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Macro Rings. 48. Transannular Effects of Acidity of Heteroannularly Disubstituted [2.2]Paracyclophane

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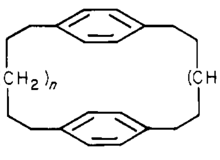
Abstract: The acidity constants of a series of heteroannularly substituted 4-carboxy[2.2]paracyclophanes and heteroannularly substituted 4-amino[2.2]paracyclophanes have been determined in 2-methoxyethanol–water (80/20, w/w) at 25 and 31 °C, respectively. The results are analyzed in terms of empirical substituted parameters and by means of the Tanford modification of the Kirkwood–Westheimer electrostatic cavity model.

[*m.n*]Paracyclophanes (**1**) represent a unique class of strained



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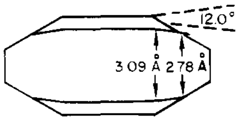
ring compounds where the close proximity of the benzene rings produces severe perturbational interactions of the π systems and marked transannular effects. Previous investigations of [*m.n*]paracyclophanes have shown that by decreasing the values of *m* and *n*, steric and electronic interactions between the benzene rings were enhanced. The presence of these interactions is pointed out by the following evidence. (1) X-ray structural determinations of [2.2]paracyclophane (**2**)[1] and [3.3]paracyclophane (**3**)[2] show



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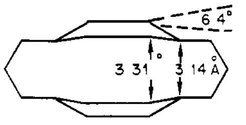

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the severe deformation of the benzene rings as they are forced close together. (2) Ultraviolet absorption studies[3] of [*m.n*]paracyclophanes, in which *m* and *n* are progressively decreased from 4 to 2, show a shift toward longer wavelength of three major absorption bands. (3) The rates of acetylation[4] of [*m.n*]paracyclophanes, in which *m* and *n* vary from 6 to 2, increase by a factor of 30 as *m* and *n* are decreased. (4) Both rings of the smaller paracyclophanes are deactivated to further electrophilic atack[5] by an electron-withdrawing substituent in one ring. (5) Upfield or downfield chemical shifts for protons of both rings are seen in the NMR spectra of [*m.n*]paracyclophanes when an electron-donating or electron-withdrawing substituent, respectively, is found in one ring.[6] While these studies leave no doubt about the presence of ring-to-ring interaction, especially in the smaller [*m.n*]paracyclophanes, the question of the nature of the electronic interaction has not been fully explored.

The mechanism by which electronic effects are transmitted between the phenyl rings of the [*m.n*]paracyclophanes can be probed by investigating the effect that a substituent on one ring has on a substituent on the other ring. Such information can be quantitatively derived from the acidity constants of appropriately substituted [2.2]paracyclophane carboxylic acids and amines by evaluation of the data empirically by means of substituent parameters and theoretically by means of the electrostatic model of Kirkwood and Westheimer and modifications thereof.[7,25,26] This paper reports the pK_a values of a wide variety of heteroannularly substituted 4-carboxy- and 4-amino[2.2]paracyclophanes and a detailed empirical and electrostatic analysis to elucidate the nature of the phenyl–phenyl interactions.

Table I. Acidities and Substituent Constants of Heteroannularly Substituted 4-Carboxy[2.2]paracyclophanes

substituent	pK_a[a]	σ^{PCP}
H	7.524 ± 0.055 (7.46 ± 0.07)[b]	0.000
Ψ-*gem*-nitro	7.745 ± 0.038 (7.70 ± 0.07)[c]	−0.221
Ψ-*o*-nitro	7.530 ± 0.044 (7.50 ± 0.07)[c]	−0.006
Ψ-*o*-bromo	7.748 ± 0.022	−0.224
Ψ-*o*-cyano	7.493 ± 0.038	0.031
Ψ-*o*-carboxy[d]	6.991 ± 0.039	0.533
Ψ-*o*-carboxylate[d]	9.667 ± 0.039	−2.143
Ψ-*m*-nitro	6.930 ± 0.033 (6.90 ± 0.07)[c]	0.594
Ψ-*m*-bromo	7.276 ± 0.054	0.248
Ψ-*m*-cyano	6.969 ± 0.042	0.565
Ψ-*m*-carboxy[d]	7.365 ± 0.048	0.117
Ψ-*m*-carboxylate[d]	8.210 ± 0.060	−0.710
Ψ-*p*-nitro	6.891 ± 0.051 (6.90 ± 0.07)[c]	0.633
Ψ-*p*-bromo[e]	7.338 ± 0.047	0.186
Ψ-*p*-cyano	6.977 ± 0.054	0.547
Ψ-*p*-carboxy[d]	7.342 ± 0.052	0.182
Ψ-*p*-carboxylate[d]	7.898 ± 0.033	−0.374

[a] Values in parentheses refer to acidity constants determined by others, under the same conditions as used in this work. For sources of compounds, see ref 8a. [b] Reference 3b. [c] W. Simone, private communication. [d] Statistically corrected by (1) addition of log 2 to the diacid acidity constants, (2) by subtraction of log 2 from the monocarboxylate acidity constant. [e] Prepared by H. J. Reich, ref 9.

