Transmission of Polar Effects. Part 15.[1] Ionisation and Esterification with Diazodiphenylmethane of [2.2]Paracyclophane-4-carboxylic Acid and its Pseudo-bromo-substituted Derivatives, and the Alkaline Hydrolysis of their Methyl Esters

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The pK_a values of [2.2]paracyclophane-4-carboxylic acid and its four pseudo-bromo-substituted derivatives have been determined in 80% (w/w) 2-methoxyethanol–water at 25 °C. The rate coefficients for the esterification of these acids with diazodiphenylmethane have been measured in 2-methoxyethanol at 30 °C. The rate coefficients for the alkaline hydrolysis of the corresponding methyl esters have been determined in 70% (v/v) dimethyl sulphoxide–water at both 56.3 and 76.3 °C. In the ionisation and esterification reactions both normal and reversed substituent polar effects were detected. Kirkwood–Westheimer calculations were carried out for the ionisation reaction and account for ΔpK_a values both qualitatively and (for the pseudo-*ortho*-, -*meta*-, and -*para*-isomers) quantitatively. In the alkaline hydrolysis of the esters, significant steric retardation was observed for the pseudo-*gem*-isomer.

From previous work on inductive and electrostatic-field effect models,[2–9] a field-effect model appears to give the more satisfactory description of the substituent polar effect. A reversal of the normal polar effect has been detected in some of these systems[6–9] and such behaviour has been accounted for in terms of the angular dependence of the polar effect. Thus either the normal or the reverse of the normal substituent polar effect would be expected on the basis of the geometrical disposition of the substituent with regard to the reaction centre.

We describe here the ionisation of [2.2]paracyclophane-4-carboxylic acid and its four pseudo-bromo derivatives (**1**), their esterification with diazodiphenylmethane (DDM), and the alkaline hydrolysis of the corresponding methyl esters.[10] The results are related to Kirkwood–Westheimer calculations of the electrostatic field effect.

Results and Discussion

Few organic compounds are as 'globular,' rigid and symmetrical as [2.2]paracyclophane; this makes it very suitable as the framework for a study of substituent effects.

pK_a Values.—In Table 1 are shown the pK_a values of the acids (**1**) and the four pseudo-bromo derivatives in 80% (w/w) 2-methoxyethanol–water at 25 °C. The unsubstituted acid is considerably less acidic than might have been considered likely from the pK_a values of benzoic (6.67) and 2,5-dimethylbenzoic (6.92) acids.[11] It is likely that this results from increased resonance stabilisation of the acid due to the 'semiaromatic' character of [2.2]paracyclophane.[12] The pseudo-*gem*- and pseudo-*ortho*-bromo substituents are acid-weakening; the pseudo-*para* and pseudo-*meta* substituents are acid-strengthening. The former result is unexpected as the normal substituent effect of a bromo group is acid-strengthening. This cannot be explained in terms of an inductive effect and must be due to a reversal of the substituent field effect.

Calculations (see Experimental section) of the field effect of the substituents in the paracyclophanecarboxylic acids have been carried out by using Kirkwood and Westheimer theory for a spherical model,[13] as shown in Table 2. The two-point charge and point dipole approximation models have both been used. Both models give good agreement with ΔpK_a qualitatively and quantitatively for the pseudo-*meta*- and pseudo-*para*-isomer. Only qualitative agreement exists for the pseudo-*gem*-isomer. Both qualitative and quantitative agreement is found between the point dipole approximation model and ΔpK_a for the pseudo-*ortho*-isomer. These results probably reflect the critical character of the assumptions underlying the two-point charge approximation model. The reversal found for the pseudo-*gem*-isomer is larger than those observed for other systems.[6,7] The present result makes it unlikely that such an effect arises from hydrogen bonding.[14] The calculations also show the relative unimportance of the solvent route for transmission.

