12*a*, Table 1. † Ref. 12*a*, Table 5. ‡ T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, 1965, **87**, 4851. § L. Eberson, in 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Wiley, London, 1969, ch. 6. ¶ G. H. Jeffrey and A. I. Vogel, *J. Chem. Soc.*, 1936, 1756.

The difference in pK_1, [$\Delta pK_1 = pK_1(Me,Me) - pK_1(Et,Et)$], for the barbituric acid series (ΔpK_1 *ca.* 0.5) is rather less than for the malonic acid derivatives (ΔpK_1 *ca.* 1.0). This difference may be due to: (a) the greater extent to which internal rotations may occur in the acyclic malonic acids than in the corresponding cyclic barbituric acids; (b) the presence of nitrogen in the barbituric acids in place of the more electronegative oxygen of the malonic acids; (c) the fact that the much stronger malonic acids

* The trend noted [1,2] in the barbituric acid derivatives for the steric effect of the Pr^i group has been further confirmed in the Bu^t group.

† Discontinuities in the changes for the standard thermodynamic functions for dissociation, $\Delta G°$, $\Delta H°$, and $\Delta S°$ at propanoic acid, in the series of n-alkylcarboxylic acids.

‡ Possibly due to the highly strained nature of the cyclopropane ring and the increased *p*-character of its *endo*-orbitals.

have two carboxy-groups in which all oxygen atoms may be sterically influenced by the substituents, relative to the barbituric acids where the nitrogen atoms in the heterocyclic ring (replacing corresponding oxygen atoms) are less favourably placed for steric interactions with 5-substituents.

The order of acid strengths (pK_1) for each class of acid under comparison, (VII) > (VIII) > (V) > (I), could have been anticipated from: (a) the nature of the acid reaction centre; (b) the number of carboxy-groups in the molecule; (c) the distance between the carboxy-groups in the molecule. It is the substituent effects within each class that require explanation. This is particularly so for alkyl substituents (*e.g.* $R^1 = R^2 =$ Me, Et, Pr^i, or Bu^t) where differences in electronic effects are small, but steric effects increase rapidly. It should be noted that the *o*-alkylbenzoic acids display an acid-strengthening trend as the substituent is increased in size from Me to Bu^t. Although solvation effects may have some role in this trend, it is generally accepted that the acid-strengthening mechanism is based on steric inhibition of mesomerism involving loss of mesomeric stabilization of the undissociated form of the acids through out-of-plane twisting of the carboxy-group by the *ortho*-substituent.[28b, c] It is unlikely that interactions of this kind will be significant in the present series of compounds.

In the malonic (VII) and glutaric (VIII) acid series, the effect of replacing methyl groups by isopropyl groups may be seen in Table 5. As with substitution by ethyl groups the effect, contrary to that expected from the electronic effect, is acid strengthening. However in both acid series (VII) and (VIII) the acid-strengthening effect of the isopropyl group is only very slightly more than that of the ethyl group. It was noted previously [1,2] that in the 5,5-disubstituted barbituric acids (I), the isopropyl group, while acid-strengthening with respect to the methyl group, was less effective than the ethyl group. In that instance, two possible explanations (not necessarily mutually exclusive) were offered to account for the diminished steric influence of the isopropyl group, relative to ethyl, and only one of these would appear to be relevant to the acids (V), (VII), and (VIII). This explanation [1] is based on the relative steric effect of substituents on solvation in the initial and the final state for the dissociation reaction. For the isopropyl group, the situation envisaged is desolvation of the undissociated molecule (acid strengthening) and, to some degree, of the anion (acid weakening) with the difference between initial and final states corresponding to an ' effective steric effect ' close to that for the ethyl group in the malonic acids.

Interest in substituent effects in dicarboxylic acids and particularly for the malonic acids has existed for many years.[22-27] The two questions which have been examined have been: (i) the lack of alkyl substituent inductive effect dependence of first dissociation constants in the dialkylmalonic acids in contrast to the apparent dependence on inductive effects found for the second dissociation constants and (ii) the deviations from the anticipated statistical value of 4 observed for the ratio K_1/K_2. General accounts of this work on dicarboxylic acids are to be found in the literature.[28-31]