Table II. Acidities and Substituent Constants of Heteroannularly Substituted 4-Amino[2.2]paracyclophanes

substituent[a]	pK_a	σ^{PCP}
H	3.032 ± 0.023	0.000
Ψ-*gem*-nitro	1.379 ± 0.068	1.653
Ψ-*o*-nitro	2.138 ± 0.057	0.894
Ψ-*m*-nitro	2.062 ± 0.061	0.970
Ψ-*m*-bromo	2.612 ± 0.048	0.420
Ψ-*m*-acetyl	2.816 ± 0.042	0.216
Ψ-*m*-acetamido	2.960 ± 0.059	0.072
Ψ-*m*-amino[b]	3.392 ± 0.031	−0.360
Ψ-*p*-nitro	2.254 ± 0.054	0.778
Ψ-*p*-bromo	2.915 ± 0.060	0.117
Ψ-*p*-acetyl	2.993 ± 0.052	0.039
Ψ-*p*-acetamido	3.106 ± 0.061	−0.074
Ψ-*p*-amino[b]	3.875 ± 0.048	−0.843

[a] For source of compounds, see ref 8a. [b] Statistically corrected (see Table I).

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(1) H. Hope, J. Bernstein, and K. N. Trueblood, *Acta Crystallogr. Sect. B*, **28**, 1733 (1972).

(2) P. K. Gantzel and K. N. Trueblood, *Acta Crystallogr., Sect. B*, **18**, 958 (1955).

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Table III. A Comparison of [2.2]Paracyclophane Carboxylic Acid Substituent Constants (σ) with Literature Values

σ	$\sigma\Psi$-meta r^a	$\sigma\Psi$-meta m	$\sigma\Psi$-para r^a	$\sigma\Psi$-para m	ref^b
σ_m	0.984	1.28	0.993	1.39	11
σ_p	0.884	0.75	0.951	0.87	11
$\sigma_{[2.2.1]}{}^c$	0.994	1.61	0.971	1.12	12
$\sigma_{[2.2.2]}{}^c$	0.986	1.93	0.956	1.34	12
T	0.984	1.01	0.970	0.77	13
R	0.047	0.17	0.191	0.51	13
σ_I	0.991	1.34	0.957	0.99	14
σ_m(pyridines)	0.947	0.32	0.986	0.26	15
σ_m	0.985	1.68	0.990	1.29	16
σ_p	0.903	1.48	0.958	1.21	16
$\sigma_{[2.2.2]}{}^d$	0.991	0.95	0.973	0.72	17
σ_m^+	0.982	1.89	0.991	1.46	18
σ_p^+	0.867	1.32	0.935	1.10	18
σ_m(ArOH)	0.946	0.78	0.984	0.62	19
σ_p(ArOH)	0.724	0.37	0.843	0.33	19
σ_m($ArNH_3^+$)	0.954	0.60	0.990	0.47	19
σ_p($ArNH_3^+$)	0.668	0.27	0.792	0.25	19
σ_m(ArOH)	0.987	0.86	0.997	0.66	20
F	0.914	0.90	0.990	0.75	21
M	0.217	0.14	0.357	0.17	21
σ_p^-(ArOH)^d	0.747	0.91	0.851	0.79	22

^{a} Correlation coefficient. ^{b} See Table IV, footnote b. ^{c} Determined in 50% EtOH.

Table IV. A Comparison of [2.2]Paracyclophane Amine Substituent Constants (σ) with Literature Values

σ	$\sigma\Psi$-meta r^a	$\sigma\Psi$-meta m	$\sigma\Psi$-para r^a	$\sigma\Psi$-para m	ref^b
σ_m	0.978	1.50	0.992	1.81	16
σ_p	0.911	0.81	0.951	1.00	16
T	0.995	1.24	0.989	1.46	13
R	0.785	1.07	0.850	1.37	13
σ_I	0.987	2.40	0.955	2.76	23
F	0.978	0.87	0.992	1.04	21
M	0.802	0.20	0.866	0.25	21
σ_m	0.982	1.54	0.990	1.84	11
σ_p	0.931	0.83	0.968	1.03	11
σ_I	0.993	2.17	0.961	2.49	11
σ_R	0.732	0.71	0.843	1.10	11
σ_m(pyridines)	0.992	0.26	0.999	0.31	15
σ_m(ArOH)	0.997	0.79	0.969	0.91	20
σ_p°	0.940	1.03	0.976	1.29	24
σ_m°	0.987	1.57	0.999	1.92	24
σ_m($ArNH_3^+$)	0.989	2.60	0.962	3.06	24

^{a} Correlation coefficient. ^{b} Literature substituent constants were taken from these references, and a detailed discussion of these substituent constants can be found therein.