The inductive model can be used to calculate the substituent effect by use of the transmission coefficients tabulated previously.[15] As ρ_0 for the ionisation of benzoic acids in the medium used in this study is 1.68,[16] a ρ value of about 0.3 can be calculated for the system under study. As this would indicate ΔpK_a values of *ca.* −0.1 for a pseudo-bromo substituent, it can be concluded that the inductive model is both unreal and unreasonable in accounting for substituent effects in this model.

A steric effect on solvation does not appear likely in the pseudo-*ortho* and pseudo-*gem*-isomers but it cannot be completely excluded. Suitable models for this are under study.

Esterification with Diazodiphenylmethane (DDM).—The rate coefficients for the esterification of the acids with DDM in 2-methoxyethanol at 30 °C are shown in Table 1. This reaction has been used successfully in the estimation of the polar effects of substituents,[17] with the rate-determining step being the transfer of a proton from the acid to DDM. Linear relationships between log k_2 for the esterification and pK_a values have frequently been found.[17] However, in this study, although the order of reactivity of the four bromo acids is the same, the reactivity of the pseudo-*gem*- and pseudo-*ortho*-isomers is greater than would be expected from their pK_a values. A similar effect has been noted for 8-substituted 1-naphthoic acids.[7] The geometrical disposition of the bromo group in the pseudo-*gem*- and pseudo-*ortho*-isomer is such that the negative end of the dipole can interact significantly with both incipient negative *and* incipient positive charges in the transition state for esterification. In equilibria ionisation the final state is anionic alone. For the unsubstituted, pseudo-*para*-, and pseudo-*meta*-isomer, the response to polar effect is about 0.7 of that for the ionisation reaction.

Alkaline Hydrolysis.—The alkaline hydrolysis of the methyl pseudo-bromo-[2.2]paracyclophane-4-carboxylates has been

Table 1. pK_a Values in 80% (w/w) 2-methoxyethanol–water at 25 °C, and rate coefficients (k_2) for the esterification (with DDM in 2-methoxyethanol at 30 °C) of pseudo-bromo-[2.2]paracyclophane-4-carboxylic acids[a]

Substituent	pK_a	k_2/l mol^{-1} min^{-1}
H	7.59	0.184
Pseudo-*gem*-bromo	7.99	0.176
Pseudo-*ortho*-bromo	7.75	0.211
Pseudo-*para*-bromo	7.28	0.309
Pseudo-*meta*-bromo	7.34	0.261

[a] The measurements are the mean values of at least two determinations. The pK_a values are reproducible to within ±0.02 units and the rate coefficients to within ±3%.

Table 2. Kirkwood–Westheimer calculations for the pseudo-bromo-[2.2]paracyclophane-4-carboxylic acids in 80% (w/w) 2-methoxyethanol–water at 25 °C

					ΔpK_a		
Substituent	Δ_+^S	Δ_+^C	Δ_-^S	Δ_-^C	Calcd.[a]	Calcd.[b]	Found
Pseudo-*gem*	−0.20	−1.65	+0.25	+2.65	1.01	0.73	0.40
Pseudo-*ortho*	−0.19	−1.16	+0.21	+0.93	−0.20	0.06	0.16
Pseudo-*para*	−0.15	−0.50	+0.13	+0.13	−0.39	−0.33	−0.31
Pseudo-*meta*	−0.16	−0.65	+0.18	+0.23	−0.39	−0.31	−0.25

[a] By two-point charge approximation. [b] By point dipole approximation.

Table 3. Rate coefficients (k_2) for the alkaline hydrolysis of methyl pseudo-bromo[2.2]paracyclophane-4-carboxylates in 70% (v/v) dimethyl sulphoxide–water[a]

	10k_2/l mol^{-1} min^{-1}	
Substituent	At 56.3 °C	At 76.3 °C
H	6.45	27.3
Pseudo-*gem*-bromo	0.310	2.26
Pseudo-*ortho*-bromo	8.52	31.3
Pseudo-*para*-bromo	16.3	52.3
Pseudo-*meta*-bromo	14.7	46.0

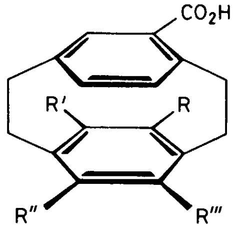
[a] Rate coefficients are reproducible to within ±3%.

