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Macro Rings. XXVI. [2.2]Paracyclophanyl as a Neighboring Group[1]

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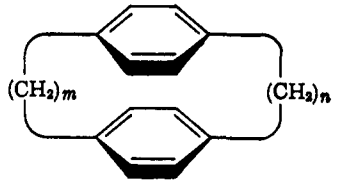
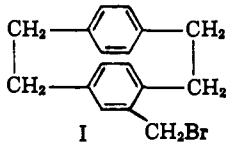
The ability of [2.2]paracyclophane to act as a neighboring group when attached to C_α or C_β of a carbonium ion-forming system has been determined through reactivity comparisons of I, II, III and IV. Solvolysis rate measurements and activation parameters demonstrated that the [2.2]paracyclophanyl system is a better neighboring group in solvolytic reactions than its open-chain counterpart. Hydrolysis of optically pure bromide I in 80% dioxane–20% water gave optically pure alcohol, which demonstrated that the transannular ring participated in carbonium ion formation only through π–σ charge delocalization. Deuterium at C_α in IV was found to be scrambled in the acetolysis (46% C_β-D) and hydrolysis (26% C_β-D) products. Deuterium at C_α in III was not disturbed during acetolysis or formolysis, in the latter case under conditions where carbonium ion was formed repeatedly. Clearly the transannular ring was involved in carbonium ion formation only through π–σ charge delocalization. Although a paracyclophanyl phenonium ion was undoubtedly involved, it must have opened for steric reasons only in the direction from which it was formed.

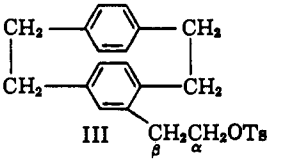
Earlier studies of the relationship between structure and reactivity of the [*m.n*]paracyclophanes have established that π-base strength,[2] susceptibility to electrophilic substitution[3,4] and to catalytic hydrogenation[4] were a function of the values of *m* and *n*.

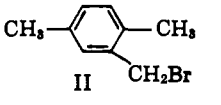


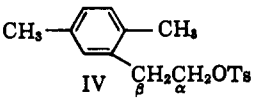
Other evidence of transannular effects was found in spectral abnormalities[2b,5] and in abnormal bond angles and lengths in crystal structures.[6]

The ability of the [2.2]paracyclophanyl structure to act as a neighboring group in solvolysis reactions is the subject of the present study. The relative reactivities of I and II, and of III and IV, have been determined through kinetics of hydrolysis, acetolysis and ethanolysis. The special symmetry properties of I have been used to determine whether the transannular ring becomes involved in carbonium ion formation. Deuterium labels at C_α in III and IV have been used to find if C_α and C_β exchange places during solvolysis reactions, and whether the transannular ring becomes involved in carbonium ion formation in III.

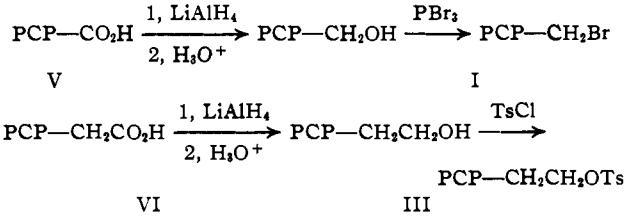








Starting Materials.—Bromide I was prepared in both a racemic and optically active state from acid V, whose resolution has been reported.[4c] Tosylate III was similarly obtained from acid VI.[7] The open-chain model compounds II and IV were prepared through conventional reactions (see Experimental). Substitution of lithium aluminum deuteride for lithium aluminum hydride in the reduction step provided III and IV deuterated in the α-positions.



Solvolysis of Bromides I and II.—The kinetics of hydrolysis of bromides I and II were carried out in 80% dioxane–20% water at 36.4° and 52.4°. Reaction rates were followed by titrating the acid produced with standard base. No salt was added in any of the runs, since good first-order kinetics were observed through 50% reaction in all cases. Drifts in rates were observed after this point due to the effect of the liberated hydrobromic acid. The rate constants of Table I were calculated from a minimum of 8 points. Activation parameters for bromide hydrolysis are also included in Table I. Similar hydrolysis of optically pure bromide I gave the corresponding alcohol with complete retention of configuration.

Solvolyses of tosylates III and IV were followed with titration procedures at two temperatures in acetic acid, 80% acetone–20% water and absolute ethanol. No salt was added, and good first-order kinetics were observed through one half-life, after which drifts in rate were observed due to the liberated *p*-toluenesulfonic acid. The rate constants and activation parameters reported in Table I were calculated from at least eight points taken before rate drift occurred.

Acetolysis of tosylate IV, 97% deuterated at C_α (carbon carrying the tosyl group), was conducted at 100° for 48 hr. The acetate ester produced was cleaved with lithium aluminum hydride to give 2-(2,5-dimethylphenyl)-ethanol, which was analyzed for isotope scrambling with n.m.r. techniques. Peak assignments for α- and β-methylene protons were made through comparison of the spectra of authentic α-deuterated alcohol and non-deuterated material. A similar experiment was conducted in 80% acetone–20% water at 95.8° for 72 hr. Table II records the results.