Results and Discussion

Empirical Analysis. The heteroannularly substituted 4-carboxy- and 4-amino[2.2]paracyclophanes used in this study either had been previously synthesized or were prepared by literature procedures from heteroannularly disubstituted [2.2]paracyclophane precursors of known structure.[8a,9] Acidity constants of the 4-carboxy[2.2]paracyclophanes were determined potentiometrically at 25 °C in 2-methoxyethanol–water (80/20, w/w); acidity constants of the 4-amino[2.2]paracyclophanes were determined spectrophotometrically at 31 °C in the same solvent mixture. The diamino[2.2]paracyclophane acidity contants were determined potentiometrically. Tables I and II summarize the values of the acidity constants for the heteroannularly substituted 4-carboxy- and 4-amino[2.2]paracyclophanes, respectively. Also included in the tables are the substituent constants (σ^{PCD}) calculated by using eq 1, where K_x/K_0 is the acidity constant ratio of substituted

$$\sigma^{PCP} = \log (K_x/K_0) \tag{1}$$

to parent 4-carboxy- or 4-amino[2.2]paracyclophane. The agreement between the acidity constants determined in this work and those determined by others using the same conditions is excellent.

The Ψ-para[8] substituted 4-carboxy[2.2]paracyclophane substituent constants were initially compared with substituent constants obtained for the Ψ-meta carboxylic acid series by means of eq 2. A correlation coefficient of 0.983 was obtained by

$$\log (K_x/K_0)^{\Psi\text{-meta}} = m \log (K_x/K_0)^{\Psi\text{-para}} \tag{2}$$

linear-least-squares analysis. A similar comparison of the two amino[2.2]paracyclophane series gave a correlation coefficient of 0.981. These correlation coefficients in both the acid and amine cases are considered quite satisfactory.[10]

Since substituent constants are a measure of the relative effect of a substituent on a reaction center, the correlation of Ψ-meta substituents with Ψ-para substituents for the same reaction series suggests that substituents at these two positions interact with the reaction center by a similar mechanism.

The Ψ-ortho-, Ψ-meta-, Ψ-para-substituted 4-carboxy[2.2]paracyclophane substituent constants were next compared with substituent constants found in the literature by means of eq 3.

$$\log (K_x/K_0)^{PCP} = m\sigma^{(\text{lit.})} \tag{3}$$

The correlation coefficients and slopes (m) that were obtained for the Ψ-meta- and Ψ-para-substituted 4-carboxy[2.2]paracyclophanes are summarized in Table III. Substituent constants obtained for the Ψ-meta- and Ψ-para-substituted 4-amino[2.2]paracyclophane series were also compared with literature values. These results are summarized in Table IV.

Substituent constants for Ψ-ortho-substituted 4-carboxy[2.2]paracyclophanes, which are found in Table I, did not correlate well with any substituent constants found in the literature. The lack of correlation of Ψ-ortho-substituted 4-carboxy[2.2]paracyclophanes with literature substituent constants indicates that factors are at play in this system, with respect to the interaction of substituent with reaction center, which are not found in other systems examined. This may be a consequence of the close proximity of the substituent and reaction center found in this system. Solvation effects, intramolecular hydrogen bonding, and steric effects may all be partially involved. These results appear to be in direct contrast to the singular result of Acevedo and Bowden.[27] These authors found the acidity of the Ψ-*o*-bromocarboxy[2.2]paracyclophane to be adequately described by the electrostatic cavity model of Kirkwood and Westheimer, a model which does not directly address steric interactions between substituent and reaction center. A similar analysis for the heteroannularly substitued 4-amino[2.2]paracyclophanes was not performed.

Resonance interactions in benzene systems are considered to be slight or absent when substituent and reaction center are

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(3) (a) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 6132 (1954); (b) D. J. Cram, R. H. Bauer, N. L. Allinger, R. A. Reeves, W. J. Wechter, and E. Heilbronner, *ibid.*, **81**, 5977 (1959).

(4) D. J. Cram, W. J. Wechter, and R. W. Kierstead, *J. Am. Chem. Soc.*, **80**, 3126 (1958).

