Carbanion–Carbonium Ion Intermediates in Racemizations and Solvolyses of Cyclopropanes[1]

Sir:

Although heterocyclic three-membered rings[2] and cyclopropanones[3] appear to undergo thermal cleavage to give polar species, the usual thermal cleavage of cyclopropane compounds[4a,b] assumes a homolytic course. However, solvolysis-like products have been reported to result from photolysis.[4c,d] We report here confirmation in a different system of an alternate mechanism suggested earlier[5] that involved heterolytic cleavage of 2,2-dimethyl-1-carbomethoxy-1-phenylsulfonylcyclopropane to form a carbon–carbon zwitterion that racemized, solvolyzed, and ring expanded.

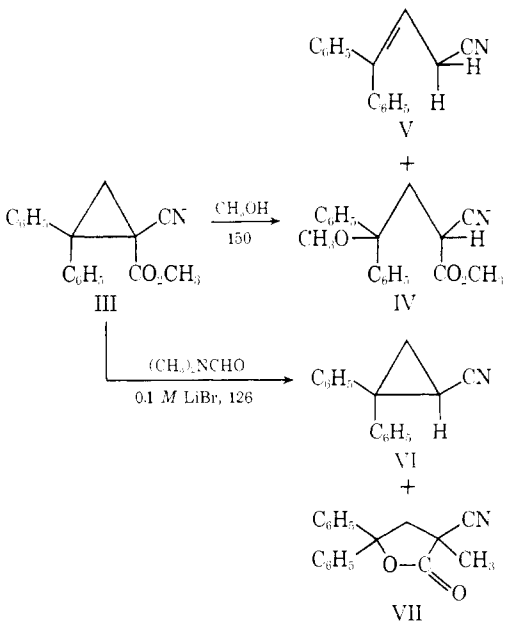
Table I. Solvent and Salt Effects on Rates and Activation Parameters for Racemization of 0.05 *M* Solutions of (+)-III

Run no.	Medium	Temp, °C	$k \times 10^5$, sec^{-1} [a]	$\Delta H^{\pm}$, kcal/mol[b]	$\Delta S^{\pm}$, eu[b]
1	C_6H_6	126.0 ± 0.05	0.439 ± 0.001	30.4 ± 0.2	−7.6 ± 0.6
2	C_6H_6	149.2 ± 0.02	3.80 ± 0.01		
3	$(CH_3)_2NCHO$	126.0 ± 0.05	2.16 ± 0.02	27.7 ± 0.3	−11 ± 1
4	$(CH_3)_2NCHO$	149.2 ± 0.02	15.2 ± 0.1		
5	CH_3OH	126.0 ± 0.05	8.74 ± 0.17	25.5 ± 0.3	−14 ± 1
6	CH_3OH	100.5 ± 0.02	0.912 ± 0.011		
7	$(CH_3)_2NCHO$–0.1 *M* LiBr	126.0 ± 0.05	32.3 ± 0.5	22.9 ± 0.4	−18 ± 1
8	$(CH_3)_2NCHO$–0.1 *M* LiBr	100.7 ± 0.02	4.28 ± 0.02		

[a] Sealed ampoules of degassed, dry solutions were used, and rate constants calculated from loss of optical activity of solutions. Runs were followed through 92–95% racemization with 7 points beyond time zero except in run 3 (4 points, 62%), run 4 (5 points, 65%), run 7 (6 points, 65%), and run 8 (4 points, 62%). [b] Limits of error are based on two standard deviations (95% confidence) in the rate constants from a least-squares analysis, and on the temperature limits.