Tosylate III, 97% deuterated at C_α, was acetolyzed at 98° for 48 hr. The acetate produced was reduced with lithium aluminum hydride to the corresponding alcohol, which was analyzed for isotopic scrambling with n.m.r. techniques. The curves for non-deuterated alcohol, α-deuterated alcohol and for the alcohol

(1) This investigation was supported by a grant from the National Science Foundation.

(2) (a) D. J. Cram and R. H. Bauer, *J. Am. Chem. Soc.*, **81**, 5971 (1959); (b) D. J. Cram, *Rec. Chem. Progr.*, **20**, 71 (1959).

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

(4) (a) D. J. Cram and J. Abell, *ibid.*, **77**, 1179 (1955); (b) D. J. Cram and R. W. Kierstead, *ibid.*, **77**, 1186 (1955); (c) D. J. Cram and N. L. Allinger, *ibid.*, **77**, 6289 (1955).

(5) (a) J. S. Waugh and R. W. Fessenden, *ibid.*, **79**, 847 (1957); (b) S. Weissman, *ibid.*, **80**, 6462 (1958).

(6) (a) C. J. Brown, *J. Chem. Soc.*, 3265, 3279 (1953); (b) P. K. Gantzel, C. L. Coulter and K. N. Trueblood, *Angew. Chem.*, **72**, 755 (1960).

(7) D. J. Cram, R. H. Bauer, N. L. Allinger, R. A. Reeves, W. J. Wechter and E. Heilbronner, *J. Am. Chem. Soc.*, **81**, 5977 (1959).

TABLE I

FIRST-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR SOLVOLYSES OF BROMIDES I AND II AND TOSYLATES III AND IV

Run	Cmpd	T, °C.	Solvent	$k \times 10^6$, sec.$^{-1}$	$\Delta H^{\pm}$, kcal./mole[a]	$\Delta S^{\pm}$, e.u.[b]
1	I	34.6	80% dioxane–20% water[c]	13.3 ± 1.5	21.1	−12
2	I	52.4	80% dioxane–20% water[c]	94.0 ± 0.40		
3	II	34.6	80% dioxane–20% water[c]	2.33 ± 0.16	18.9	−22
4	II	52.4	80% dioxane–20% water	13.5 ± 1.3		
5	III	74.8	Acetic acid	5.11 ± 0.33	24.7	−11.7
6	III	110.5	Acetic acid	160 ± 9		
7	III	76.6	80% acetone–20% water[d]	9.68 ± 0.31	23.2	−15.0
8	III	95.5	80% acetone–20% water[d]	56.7 ± 2.6		
9	III	74.9	Ethanol	11.1 ± 0.6	21.6	−18.8
10	III	95.8	Ethanol	69.3 ± 3.8		
11	IV	74.8	Acetic acid	0.89 ± 0.08	26.1	−11.1
12	IV	110.5	Acetic acid	33.9 ± 1.2		
13	IV	76.6	80% acetone–20% water[d]	2.33 ± 0.29	22.2	−20.2
14	IV	95.8	80% acetone–20% water[d]	13.0 ± 1.7		
15	IV	74.9	Ethanol	4.61 ± 0.26	21.3	−21.4
16	IV	95.8	Ethanol	27.8 ± 1.9		

[a] Probable error ±1.5 kcal./mole. [b] Probable error ±2.0 e.u. [c] Weight %. [d] Volume %.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA[a]

Compound[b]	Source	—Ar–H— τ[c]	—Ar–H— No. H's	Bridge–CH_2 τ[c]	Bridge–CH_2 No. H's	—α-CH_2— τ[c]	—α-CH_2— No. H's	—β-CH_2— τ[c]	—β-CH_2— No. H's	—C–OH— τ[c]	—C–OH— No. H's	—CH_3— τ[c]	—CH_3— No. H's	—O_2CH— τ[c]	—O_2CH— No. H's	Total H's	Recovery, %
$PCPCH_2CH_2OH$	Direct synth.	3.7	..	7.0	7.37[e]	6.5	2.37[e]	7.3	2.08	7.8	1.02	..	..	..	..	12.74[d]	..
$PCPCH_2CD_2OH$	Direct synth.	3.7	..	7.0	7.28[e]	6.5	0	7.5	2.72[e]	8.1	1.04	..	..	..	..	11.04[f]	..
$PCPCH_2CD_2OH$	Acetol. deut.-III	3.7	..	7.0	7.42[e]	6.5	0	7.4	2.96[e]	8.0	1.02	..	..	..	..	11.40[f]	0
$PCPCH_2CH_2O_2CH$	Formol. III	3.6	6.86	7.0	8.35[e]	5.9	1.89	7.2	1.66[e]	..	..	..	..	2.1	0.95	19.71[g]	..
$PCPCH_2CD_2O_2CH$	Formol. deut.-III	3.6	7.10	7.0	7.30[e]	5.9	0	7.2	2.83[e]	..	..	..	..	2.1	.89	18.12[h]	0
$DPCH_2CH_2OH$	Direct synth.	3.2	..	..	..	6.3	..	7.3	..	6.9	..	7.8	..	..	..	....	..
$DPCH_2CD_2OH$	Direct synth.	3.2	2.99	..	..	..	..	7.3	1.92	6.9	1.05	7.8	5.90	..	..	11.86[i]	..
$DPCH_2CD_2OH$ / $DPCD_2CH_2OH$	Acetolysis deut.-IV	3.2	3.10	..	..	6.3	0.94	7.3	1.10	6.9	1.07	7.8	5.96	..	..	12.16[i]	46
$DPCH_2CD_2OH$ / $DPCD_2CH_2OH$	Hydrolysis deut.-IV	3.2	2.86	..	..	6.3	0.54	7.3	1.51	6.9	0.96	7.8	6.15	..	..	12.01[i]	26