(5) (a) D. J. Cram and R. W. Kierstead, *J. Am. Chem. Soc.*, **77**, 1186 (1955); (b) D. J. Cram and N. L. Allinger, *ibid.*, **77**, 6289 (1955); (c) D. J. Cram and R. A. Reeves, *ibid.*, **80**, 3094 (1958).

(6) L. A. Singer and D. J. Cram, *J. Am. Chem. Soc.*, **85**, 1080 (1963).

(7) (a) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.* **6**, 506 (1938); (b) F. H. Westheimer and J. G. Kirkwood, *ibid.*, **6**, 513 (1938); (c) F. H. Westheimer and N. W. Shookhoff, *J. Am. Chem. Soc.*, **61**, 555 (1939); (d) F. H. Westheimer, W. A. Jones, and R. A. Lad, *J. Chem. Phys.*, **10**, 468 (1942); (e) C. Tanford, *J. Am. Chem. Soc.*, **79**, 5348 (1957); (f) S. Ehrenson, *ibid.*, **98**, 7510 (1976). (g) K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, 1965, pp 282–285.

(8) (a) H. Allgeier, M. G. Siegel, R. C. Helgeson, E. Schmidt, and D. J. Cram, *J. Am. Chem. Soc.*, **97**, 3782 (1975). (b) The colloquial nomenclature is self-evident: pseudo-*gem* denotes two transannularly adjacent position on the benzene rings; pseudo-ortho, pseudo-meta, and pseudo-para specify ortho, meta, and para relationships displaced from the usual homoannular into a transannular context.

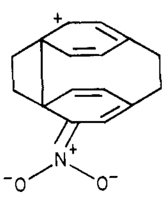
(9) H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, **91**, 3505 (1969).

(10) P. R. Wells, "Linear Free Energy Relationships", Academic Press, New York, 1968, p 3.

situated meta to one another but substantial when situated in a para relationship. Correlations of Ψ-meta- and Ψ-substituted 4-carboxy[2.2]paracyclophanes with those literature substituent constants in which resonance interactions between substituent and reaction center play a small role, or are entirely absent, range from satisfactory to excellent. Poor correlations are obtained with these carboxylic acid series when they are compared with literature substituent constants for which resonance contributions are substantial. Thus, literature σ_m values consistently give better correlations than literature σ_p values. This observation clearly indicates that resonance interactions are not involved in the heteroannular transmission of substituent effects from either the Ψ-meta or Ψ-para positions to the reaction center in the case of the substituted 4-carboxy[2.2]paracyclophanes.

The correlations of substituent constants found for the substituted 4-amino[2.2]paracyclophanes with σ_m literature values are also seen to be better than for the corresponding σ_p values, but the difference is not as large in these series as it is in the heteroannularly substituted 4-carboxy[2.2]paracyclophane series.

On the basis of the structures and isolated yields obtained in the dinitration of [2.2]paracyclophane, Cram et al.[3b] have previously postulated that transannular resonance contributions such as shown in structures **4** and **5** might be involved. If these resonance structures do play a role in transmittance of substituent effects between the benzene rings, it should be the Ψ-meta series, and not the Ψ-para series, which would be expected to correlate well with literature σ_p constants containing resonance contributions. In fact, it is the Ψ-para-substituted 4-amino[2.2]paracyclophanes that show reasonable correlations with literature σ_p constants. The correlation with Ψ-meta-substituted 4-amino[2.2]paracyclophanes is only fair. While it might be proposed that a mesomeric structure such as **6** may be responsible for the reasonable correlation found for the Ψ-para series with σ_p literature constants, lack of such an effect in the Ψ-para-substituted 4-carboxy[2.2]paracyclophane series argues against this.



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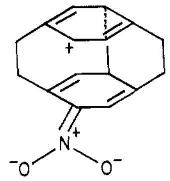

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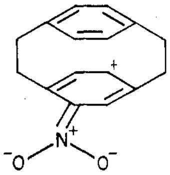

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Several approaches have been suggested to evaluate the relative importance of field and resonance effects of substituents in a particlar reaction series. With eq 4,[11-13] Swain and Lupton[13] have

$$\sigma = fF + rR \qquad (4)$$

used statistical models to derive substituent constants F and R from experimentally determined literature substituent constants.[14-17] Constants F and R are the field and resonance contributions, respectively, of a particular substituent and are independent of the substituent constant series from which they were derived, and f and r are weighing factors. This derivation assumes that the substituent constants obtained from 4-substituted bicyclo[2.2.2]octanecarboxylic acids contained only field-effect contributions. It was also assumed that the trimethylammonium substituent interacts with reaction centers only through a field effect. Dewar and Grisdale[21] have derived substituent constants F and M, using eq 5. M is a measure of the combined π in-