Table 4. Activation parameters for the alkaline hydrolysis of methyl pseudo-bromo-[2.2]paracyclophane-4-carboxylates in 70% (v/v) dimethyl sulphoxide–water at 56.3 °C[a]

Substituent	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
H	15.8	−12
Pseudo-*gem*-bromo	22.0	1
Pseudo-*ortho*-bromo	14.2	−16
Pseudo-*para*-bromo	12.4	−20
Pseudo-*meta*-bromo	12.7	−19

[a] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are considered accurate to within ±300 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively.

studied in 70% (v/v) dimethyl sulphoxide–water at 56.3 and 76.3 °C, as shown in Table 3. The activation parameters are shown in Table 4. As for the DDM reaction, there is a linear relation between log k_2 for the alkaline hydrolysis of the unsubstituted, pseudo-*meta*-, and pseudo-*para*-bromo esters and pK_a for the corresponding acids, with slopes of about 1.3_5 and 1.0_5 at 56.3 and 76.3 °C, respectively. The polar effect of the pseudo-*ortho*-isomer appears to be diminished rather than reversed. As in the DDM reaction, it is suggested that this is due to the geometry, where the charge on the transition state for the alkaline hydrolysis can be situated more 'symmetrically' with regard to the substituent dipole. However, for the pseudo-*gem*-isomer, the considerably lower rates of reaction must arise from a primary steric 'bulk' effect of the proximate substituent. While the pseudo-*ortho*-, pseudo-*para*-, and pseudo-*meta*-substituents give the expected effects on the activation parameters,[18] the pseudo-*gem*-isomer has a greatly increased $\Delta H^{\ddagger}$ value and an increased (less negative) $\Delta S^{\ddagger}$ value. The increase in $\Delta H^{\ddagger}$ arises mainly from the additional compressional energy in the transition state between reaction site and substituent.[18] The $\Delta\Delta S^{\ddagger}$ value of about 13 cal mol^{-1} K^{-1} is more difficult to understand. It might be expected that the steric 'bulk' effect would result in a rather negative $\Delta\Delta S^{\ddagger}$ value, due to an increase in steric inhibition of motions in going from the reactant to the transition state.[18] However, the effect observed could arise from steric inhibition of solvation in the transition state, as has been previously suggested for certain ester hydrolyses.[18]



(1)
R: pseudo-*gem*
R': pseudo-*ortho*
R'': pseudo-*para*
R''': pseudo-*meta*

An interesting final point regarding the effects of pseudo-*para*- and pseudo-*meta*-substitution is that the relative susceptibility of the system to the ionisation, esterification, and hydrolysis reactions is similar to that observed for *meta*-/*para*-substituted benzoic acids and esters.[19] This must arise from the dependence of reaction constants on the shape of cavities. The two systems in question must have transmissive cavities of similar relative content of molecular model and solvent.

Experimental

Materials.—The pseudo-*gem*-, pseudo-*meta*-, and pseudo-*para*-bromo[2.2]paracyclophane-4-carboxylic acids, as well as the corresponding methyl esters, were prepared by previously reported methods.[20–22] A sample of the pseudo-*ortho*-bromo acid was kindly provided by Professor D. J. Cram. The methyl ester of this acid was prepared by esterification with diazomethane in ether.[20] The acids and their methyl esters were recrystallised to constant m.p. (identical with or very close to literature values[20–22]). The solvents and DDM were prepared as previously described.[23]