[a] Varian Associates model A-60 n.m.r. spectrophotometer; ~1 M solutions in carbon disulfide, with tetramethylsilane as internal standard. [b] PCP = 4-[2.2]paracyclophanyl; DP = 2,5-dimethylphenyl. [c] When peaks are split, their centers are reported. [d] Theoretical total 13.00 H, aromatic H not included. [e] Overlap between position of bridge CH_2's and α- and β-CH_2's made an exact analysis difficult. [f] Theoretical total 11.00 H, aromatic H not included. [g] Theoretical total 20.00. [h] Theoretical total 18.00. [i] Theoretical total 12.00.

from the acetolysis experiment were compared, and the two latter curves proved identical (see Table II). Thus no scrambling occurred during acetolysis. In a second experiment, deuterated tosylate III was solvolyzed in formic acid, 0.01 M in p-toluenesulfonic acid, for 24 hr. at 100°. Non-deuterated III was subjected to the same treatment. Although these conditions should lead to repeated carbonium ion formation, comparison of the n.m.r. curves demonstrated that no isotopic scrambling occurred during formolysis of deuterated III (see Table II).

Discussion

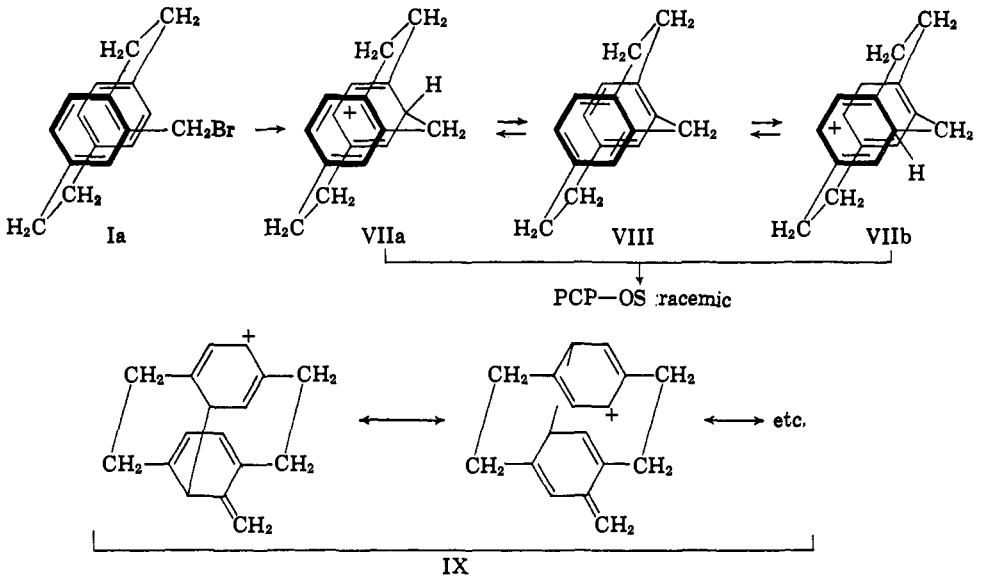
Charge Delocalization into Paracyclophane Nucleus.—Comparison of the rates of hydrolysis of the paracyclophanylmethyl bromide (I) and its open-chain model II indicates that the former system reacts 6–7 times faster than its model, which does not contain the transannularly located benzene ring. More striking than this relatively small rate factor is the comparison between $\Delta H^{\pm}$ and $\Delta S^{\pm}$ for the two systems. The open-chain bromide has a lower $\Delta H^{\pm}$ by about 2 kcal., but $\Delta S^{\pm}$ for the paracyclophanyl bromide is less negative by 10 e.u. Others[8] have thoroughly established that in solvolysis of β-arylethyl tosylates, the magnitude of entropy of activation is a reliable indication of the balance between neighboring aryl and solvent participation in carbonium ion formation (see Table III). In those solvents and systems in which aryl involvement dominated, entropies of approximately −9.2 e.u. were observed, whereas when solvent involvement dominated, entropies of about −18 e.u. were obtained. Although arylmethyl and not 2-arylethyl systems are involved, and although the scale is moved toward more negative entropies by 3–4 e.u., the data point toward a similar effect in acetolysis of I and II. The shift in scale could be due to the steric effect of the *ortho*-substituents in bromides I and II. Thus aryl participation (charge delocalization) is much more important in the ionization of the paracyclophanyl bromide than in its open-chain model.