$$O_{ij} = F/r_{ij} + Mq_{ij} \qquad (5)$$

ductive–mesomeric effect of the substituent, F is a measure of the field set up by a substituent at position i, and r_{ij} is the distance between atoms i and j and q_{ij} is the formal charge at position j produced by the group CH_2^- at position i. Brown and Okamoto[18] determined substituent constants (σ^+) from the solvolysis of *tert*-cumyl chlorides in order to evaluate the magnitude of interaction of a substituent with a catonic center, and substituent constants for the dissociation of phenols[22] (σ^-) have been determined to access substituent interaction with an anionic center. In both cases, the subscripts m and p refer to substituents located meta or para to the reaction center. As discussed above, resonance contributions of these substituent constants are assumed to be slight or absent when located in the meta position but substantial from the para position. Where applicable, the superscript "small zero" indicates that an insulating group has been introduced somewhere between the substituent and the reaction center to reduce resonance interactions between them. In order to quantitatively separate inductive from resonance effects, Taft introduced the substituent constants σ_I and σ_R.[23,24] The σ_I constants were derived from reactions of aliphatic substrates and are assumed to contain only inductive (field) contributions. The σ_R constants were determined from eq 6 and are assumed to primarily contain resonance con-

$$\sigma_R = \sigma - \sigma_I \qquad (6)$$

tributions. The poor correlations found for both the acid and amine [2.2]paracyclophane series with substituent constants considered to reflect large resonance contributions (vida supra) argues against transannular resonance and mesomeric effects.

Table V. Parameters Used for the Electrostatic Analysis of the Pseudo-Para and Pseudo-Meta [2.2]Paracyclophane Carboxylic Acids

	substituent	μ, D	R, Å	θ
pseudo meta	H	0.40	7.28	26°6'
	Br	2.20	8.05	24°4'
	CN	3.90	8.68	22°3'
	CO_2H	2.14	9.02	21°1'
	NO_2	3.55	8.10	23°5'
pseudo para	H	0.40	7.58	23°1'
	Br	2.20	8.37	20°5'
	CN	3.90	8.96	22°2'
	CO_2H	2.14	9.37	18°2'
	NO_2	3.55	8.43	20°4'

In the carboxylic acid series, satisfactory to excellent correlations are found with literature substituent constants obtained from 4-substituted bicyclo[2.2.1]heptane ($\sigma_{[2.2.1]}$) and bicyclo[2.2.2]-octane ($\sigma_{[2.2.2]}$) carboxylic acids. Substituent effects in these cases are felt to be transmitted to the reaction center by means of an electrostatic field model.[25] Further evidence that transannular interaction by 4-carboxy[2.2]paracyclophane substituents and also by substituents in the amine series proceeds through a field effect is seen in the good correlation of substituent constants for these systems with literature substituent constants which are assumed to represent only field-effect contributions (vida supra).

Electrostatic Analysis. The ratio of the dissociation constants

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(11) O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966).

(12) C. F. Wilcox and C. Leung, *J. Am. Chem. Soc.*, **90**, 336 (1968).

(13) C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968).

(14) R. W. Traft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).

(15) A. Bryson, *J. Am. Chem. Soc.*, **82**, 4871 (1960).

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

(17) F. W. Baker, R. C. Parish, and L. M. Stock, *J. Am. Chem. Soc.*, **89**, 5677 (1967).

(18) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

(19) J. Hine, *J. Am. Chem. Soc.*, **82**, 4877 (1960).

(20) A. Bryson and R. W. Matthews, *Aust. J. Chem.*, **16**, 401 (1963).

(21) M. J. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).

(22) L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **85**, 3397 (1963).

(23) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

(24) R. W. Taft, Jr. *J. Phys. Chem.*, **64**, 1805 (1960).

(25) H. P. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **86**, 5186 (1964).

Table VI. Experimental and Calculated Log (K_X/K_H) Values for Pseudo-Para and Pseudo-Meta Paracyclophane Carboxylic Acids

	substituent	D_E	log (K_X/ K_H) (calcd)	D_E	log (K_X/ K_H) (calcd)	log (K_X/ K_H) (exptl)
pseudo meta	H	5.08	0.00	3.95	0.00	0.00
	Br	5.43	0.23	3.95	0.33	0.25
	CN	5.61	0.39	3.95	0.55	0.57
	CO_2H	5.75	0.17	3.95	0.26	0.16
	NO_2	5.46	0.41	3.95	0.56	0.59
pseudo para	H	4.81	0.00	3.35	0.00	0.00
	Br	4.98	0.24	3.35	0.36	0.19
	CN	5.05	0.40	3.35	0.61	0.55
	CO_2H	5.25	0.18	3.35	0.28	0.18
	NO_2	5.00	0.42	3.35	0.63	0.63