Treatment of ethyl 2-cyano-3-phenylcinnamate with dimethyloxosulfonium methylide in dimethyl sulfoxide gave (80%) ethyl 1-cyano-2,2-diphenylcyclopropanecarboxylate (I): mp 132–133°;[6] nmr spectrum, δ 1.07 (t, *J* = 3, 7 Hz), 2.33 and 2.68 (AB quartet, *J* = 2, 5.5 Hz), 4.05 (q, *J* = 2, 7 Hz), and 7.1–7.7 (m, 10); mass spectrum, *m/e* 291. Derived acid II,[6] mp 177–178° (90%), was obtained by basic hydrolysis of I at 25°. Decarboxylation of I in ethylene glycol–potassium hydroxide at 165° gave the known[7] 2,2-diphenylcyclopropanecarbonitrile (50%): mp 106–107°; nmr spectrum, δ 1.6–2.3 (m, 3), 7.1–7.5 (m, 10); mass spectrum, *m/e* 219. One recrystallization of the brucine salt of II from hot methanol provided (+)-II (51%), $[\alpha]^{25}_{546}$ +128° (*c* 0.71, ethyl acetate). The mother liquor gave (−)-II (49%), $[\alpha]^{25}_{546}$ −121° (*c* 0.53, ethyl acetate). Diazomethane and (+)-II gave methyl ester (+)-III[6] (95%), which after four recrystallizations (ethanol) gave (42%) maximum rotation, $[\alpha]^{25}_{546}$ +111° (*c* 0.63, ethyl acetate), mp 168.5–169.5°. Similarly (−)-II[6] gave (5%) (−)-III, $[\alpha]^{25}_{546}$ −112° (*c* 0.59, ethyl acetate), mp 168.5–169.5°. Racemic III[6] gave mp 146–147°.

Methanolysis of III (150° for 3 days) gave ether IV[6] (46%) as an oil chromatographically pure: nmr (δ) complex absorptions 2.9–3.6 (6) (including a singlet at 3.04), 3.62 (s, 3), and 7.28 (s, 10); ir (cm^{-1}) 3000 (m), 2250 (w), 1750 (s), 1200–1283 (s), 1160 (s), and 1080 (s); mass spectrum, *m/e* 309. Olefin V[6] (36%) was also produced: mp 96–97°; nmr δ 3.07 (d, 2, *J* = 8 Hz), 6.02 (t, 1, *J* = 8 Hz), and 7.0–7.5 (m, 10); ir (cm^{-1}) 3000 (m), 2240 (m), and 1650 (w); mass spectrum, *m/e* 219. When heated for 1 day at 126° in 0.1 *M* lithium bromide, III gave nitrile[7] VI (54%) and lactone VII[6] (23%): mp 132–133°; nmr δ 1.55 (s, 3), 3.03 and 3.52 (AB quartet, *J* = 2, 14 Hz), and 7.1–7.5 (m, 10); ir (cm^{-1}) 3000 (m), 2250 (m), 1770 (s), 1250 (m), 1190 (s); mass spectrum, *m/e* 277. Nitriles VI and VII were separated chromatographically.



The products in methanol suggest a zwitterionic intermediate, whereas those in dimethylformamide–lithium bromide suggest bromide ion substitution on the methyl group of the ester.[8] Optically active III *race-*

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) (a) R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **8**, 602 (1969), and cited prior work; (b) W. J. Linn, *J. Amer. Chem. Soc.*, **87**, 3665 (1965); (c) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, **30**, 1951 (1965).

(3) S. S. Edelson and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 2770 (1970), and cited prior work.

(4) (a) J. A. Berson and J. M. Balquist, *ibid.*, **90**, 7343 (1968); (b) R. G. Bergman and W. L. Carter, *ibid.*, **91**, 7411 (1969), and cited prior work; (c) C. S. Irving, R. C. Petterson, I. Sarker, H. Kristinsson, C. S. Aaron, G. W. Griffin, and G. J. Boudreaux, *ibid.*, **88**, 5675 (1966); (d) H. Kristinsson, K. N. Mehrotra, G. W. Griffin, R. C. Petterson, and C. S. Irving, *Chem. Ind. (London)*, 1562 (1966).

(5) D. J. Cram and A. Ratajczak, *J. Amer. Chem. Soc.*, **90**, 2198 (1968).

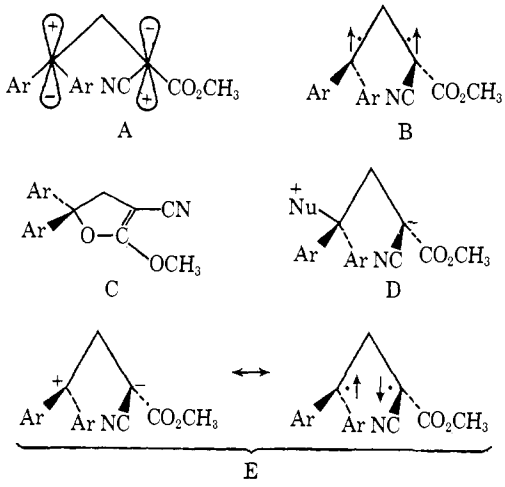
(6) All new compounds gave elemental analyses within ±0.3% of theory.