Substituent Effects in Dicarboxylic Acids.—Jones and Soper,[24] in an investigation of the acid strengths of some dicarboxylic acids, suggested that intramolecular hydrogen-bonding enhancing the K_1 value for *cis*-caronic acid might explain the very high value (929 000) for K_1/K_2 found for this derivative. Hydrogen-bonding between carboxy-groups in solid maleic acid * led to proposed hydrogen-bond formation in the anion.[32] In this way the greater acid strength of maleic acid over that for fumaric acid (*trans*-isomer) could be accounted for. Also, similar stabilization of the monoanion accounted for the lower K_2 value for maleic acid (*cis*-isomer) than for fumaric acid. Further examples, since advanced, include the isomeric citraconic–mesaconic, phthalic–isophthalic–terephthalic, caronic (*cis* and *trans*) acid systems, the acyclic alkyl-substituted malonic acids and tetramethylsuccinic acid. A superimposed rotational barrier, due to the alkyl substituents, is considered to hold carboxy–carboxylate ion groups in orientations favourable to hydrogen-bond formation in aqueous solution in some of these structures.[25] Differences in rate constants for acid-base reactions of 2,2-disubstituted malonic acids (VII) were similarly explained with the steric effect of alkyl substituents having the primary influence and electronic effects being less important. For alkyl groups larger than ethyl, the chain length has little effect, as has branching at a remote carbon atom. Branching at C(3), *e.g.* Pr^i, was seen to be highly effective in perturbing the tetrahedral arrangement of the C(2)-carbon, forcing the carboxy groups closer together (' closing the jaws ') to form a stronger intramolecular hydrogen-bond. Solvation effects were also considered to be a significant factor in the reactions studied.[26] Most recently, very accurate pK_1 and pK_2 values at temperatures between 5 and 45 °C with changes in the derived standard thermodynamic functions $\Delta G°$, $\Delta H°$, and $\Delta S°$ have been determined by Ives' group [27] for malonic (VII; $R^1 = R^2 =$ H), diethylmalonic (VII; $R^1 = R^2 =$ Et), and di-isopropylmalonic acid (VII; $R^1 = R^2 =$ Pr^i). Ives and Marsden [33] proposed that the effects of alkyl substituents on hydrational changes in the dissociation of some acids are mainly confined to differences in $\Delta H°$ and $\Delta S°$ which almost disappear in $\Delta G°$ by compensation. However, this compensation was not considered to apply to the first and second dissociation constants of malonic acids because of the different ways in which K_1 and K_2 are affected by alkyl substitution.[27] Changes in enthalpies and entropies for dissociation must be studied, if hydrational effects are considered to have a major effect. Also, it was pointed out [27] that such effects have not been included in the classical treatments of these matters and that the electrostatic models [34] are inadequate in accounting for the temperature dependence of dissociation.[30] The models are considered to confine attention

* From *X*-ray evidence.

to free energy effects and the possibility of a need for a new approach to the general problem is recognised by Ives' group. Also, in examining the K_1/K_2 ratio, they note that the value for dimethylmalonic acid is not abnormal with respect to malonic acid and past findings for dicarboxylic acids, but on going from (VII; $R^1 = R^2 = Me$) through (VII; $R^1 = R^2 = Et$) to (VII; $R^1 = R^2 = Pr^i$) profound effects are produced. Symmetry of substitution is also considered to enter into this problem because of the dissimilarity of K_1/K_2 for (VII; $R^1 = H$, $R^2 = Pr^i$) and (VII; $R^1 = R^2 = Et$) [27] (Table 6).

TABLE 6

Dissociation constants for malonic acid derivatives in water at 25 °C

(VII) R^1	R^2	pK_1	pK_2	K_1/K_2
H	H	2.8469 [27]	5.6957 [27]	7.06×10^2
Me	Me	3.151 *		
		3.17 [22]	6.06 [22]	7.83×10^2
Et	Et	2.1513 [27]	7.4166 [27]	1.84×10^5
Pr^i	Pr^i	2.1240 [27]	8.8480 [27]	5.30×10^6
H	Pr^i	2.94 [22]	5.88 [22]	8.64×10^2

* G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1936, 1756.

The argument in favour of the intramolecular hydrogen-bonded univalent anion hypothesis has not remained unchallenged and attempts have been made to obtain evidence for its presence in aqueous solutions. The solid state evidence (maleic acid) [32] was not supported by i.r. spectroscopic studies of solutions.[35] In a comparison of K_1 values of dibasic acids with the dissociation constants of their monomethyl esters the electrostatic effect was regarded as the significant factor for the differences observed.[36] The hydrogen-bond breaking characteristics of urea (in proteins) failed to have any effect on proposed internal hydrogen bonds in the dicarboxylic acids examined, which included malonic acids in addition to maleic and fumaric acids.[37] Internal hydrogen-bonding is regarded as unimportant in determining acid strengths in dicarboxylic acids where the values for the first and second thermodynamic dissociation constants differ by less than four pK units.[38] The original proposal for acid-strengthening intramolecular hydrogen-bonding in *cis*-caronic acid actually involved the undissociated molecule; [24] however, such bonding is now regarded as unlikely in maleic acid,[39] and probably for other molecular dibasic acids.