of a dipolar substituted carboxylic acid relative to the parent (H substituted) acid may be calculated by means of the electrostatic eq 7, where μ is the bond or group moment of the substituent

$$\log (K_X/K_H) = (e\mu \cos \theta)/(2.3kTR^2D_E) \qquad (7)$$

relative to the moment of the carbon–hydrogen bond, R is the distance between the center of the dipole and the reaction center, θ is the angle between R and the substituent dipole, D_E is the "effective" dielectric constant as calculated by means of the Kirkwood–Westheimer cavity treatment, and e, k, and T have their usual meaning.[7] Table V summarizes the parameters used for the pseudo para and pseudo meta [2.2]paracyclophane carboxylic acids. Table VI summarizes the experimental and calculated log (K_X/K_H) values. In these analyses all parameters except D_E are fixed. D_E was calculated by a variety of methods. (1) Tanford[7] has suggested that when analyzing for the interaction of a dipole with a reaction center, the center of the dipole should be placed 1.5 Å below the surface of the cavity in the calculation of D_E. These values are shown in column 1 of Table VI along with the corresponding log (K_X/K_H) values. The agreement is only fair. It appears that this method overestimates D_E. This is perphaps what should be expected in light of the fact that Tanford's suggestion was specifically for ionization processes in the solvent water (D = 78). In the present case we are dealing with solvent of dielectric constant equal to 32. (2) The calculation of D_E from spherical volumes obtained by the application of Traube's rule produced log (K_X/K_H) values in poor agreement with the experimental values.[7g] Again we are deailing with a solvent system of low dielectric constant where Traube's rule may not be expected to work. (3) Plots of log $(K_X/K_H)_{exp}$ vs. $\mu \cos \theta/R^2$ should produce a strainght line if the electrostatic model can adequately describe the ionization process for the pseudo para and pseudo meta [2.2]paracyclophane carboxylic acids. The slope should be equal to $e/2.3kTD_E$ from which D_E may be easily calculated. Such plots were made and D_E values of 3.95 and 3.35 D were obtained for the pseudo meta and pseudo para paracyclophane carboxylic acids, respectively. These are shown in column 3 of Table VI along with the calculated log (K_X/K_H) values. Agreement is quite good between the experimental and calculated values, indicating that the electrostatic model adequately describes the relative dissociation constants of these acids.[26]

It is very interesting to compare the calculated results for the pseudo meta and pseudo para acids. As one proceeds from the former to the latter, the distance between the center of the dipole and the reaction center increases, while the angle θ decreases.[26i,j] This partial compensation produces log $(K_X/K_H)_{calcd}$ values very close to one another.

In conclusion, it appears that both the empirical and electrostatic analyses suggest very strongly that ground-state transannular interaction between the benzene rings of the substituted [2.2]-paracyclophane carboxylic acids and amines is predominantly, if not totally, one of a field effect. This conclusion supports Acevedo and Bowden's[27] recently reported electrostatic analysis of the pK_a values of four pseudo-substituted bromo- and unsubstituted 4-carboxy[2.2]paracyclophanes.

Experimental Section

Paracyclophane Derivatives. The preparation and characterization of the compounds used in this study have been reported.[8a] Analytically pure samples were employed in the measurements reported in Table I and II.

Potentiometric Determination of Acidities. The procedure used was that of Albert and Serjeant.[28] A Radiometer Model PH4M pH meter, calibrated in 0.01 pH unit and accurate to ±0.002 pH unit, was used in conjunction with an A.H. Thomas combination electrode. The acids were weighed on a Cahn microbalance and then added to the titration flask, followed by 15 mL of 2-methoxyethanol–water (80/20, w/w). The solutions titrated were approximately 5×10^{-4} M. The potassium hydroxide solution was decarbonated by treatment with barium hydroxide. Residual barium ions were removed by use of Amberlite ion-exchange resin IR-120H, which had previously been converted to the K^+ form. This solution was then standarized against potassium hydrogen phthalate, primary standard, which had been dried for 1 h at 120 °C. Phenolphthalein was used as indicator. The concentration, after standardization against three different solutions, was found to be 0.1618 ± 0.0004 N in potassium hydroxide. A 0.1303 ± 0.001 N hydrochloric acid solution was used for the titration of amines. A Glimont microburet, accurate to ±0.0002 mL, was used for addition of titrant. The buret tip was immersed in the acid solution and remained there throughout the titration. After each addition of base, the solution was stirred magnetically for 1 min. Stirring was then stopped, and the pH was read after the system had come to equilibrium. This generally required 2–4 min. The pH meter was calibrated against pH 7 buffer prior to and immediately following each titration. In no case did the final pH of the buffer differ from its initial pH by more than 0.02 pH unit. The solution was kept under a positive pressure of argon during each titration. All determinations were conducted at 25 ± 0.5 °C.