Measurements.—The pK_a values and the rate coefficients for esterification were determined as described previously.[23,24] The low solubility of the pseudo-*para*-bromo acid presented a problem. Thus, for the ionisation of the four more soluble acids, the acid concentration was 0.004M. The unsubstituted, pseudo-*meta*-, and pseudo-*para*-bromo isomers were also studied at 0.001M. For the esterification, the four more soluble acids were in ten-fold excess over DDM (3 × 10^{-2}M concentration). The unsubstituted and pseudo-*para*-bromo acids were also studied in equal acid and DDM concentrations of 3 × 10^{-3}M. Only small corrections were required for the dilution effect (where needed). The rate coefficients for the alkaline hydrolysis of the methyl esters were measured as previously described.[25] The substrate and hydroxide anion concentrations were 2.5×10^{-4} and 1×10^{-2} to 1×10^{-1}M, respectively. The reactions were followed at the λ value showing maximum difference between substrate and product, *i.e.* 280—300 nm. The reactions were first-order in both substrate and hydroxide; as the reaction was carried out in excess of base, the resulting first-order behaviour was observed without deviation for at least three half-lives. The products, the anions of the corresponding acids, were obtained quantitatively from preparative-scale reactions and their identities were confirmed by spectral comparison with the acid in basic solution.

Kirkwood and Westheimer Calculations.—These calculations for a spherical model[13] were carried out for the bromo-substituted [2.2]paracyclophane-4-carboxylic acid system. The molecular parameters required were taken from the literature.[26,27] In accord with the procedures of Sarmousakis[28] and Ehrenson,[29] the bromo substituent was placed inside and 1.85 Å from the cavity wall, and the acidic hydrogen midway between the oxygens of the carboxy group (1.45 Å from the carboxy carbon) and 1.6 Å from the cavity wall. The two-point charge model of Kirkwood and Westheimer[13] was used as shown in equation (1), where μ is the dipole moment (in Debyes), T the

$$\Delta pK_a = C(H_+ - H_-)\mu/Td \qquad (1)$$

absolute temperature, C a constant [15 104 when $(H_+ - H_-)$ is in Å^{-1}], and d the carbon–bromine bond distance (in Å); H_k is a measure of the electrostatic interaction between charge δ_k and the reaction site. According to the two-point charge approximation,[13] the electrostatic effect of the dipolar substituent is transmitted through both the solvent and the cavity. The expression for ΔpK_a can be written as in equation (2), where $\Delta_k{}^i$

$$\Delta pK_a = \Delta_+{}^S + \Delta_+{}^C + \Delta_-{}^S + \Delta_-{}^C \qquad (2)$$

is the through-solvent or -cavity contribution to ΔpK_a due to a charge of δ_k on the substituent dipole. The spherical point dipole model of Kirkwood and Westheimer[13] was also used; according to this treatment, ΔpK_a can be calculated from equation (3), where C, μ, and T have their usual meanings; θ is

$$\Delta pK_a = C\mu \cos\theta/TR^2D_e \qquad (3)$$

the angle between the line joining the reaction centre to the centre of the dipole and the axis of the dipole, R is the distance between the centre of the dipole and the reaction centre, and D_e is the effective dielectric constant (see tabulated values of Westheimer *et al.*,[30] which assume that both the dipole and the acidic hydrogen are located on a diameter). The dielectric constant of the molecular cavity here is taken[13] as 2 and that of the solvent [80% (w/w) aqueous 2-methoxyethanol] as 32.[31] The dipole moment was taken from the literature for bromobenzene.[32] Calculations by Orttung's method[33] for the pseudo-*meta*- and pseudo-*para*-isomer gave similar results in our hands to that just described.

Acknowledgements

We are grateful to CONICIT for the support of one of us (S. A.). We thank Professor D. J. Cram for advice and a sample, and Drs. E. J. Grubbs, S. Ehrenson, and W. H. Orttung for discussions.

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Received 27*th March* 1986; *Paper* 6/608