A number of different factors are probably responsible for this difference in I and II. Bromide I is much more hindered than II, since the transannularly located ring in I effectively blocks solvent approach from one whole side of the incipient carbonium ion. In spite of this effect, the rate of solvolysis of I exceeds that of II, so electron release of the paracyclophanyl group to the incipient carbonium ion must more than compensate for steric inhibition of solvation.

The question arises as to the relative magnitude of the inductive effect of the [2.2]paracyclophanyl and 2,5-dimethylphenyl groups. The difference is too small to produce any difference in chemical shift for the methylene protons alpha to the ring in $PCPCH_2CH_2OH$ and $DPCH_2CH_2OH$. Both have τ-values of 7.3 (Table II). The near identity of the pK_a's of the paracyclophanecarboxylic acids whose bridges each contained 2, 4 and 6 methylene groups also points to the absence of a unique inductive effect in the [2.2]paracyclophanyl group.[7]

In a formal sense, charge could be distributed into the second ring of the paracyclophanyl carbonium ion

(8) S. Winstein and R. Heck *J. Am. Chem. Soc.*, **78**, 4801 (1956), and earlier papers.



by either of two means. In the first, the remote ring could itself participate directly in bromide displacement to give a transannularly bridged carbonium ion such as VIIa. In the second, the near ring could relay positive charge to the remote ring by σ–π resonance interactions as is visualized in IX. The fact that optically pure bromide Ia produced no racemized product indicates that if VIIa was indeed formed, it did not go to VIII (plain of symmetry) or VIIb (enantiomeric to VIIa). Otherwise racemized product would have been obtained.

Table III presents the data from the literature as well as that from the present investigation.

The 2-(2,5-dimethylphenyl)-ethyl tosylate (IV) system exhibits the same correlation between solvent nucleophilicity, neighboring group participation and $\Delta S^{\pm}$ as do the other tosylates. In acetic acid IV gives a $\Delta S^{\pm}$ of -11.1 e.u. and 92% aryl participation; in 80% acetone–20% water, $\Delta S^{\pm} = -20.2$ e.u. and aryl participation dropped to 52%. Thus it is safe to conclude that $\Delta S^{\pm}$ values can be used as an index of β-aryl participation in the paracyclophane system III.

TABLE III

CORRELATIONS BETWEEN REARRANGEMENT AND $\Delta S^{\pm}$ IN SOLVOLYSIS OF β-ARYLETHYL TOSYLATES

Compound	Solvent	$\Delta S^{\pm}$, e.u.	% Ar partic.	Ref.
$C_6H_5C^{14}H_2CH_2OTs$	HCO_2H	− 9.5	90	8,9b
$C_6H_5C^{14}H_2CH_2OTs$	CH_3CO_2H	−17.3	10	8,9b
$C_6H_5C^{14}H_2CH_2OTs$	C_2H_5OH	−20.2	1	8,9b
$C_6H_5CH_2CD_2OTs$	HCO_2H	− 9.5	~90	8,9c
$C_6H_5CH_2CD_2OTs$	CH_3CO_2H	−17.3	~10	8,9c
p-$CH_3OC_6H_4CH_2C^{14}H_2OTs$	HCO_2H	− 9.2	100	9a
p-$CH_3OC_6H_4CH_2C^{14}H_2OTs$	CH_3CO_2H	− 8.8	100	9a
p-$CH_3OC_6H_4CH_2C^{14}H_2OTs$	C_2H_5OH	−15.5	48	9a
2,5-$(CH_3)_2C_6H_3CH_2CD_2OTs$	CH_3CO_2H	−11.1	92	Present investigation
2,5-$(CH_3)_2C_6H_3CH_2CD_2OTs$	80% $(CH_3)_2CO$–20% H_2O	−20.2	52	Present investigation
2,5-$(CH_3)_2C_6H_3CH_2CD_2OTs$	C_2H_5OH	−21.4	..	Present investigation
$PCPCH_2CD_2OTs$	CH_3CO_2H	−11.7	..	Present investigation
$PCPCH_2CD_2OTs$	80% $(CH_3)_2CO$–20% H_2O	−15.0	..	Present investigation
$PCPCH_2CD_2OTs$	C_2H_5OH	−18.8	..	Present investigation

Actually VIIa and IX could be nothing but resonance structures which contribute to the same hybrid. The rigid structure of the ring system permits little flexibility with respect to positions of nuclei. Evidence for π–σ delocalization of charge has been obtained previously in electrophilic substitution of the paracyclophanes.[2a,3,4]