Spectrophotometric determination of Acidities. The procedure used was that of Albert and Serjeant.[28] A solution approximately 10^{-3} M in the amine whose pK_a value was to be determined was made with 2-methoxyethanol–water (80/20, w/w) as solvent. This stock solution was then added to nine 5-mL volumetric flasks in 0.5-mL amounts. One flask was filled to the mark with a solution made by mixing 1.76 mL of concentrated hydrochloric acid, 7.24 mL of 2-methoxyethanol, and 0.5 mL of 2-methoxyethanol–water (80/20, w/w). A second flask was filled to the mark with a solution made by mixing 1.76 mL of Mallinckrodt pH 10.00 buffer, 7.24 mL of 2-methoxyethanol, and 0.5 mL of 2-methoxyethanol–water (80/20, w/w). Ultraviolet spectra were then taken of these solutions, and the wavelength where the difference in spectra was greatest was chosen as the analytical wavelength.

The seven remaining flasks were then filled to the mark with solutions of known pH values. These solutions were made by adding acid to a 2-methoxyethanol–water (80/20, w/w) solution that was 0.01 N in formic acid.

A Beckman DU spectrophotometer was set to the analytical wavelength, and optical densities for the amine in strong acid (solution 1), d_I, and a strong base (solution 2), d_M, were determined. The optical density, d, of the solutions in each of the remaining flasks was then determined, and the pH of these solutions were recorded. Measurements of pH were made at 31 °C with the cuvettes still in the spectrophotometer. Acidities were determined by means of eq 8. Using all seven pK_α values, we

$$pK_a = pH + \log (d - d_M)/(d_I - d) \qquad (8)$$

determined an average pK_a value. The error in this value was taken as the difference between this value and the value deviating furthest from it.

Calculations. The calculations to determine distances and angles were carried out by using three-dimensional vector analysis and trigonometry. The bond lengths and angles used in the calculations were based upon the X-ray analyses of the solid-state structure of the [2.2]para-

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(26) (a) J. D. Roberts and W. T. Moreland, *J. Am. Chem.* Soc., **75**, 2167 (1953); (b) S. Siegel and J. M. Kormarmy, *ibid.*, **82**, 2547 (1960); (c) L. M. Stock and H. D. Holtz, *ibid.*, **86**, 5188 (1964); (d) F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967); (e) L. M. Stock, *J. Chem. Educ.* **49**, 400 (1972); (f) E. J. Grubbs, R. Fitzgerald, R. E. Phillips, and R. Petty, *Tetrahedron*, **27**, 935 (1971); (g) C. L. Liotta, W. F. Fisher, E. L. Slighton, and C. L. Harris, *J. Am. Chem. Soc.*, **94**, 2129 (1972); (h) C. T. Wang and E. J. Grubbs, *J. Org. Chem.*, **42**, 534 (1977); (i) C. L. Liotta, W. F. Fisher, and C. L. Harris, *Chem. Commun.*, 1312 (1971); (j) C. L. Liotta, W. F. Fisher, G. H. Greene, and Jr., and B. L. Joyner, *J. Am. Chem. Soc.*, **94**, 4891 (1972).

(27) S. Acevedo and K. Bowden, *J. Chem. Soc., Chem. Commun.*, 608 (1977).

(28) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Butler and Tanner, Ltd., London, 1962.

cyclophane.[1,2] The lengths of dipoles were considered to be standard C–X bond distances when X was a single atom. When X was a group of atoms, the dipole length was considered to be the maximum extension of the group as projected on the C–X bond axis. The dipole lengths used were C–H (1.09 Å), C–CN (2.62 Å), C–Br (1.94 Å), and CO_2R (2.99 Å). The position of the ionizable hydrogen was fixed at 1.45 Å beyond the carboxyl carbon on the extension of the C–C bond in accordance with the suggestion of Kirkwood and Westheimer.[7]

Bond or group moments were assessed from data tabulated by Smyth[29] for the dipole moments of substituted methanes in benzene solution. It is suggested that these values be used as they present a better interpretation than those based on gas-phase measurements.[29] It has been assumed that the bond moment of the C–H bond is 0.4 with hydrogen as the negative terminus.[7] Symth[29] devotes considerable discussion to this point and concludes that popular opinion supports 0.4 as the magnitude, but the controversy continues over the direction.