Survival of an intramolecular hydrogen-bond in the univalent anion of a dibasic acid in aqueous solutions, against competitive intermolecular associations with water molecules would require a special gain in energy in the intramolecular hydrogen-bonded structure. It is difficult to see this energy gain over that in an extensively solvated anion in which intermolecular hydrogen-bonding with water molecules would be presumed to be the largest contributing factor to the total solvation of the anion. Also, the close parallel for alkyl substituent effects in the 5,5-disubstituted barbituric acids and the corresponding malonic acids suggests that the cause of these effects is of similar origin. *It is difficult to imagine how the intramolecular hydrogen-bonded anion hypothesis might apply in the barbituric acid derivatives.* In addition, the acid-weakening solvation hypothesis has so far withstood further testing in this laboratory in work on 5,5-disubstituted barbituric acid derivatives. For every example in which the intramolecularly hydrogen-bonded anion hypothesis has been used to account for increased acid strengths in dicarboxylic acid first dissociations [17,25,26] both in relative magnitude and for given structural changes, an equally plausible case could be given in terms of steric hindrance to solvation in the initial (acid-strengthening) and final (acid-weakening) states.

Ives' group also appear to consider that alkyl-substituent effects on acid strength in malonic acids are determined by solvation effects, but have been seeking an explanation in terms of trends in $\Delta H°$ and $\Delta S°$ and the effect of temperature on these changes in the thermodynamic functions for dissociation.[27] Because of the pivotal place of (I; $R^1 = R^2 = Me$) in the original barbituric acid reaction series,[1] the temperature dependence of the first thermodynamic dissociation constant was determined in this laboratory and the changes in the derived thermodynamic functions $\Delta G°$, $\Delta H°$, and $\Delta S°$ were evaluated at temperatures between 10 and 45 °C.[13] These changes in the thermodynamic functions for dissociation for (I; $R^1 = R^2 = Me$) have been compared with corresponding values for other derivatives and will be reported in a later part of this series, but so far we have not recognised an advantage in considering a division into $\Delta H°$ and $\Delta S°$ over the use of $\Delta G°$ in attempting to explain substituent effects. This experience has also been noted elsewhere.[40]

pK_2 Values of Malonic Acid Derivatives.—While the pK_1 values for the malonic acids (VII; $R^1 = R^2 = Me$, Et, or Pr^i) may be explained in terms of the acid-strengthening and acid-weakening steric effects of alkyl substituents on the initial (undissociated molecule) and final (univalent anion) states respectively, the fact that the pK_2 values follow qualitatively the expected order in acid strengths for the inductive effects of the substituents must also be accounted for. In the second stage of dissociation, solvation in the initial (univalent anion) and final state (bivalent anion) will be due to stronger ion–dipole interactions and generally less susceptible to steric effects. The magnitude of the changes in pK_2 values in traversing the series (VII; $R^1 = R^2 = Me$, Et, or Pr^i) (Table 6) is surprising in view of the small differences in the σ^* values for the electronic effects of these substituents.[1] An exceptionally large ρ_2^* value for the Taft equation would be needed to produce changes of the order observed. While the origin of the forces responsible for solvation are the same in both the univalent and bivalent anions (ion–dipole), the size of the hydration shell around the bivalent anion might be expected to be greater than for the univalent anion. Substituents would then be expected to desolvate the bivalent anion (final state) more than the univalent anion (initial state), leading to destabiliz-

ation of the bivalent anion and acid-weakening. Therefore, while pK_2 values may appear to parallel the electronic effects of the substituents, this could merely be a much smaller superimposed influence on an acid-weakening steric hindrance to solvation in the bivalent anion.

The K_1/K_2 Ratio.—Estimation of the electrostatic effect on the K_1/K_2 ratio, which has a symmetry-derived value of 4, for disubstituted malonic acids requires the elimination of steric and polar effects. This situation is approached most closely by the K_1/K_2 values, 7.83×10^2 and 5.66×10^2, for dimethylmalonic (VII; $R^1 = R^2 =$ Me) and cyclobutane-1,1-dicarboxylic (VI; $n = 3$) acids, respectively, or the available data.

Steric Hindrance to Solvation.—In proposing steric hindrance to solvation, in initial and final states, for both stages in the dissociation of malonic acids, to account for substituent effects, the previously rather baffling order of acid strengths in pK_1 and pK_2 values may be considered from a different point of view. Whether this approach will be capable of quantitative trfeatment will depend on further data becoming available.

It should be noted that while a steric effect is responsible for reactivity, in addition to electronic effects of substituents, it is considered to act through modification of electronic effects in functional groups, by controlling the degree of solvation that can develop at these groups, which are used to measure reactivity.[1] These steric effects appear to be sudden in onset, as has previously been noted for such effects, such as when a methyl or an isopropyl group is introduced.

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