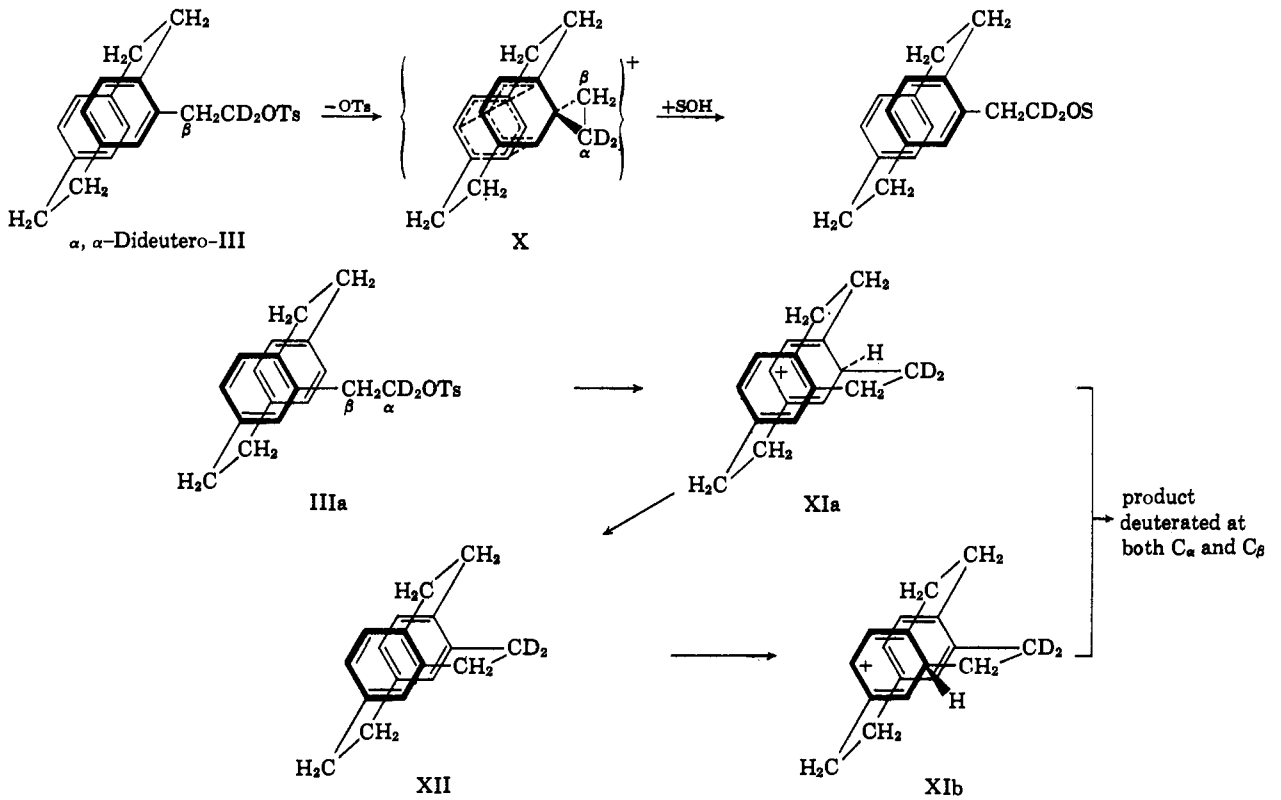
Paracyclophanyl Phenonium Ions.—Comparison of the rates of solvolysis of the two β-arylethyl tosylates III and IV indicates that III, which contains the paracyclophanyl nucleus, solvolyzes from 2.5 to 6 times as fast as its open-chain model IV. More informative with respect to mechanism are the activation parameters.

In previous studies the correlation between entropy and neighboring group *vs.* solvent participation in ionization of 2-arylethyl tosylates depended on isotopic scrambling as a measure of aryl rearrangement.[9] In acetic acid III and IV gave comparable $\Delta S^{\pm}$ values, whereas in acetone–water and ethanol $\Delta S^{\pm}$ values for III were less negative than for IV. Clearly the paracyclophanyl group is better able to aid in ionization from C_β than is the 2,5-dimethylphenyl group. In spite of this fact, the results of solvolysis in acetic and formic acids of α-deuterated-III indicated that no rearrangement occurred even under conditions where ionization occurred repeatedly.

Two types of aryl participation from C_β can be envisioned for the paracyclophane system. In the first, an ethylenephenonium ion[10] is formed in one transition state, and is disposed of by solvent in a second to give product. Examination of molecular models of the paracyclophanyl phenonium ion X indicates that this bridged ion is not symmetrical, and that C_α is far less

(9) (a) E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958); (b) C. C. Lee, G. P. Slater and J. W. T. Spinks, *Can. J. Chem.*, **35**, 1417 (1957); (c) W. H. Saunders, S. Asperger and D. H. Edison, *J. Am. Chem. Soc.*, **80**, 2421 (1958).