The effective dielectric (D_E) was calculated by the spherical cavity model of Kirkwood and Westheimer,[6] assuming an external dielectric of 32 and an internal dielectric of 2. The center of the dipole was placed 1.5 Å below the surface of the cavity, according to the suggestion of Tanford.[7c] This procedure fixes the cavity dimensions so that the effective dielectric may be calculated from the tabulations of Westheimer, Jones, and Lad.[7d]

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(29) C. P. Smyth, "Dielectric Behavior and Structure", McGraw-Hill, New York, 1955, pp 244–270.

"Mercaptan-Tail" Porphyrins: Synthetic Analogues for the Active Site of Cytochrome P-450[1]

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Abstract: The synthesis and characterization of a series of tetraarylporphyrins which bear covalently attached alkyl and aryl mercaptans designed to serve as axial ligands are described. The coordination chemistry of the iron(II) complexes of these "mercaptan-tail" porphyrins has been investigated by ^1H NMR, IR, and electronic absorption spectroscopy, magnetic circular dichroism, and magnetic susceptibility measurements. Ferrous complexes of the alkyl mercaptan-tail porphyrins appear to remain four-coordinate, intermediate spin ($S = 1$) in solution. The situation is less clear in the case of appended aryl mercaptans and a "tail-on/tail-off" equilibrium is implicated. In the presence of carbon monoxide, however, binding of thiol trans to CO is observed in both the alkyl and aryl cases. By the addition of an appropriate base, six-coordinate mercaptide–Fe(II)–CO complexes can be generated; these reproduce quite well the characteristic absorption and MCD spectra of cytochrome P-450, suggesting that such compounds are indeed viable models for the active site of cytochrome P-450.

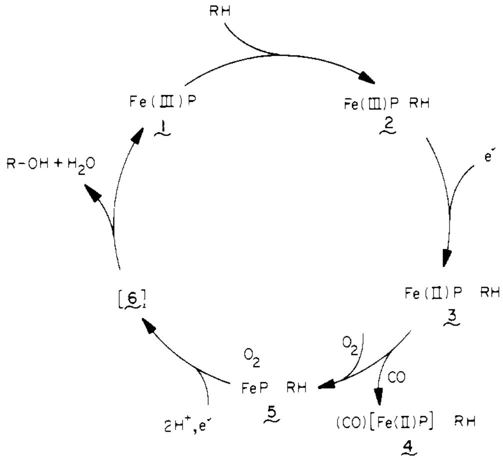
Introduction

The activation of molecular oxygen has been a topic of considerable interest in recent years.[2-5] Despite the simplicity of the O_2 molecule, the chemist's ability to direct one or both atoms of dioxygen into an organic substrate in a highly specific manner remains severely limited. Biological systems, however, carry out reactions of this type readily and efficiently;[2,6-8] an understanding of the molecular dynamics of such systems thus might prove invaluable in designing simpler, synthetically useful oxidation catalysts.

We have been particularly interested in a class of enzymes known collectively as "cytochrome P-450".[9,10] These heme proteins are monooxygenases—i.e., they catalyze the hydroxylation of a substrate RH at the expense of molecular oxygen, through the reductive cleavage of the O–O bond:

$$R\text{-}H + O_2 \xrightarrow{2e^-, 2H^+} R\text{-}OH + H_2O \qquad (1)$$

Scheme I



Cytochrome P-450, found in plants, animals, and bacteria, participates in numerous metabolic pathways. Of particular importance in mammalian systems are the roles played by P-450

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(1) This paper is abstracted from the Ph.D. thesis of S.E.G., Stanford University, 1980.

(2) Hayaishi, O., Ed. "Molecular Mechanisms of Oxygen Activation"; Academic Press: New York, 1974.

(3) Groves, J. T. In *Adv. Inorg. Biochem.* **1979**, *1*, 119–142.

(4) Taube, H. *J. Gen. Pysiol.* **1965**, *49*, 29–50.

(5) Ullrich, V. *J. Mol. Catal.* **1980**, *7*, 159–167.

(6) Boyer, P. D., Ed. "The Enzymes"; Academic Press: New York, 1975; Vol. XII, Part B.

(7) Jerina, D. M.; Daly, J. W. In "Oxidases and Related Redox Systems"; King, T. E., Mason, H. S., Morrison, M., Eds.; University Park Press: Baltimore, 1973; Vol. 1, pp 143–161.

(8) Boyd, G. S.; Smellie, R. M. S., Eds. "Biological Hydroxylation Mechanisms"; Academic Press: New York, 1972.

(9) Sato, R.; Omura, T., Eds. "Cytochrome P-450"; Academic Press: New York, 1978.

(10) White, R. E.; Coon, M. J. *Annu. Rev. Biochem.* **1980**, *49*, 315–356.

0002-7863/82/1504-1391$01.25/0