(10) (a) D. J. Cram, *ibid.*, **71**, 3863, 3875 (1949); (b) D. J. Cram, *ibid.*, **74**, 2129, 2159 (1952).



hindered than C_β. This steric effect is great enough to indicate that solvent attack would occur exclusively at C_α, and that no rearrangement of isotope originally at C_α would be expected. In the formolysis and acetolysis of III, although the paracyclophanyl group certainly aided in ionization, the bridged ion produced must have opened at the same carbon as was involved in its formation, since no rearrangement was detected. Thus the experimental evidence strongly supports X as a *discrete intermediate*, at least in the formolysis and acetolysis experiments. The fact that paracyclophanyl is a better neighboring group than its open-chain model provides additional evidence that positive charge in one ring of the paracyclophane nucleus is delocalized into the second through π–σ charge delocalization (see X).

In a second type of aryl participation, the benzene ring of the paracyclophane nucleus remote from C_β might have participated directly in ionization to give an intermediate such as XIa. The absence of XII or other compounds in the product, and the fact that the deuterium at C_α remained there makes this type of aryl participation unlikely. Particularly in formic acid under conditions where ionization of each molecule occurred repeatedly, XIa would have equilibrated with its enantiomer XIb and rearranged product would have been obtained.[11]

Experimental

4-(2-Hydroxyethyl)-[2.2]paracyclophane.—The starting material, 4-(carboxymethylene)-[2.2]paracyclophane (VI), was prepared as previously[7]; m.p. 210–212°, reported[7] m.p. 210–210.2°. To a slurry of 0.60 g. of lithium aluminum hydride and 50 ml. of tetrahydrofuran was added dropwise with stirring a solution of 2.8 g. of VI dissolved in 25 ml. of tetrahydrofuran. The mixture was stirred at 25° for 16 hr., and treated with a saturated solution of potassium carbonate in water. The crude product was isolated by the usual method as a yellow oil, which was chromatographed on a 25 by 2.5 cm. column of activated alumina. Product was eluted with 100 ml. of 50% ether–pentane as a white solid, 0.95 g., m.p. 102–103°, unaltered by recrystallization from ether–pentane.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.60; H, 7.92.

4-(2,2-Dideuterio-2-hydroxyethyl)-[2.2]paracyclophane was prepared by the above method except that 97% lithium aluminum deuteride was used. The product gave m.p. 99–100°.

Anal. Calcd. for $C_{18}H_{18}D_2O$: D, 10.00. Found: D, 9.68.

Tosylate of 4-(2-Hydroxyethyl)-[2.2]paracyclophane (III).—A solution of 0.9 g. of the alcohol and 0.95 of *p*-toluenesulfonyl chloride in 5 ml. of dry pyridine was prepared and cooled to 0° for 16 hr. The product was isolated in the usual way to give 0.92 g. of III, m.p. 111–112° from ether–pentane.

Anal. Calcd. for $C_{25}H_{26}O_3S$: C, 73.86; H, 6.45. Found: C, 73.86; H, 6.44.

The tosylate of the deuterated alcohol was similarly prepared, m.p. 110–111°.

4-Hydroxymethylene[2.2]paracyclophane.—To a slurry of 0.69 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran was added dropwise a solution of 3.15 g. of 4-carboxy[2.2]-paracyclophane (V)[4c] (m.p. 223.5–224.5°). The reaction mixture was stirred at room temperature for 6 hr. and the product isolated the usual way to give 1.62 g. of white needles (from ether–pentane), m.p. 154.5–155°.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.77; H, 6.67.

Optically pure acid V,[4c] m.p. 211–212°, $[\alpha]^{25}_{546}$ −198° (*c* 1.0, chloroform) subjected to the same reduction gave alcohol, which after two recrystallizations from carbon tetrachloride gave m.p. 152–153°, $[\alpha]^{25}_{546}$ −78.5° (*c* 1.9, chloroform). From the enantiomeric acid, m.p. 211–212°, $[\alpha]^{25}_{546}$ +189° (*c* 1.0, chloroform), was obtained, after one recrystallization from chloroform–pentane, the corresponding alcohol, m.p. 152–153°, $[\alpha]^{25}_{546}$ + 77.5° (*c* 1.7, chloroform).

4-Bromomethylene[2.2]paracyclophane (I).—To 2.0 g. of PBr_3 in 10 ml. of ether was added 2.0 g. of 4-hydroxymethylene-[2.2]paracyclophane in 40 ml. of ether. The reaction mixture was stirred for 16 hr., and shaken with a mixture of 20 ml. of carbon tetrachloride and water. The organic phase was washed with water, dried, solvent was evaporated, and the white solid produced was recrystallized from carbon tetrachloride–pentane to give 1.50 g. of white flakes, m.p. 141–141.5°.

Anal. Calcd. for $C_{17}H_{17}Br$: C, 67.78; H, 5.69. Found: C, 67.69; H, 5.89.

(11) Had XII been formed, its strain would probably have driven it to lose one of its bridges. Depending on the carbon atom protonated, the product could be a [2.2]para-, [2.2]meta- or [2.2]orthocyclophane. Equilibration would undoubtedly lead to the [2.2]orthocyclophane, which is the least strained and therefore the most thermodynamically stable. Had isotope-rearranged product been isolated, intermediates such as X and XIab could have been differentiated through use of optically active starting materials. With X as intermediate, only optically active product would be produced, whereas with XIab, racemic product would result.

By the same procedure, (+)-4-hydroxymethylene[2.2]paracyclophane gave bromide, m.p. 178.5–179°, $[\alpha]^{25}_{546}$ −31.4 (*c* 4.8, chloroform), and (−)-alcohol gave enantiomeric bromide, m.p. 179.5–180°, $[\alpha]^{25}_{546}$ +37.7° (*c* 3.0, chloroform).

2,5-Dimethylbenzyl Bromide (II).—From 5.0 g. of 2,5-dimethylbenzoic acid (m.p. 133–134°, lit.[12] m.p. 132°) was obtained 3.30 g. of the desired alcohol[13]; m.p. of urethane derivative, 85.5–86.5° (lit.[14] 86°). From 1.5 g. of PBr_3 and 2.0 g. of 2,5-dimethylbenzyl alcohol was obtained 1.63 g. of I as a clear lachrymatory liquid, b.p. (pot temperature) 90° (1 mm.).

Anal. Calcd. for $C_9H_{11}Br$: C, 54.29; H, 5.57. Found: C, 54.32; H, 5.64.

2-(2,5-Dimethylphenyl)-ethanol.—2,5-Dimethylphenylacetic acid (m.p. 125–130°, lit.[15] m.p. 128–129°) was reduced with aluminum hydride to the corresponding alcohol in the usual way. From 5.0 g. of acid was obtained 2.66 g. of alcohol as a colorless liquid, b.p. 84–87° (1 mm.), lit.[16] b.p. 110–113° (5 mm.).

Reduction of the same acid with 97% deuterated lithium aluminum deuteride gave 1,1-dideuterio-2-(2,5-dimethylphenyl)-ethanol.

Anal. Calcd. for $C_{10}H_{12}D_2O$: D, 14.29. Found: D, 13.92.

2-(2,5-Dimethylphenyl)-ethyl Tosylate (IV).—By use of the same method reported above, 1.3 g. of alcohol was converted to 2.0 g. of IV, m.p. 38–39° (recrystallized from ether–pentane at −80°).

Anal. Calcd. for $C_{17}H_{20}SO_3$: C, 67.07; H, 6.62. Found: C, 66.97; H, 6.72.

In the same way, the above deuterated alcohol was converted to its tosylate, m.p. 39.4–40.5°.

Solvents.—Dioxane was refluxed over potassium hydroxide pellets for 16 hr., and fractionally distilled. A middle cut was retained. Glacial acetic acid was refluxed for 16 hr. in the presence of 3% acetic anhydride, and fractionally distilled. A center cut was retained, and was made 1% by weight in acetic anhydride. Karl Fischer titration revealed less than 0.3% water. To 500 ml. of 98% formic acid was added 25 g. of boric acid anhydride, and after the mixture had stood for 48 hr., the mixture was filtered. The filtrate was distilled from Molecular Sieves, a middle fraction being retained, m.p. 100–101°. Absolute ethanol was allowed to stand over type 4A Molecular Sieves (Linde Co.) for 24 hr., and distilled from fresh Sieves. A center cut was retained, which in a Karl Fischer titration showed less than 0.3% water content. Acetone, Baker analyzed reagent (99.5%), was used directly. Methanol, Baker analyzed reagent, was used directly.

Standard Solutions.—Glacial acetic acid was added to a weighed quantity of dry, pure, sodium carbonate in a volumetric flask, which was diluted to the mark to give 0.01002 *N* sodium acetate solution. Clean sodium metal was added to anhydrous methanol. The resulting solution was shown to be 0.00898 *N* in sodium methoxide by standardization against pure potassium acid phthalate.

Kinetics.—Bromides I and II were hydrolyzed in 80% dioxane–water as follows. Solutions of 0.01 to 0.04 *M* substrate in solvent were prepared with solvent equilibrated in the appropriate constant temperature bath. At proper times, aliquots were withdrawn with a pipet, diluted with additional 80% dioxane–water, and titrated with standard sodium hydroxide solution to a phenolphthalein end-point.

In acetolysis of tosylates III and IV, stock solutions of known concentration of substrate (*ca.* 0.01 *M*) were prepared and 5-ml. aliquots were sealed in clean ampoules, which were placed in appropriate constant temperature baths. Zero time was taken at the moment the tubes were immersed. Periodically tubes were removed and quenched in ice-water. The liberated acid was titrated with standard sodium acetate in acetic acid to a light yellow, brom phenol blue (10 drops) end-point.[17]

Ethanolysis of tosylates III and IV was conducted in the same way as the acetolyses except that substrate concentration was lowered to about 0.002 *M* for tosylate I because of solubility limitations. The acid produced was titrated against standard sodium methoxide in methanol to a phenolphthalein end-point.

Hydrolysis of tosylates III and IV in 80% acetone–20% water was conducted the same way as the ethanolysis, the substrate concentrations being *ca.* 0.01 *M*. The produced acid was titrated with sodium methoxide in methanol to a phenolphthalein end-point.

The rate constants (Table I) were calculated by standard procedures from a minimum of 8 points which covered about the first half-life of reaction. In all cases, good first-order plots were obtained.

Hydrolysis of (−)-4-Bromomethylene[2.2]paracyclophane ((−)-I).—To 25 ml. of 80% dioxane–20% water was added 0.199 g. of (−)-I, $[\alpha]^{25}_{546}$ −31.4° (*c* 4.8, chloroform). The mixture was placed in a constant temperature bath at 52.4°, and within 2 hr. the bromide had dissolved. After 24 hr. the reaction mixture was cooled and shaken with a mixture of water and ether. The ether layer was washed three times with sodium chloride solution, dried, and concentrated to a solid, 0.147 g., m.p. 133–138° (80%), $[\alpha]^{25}_{546}$ +83.5° (*c* 2.0, chloroform). One recrystallization of this material from chloroform–pentane gave m.p. 149–152°, $[\alpha]^{25}_{546}$ +85.3° (*c* 2.3, chloroform).

Acetolysis of 1,1-Dideuterio-2-(2,5-dimethylphenyl)-ethyl Tosylate (Deuterated IV).—A solution of deuterated IV, 0.500 g., in 25 ml. of dry acetic acid was held at 100° for 48 hr. The solution was cooled, and shaken with a water–ether–pentane mixture. The aqueous layer was washed with ether–pentane, and the combined organic extracts were washed with water, dried, and concentrated to give 0.35 g. of an oil. This oil was dissolved in ether and added to a slurry of 0.20 g. of lithium aluminum hydride in ether. The mixture was stirred for 10 hr., and a small amount of saturated potassium carbonate solution was added. The resulting mixture was shaken with dilute hydrochloric acid, and the ether layer was washed with water, dilute sodium bicarbonate solution, water, and was dried. The ether was evaporated to an oil, 0.20 g. (80%), which was washed through a short column of alumina with 25% ether in pentane, and the isolated oil was analyzed for deuterium scrambling by n.m.r. techniques (see later section). The results are found in Table II.

Hydrolysis of 1,1-Dideuterio-2-(2,5-dimethylphenyl)-ethyl Tosylate (Deuterated IV).—A solution of 0.500 g. of deuterated IV in 20 ml. of 80% acetone–20% water (by volume) was sealed in a tube and held at 96° for 72 hr. The tube was cooled, opened, and the contents were shaken with a mixture of water and ether. The aqueous layer was washed with ether, and the combined ether extracts were washed with water, dried and concentrated to a light brown oil. This material was chromatographed on a short alumina column, and the product was eluted with 5% ether–95% pentane to give 0.100 g. (40%) of product. This alcohol was analyzed by n.m.r. for deuterium scrambling (see later section). The results are found in Table II.

Acetolysis of Tosylate of 4-(2,2-Dideuterio-2-hydroxyethyl)-[2.2]paracyclophane (Deuterated III).—To 20 ml. of dry acetic acid was added 0.400 g. of deuterated III. Within 5 min. after being placed in a bath at 98°, the mixture became homogeneous. After 48 hr. at 98°, the solution was cooled, and the product was isolated and reduced with lithium aluminum hydride as in the procedure applied to deuterated IV (see above). Crude product (0.24 g. or 92%, m.p. 90–100°) was chromatographed on a short column of alumina made up in pentane. Elution with pentane gave no material, whereas 50% ether–pentane eluted the desired alcohol, m.p. 101–102°, which was subjected to n.m.r analysis (see later section).

Formolysis of III.—To 40 ml. of dry formic acid (0.01 *M* in *p*-toluenesulfonic acid) was added 0.200 g. of III. The resulting solution was held at reflux for 20 hr., cooled and poured into water. The aqueous mixture was extracted with pentane, the pentane extracts were washed with water, dried and concentrated to give a white solid, 0.10 g. (73%), m.p. 119–120° (crystallized from chloroform–pentane).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: 81.23; H, 7.29.

Application of this same procedure to deuterated III (0.250 g.) gave 0.17 g. (100%) of unrecrystallized formate ester, m.p. 112–115°. This material without purification was subjected directly to n.m.r. analysis (see next section).

N.m.r. Analysis.—All n.m.r. spectral analyses were made on a Varian Associates model A-60 analytical n.m.r. spectrophotometer in ~1 *M* solution in carbon disulfide with tetramethylsilane as an internal standard. Peak areas were measured by integration allowing the total integral to be equal to the theoretical proton content of the molecule, except where indicated otherwise in Table II.

The results of analysis of the products of acetolysis and hydrolysis of deuterated-IV, of acetolysis and formolysis of deuterated-III, as well as the absorptions of their fully protonated counterparts, are listed in Table II.

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