(7) H. M. Walborsky and F. M. Hornyak [*J. Amer. Chem. Soc.*, 77, 6026 (1955)] reported mp 107–108°.

mized in both media much faster than IV–VII were produced, by a factor of at least 10^2 in methanol at 150°, and a factor of at least 23 in dimethylformamide–0.1 *M* lithium bromide at 126°. These factors were measured by product isolation experiments and first-order rate constant estimates.

Preliminary rates of loss of optical activity of (+)-III at 0.05 *M* concentration in various solvents were measured polarimetrically at 125°. About a half-life was followed by ampoule technique (1–3 points per run), and less than 3% (glc on 20% SE30 on Firebrick) of any compound other than III could be detected at the end of the run. The first-order rate constant for benzene as solvent was 0.46×10^{-5} sec^{-1}, and the ratios of rate constants in other solvents to that in benzene were: CH_3OH, 18; $(CH_3)_2SO$, 9.4; $(CH_3)_2NCHO$, 3.7; CH_3CN, 2.3; $(CH_3)_3COH$, 2.0; C_6H_6, 1.0. Careful kinetic studies (Table I) indicated racemization followed strictly first-order kinetics through at least 1.5 half-lives. The solutions used for the last two points in every run contained less than 1% of any other product (glc). In runs 1, 2, 5, and 6, the last two points yielded 94–98% of sublimed III, pure to glc.

The rate factor increase of 15 (runs 4 and 7) was demonstrated due to bromide and not lithium ion with four parallel runs in dimethylformamide at 125° from which one-point rate constants were calculated and compared: run 9, no added salt, relative rate = 1; run 10, 0.1 *M* LiBr, relative rate = 14; run 11, 0.1 *M* $LiClO_4$, relative rate = 1; run 12, 0.1 *M* $(C_2H_5)_4NBr$, relative rate = 13. Four simultaneous one-point rate constant runs were made in dimethylformamide at 125°: run 13, 0.05 *M* LiBr, 1.4×10^{-4} sec^{-1}; run 14, 0.10 *M* LiBr, 2.3×10^{-4} sec^{-1}; run 15, 0.20 *M* LiBr, 3.8×10^{-4} sec^{-1}; run 16, 0.40 *M* LiBr, 7.0×10^{-4} sec^{-1}. A plot of these rate constants against bromide ion concentration is linear. Extrapolation of the plot to zero bromide ion concentration provides a rate constant four times that calculated from runs 3 and 4 made without bromide. Thus bromide salts at low concentration produce a sizable "special salt effect"[9] superimposed on which is a second-order process.



General mechanisms for racemization of (+)-III can be envisioned in terms of intermediate structures, A–E. The π-cyclopropane intermediate[10] A is sterically improbable and is inconsistent with medium effects on rate. The triplet diradical intermediate B is inconsistent with the substantial response of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ to solvent changes. Thus $\Delta H^{\pm}$ is ~5 kcal/mol higher in benzene than in methanol, and $\Delta S^{\pm}$ is about −8 in benzene and −14 eu in methanol. Homolytic cleavage reactions show much smaller changes in $\Delta H^{\pm}$ with changes in medium, have $\Delta S^{\pm}$ values around zero,[3,4,11] and show no special salt effects. *Concerted* formation and decomposition of ketene acetal C is a mechanism also inconsistent with the large $\Delta H^{\pm}$ changes with medium and the special salt effect. The solvent-assisted zwitterionic mechanism leading to intermediate D is impossible in benzene, and if it occurred in methanol, racemization in methanol would not be $>10^2$ faster than methanolysis.

A mechanism in which E is formed as a first intermediate is consistent with all the facts. This intermediate is visualized as a resonance hybrid, since the orbitals on the 1,3-carbon atoms are close enough together to provide some overlap. Intermediate E can have high zwitterionic character and substantial response to medium. The special salt effect could reflect capture of E and in effect prevention of its direct collapse to optically active III. Although E might form C or D in a second stage, it seems unlikely that D would give III in methanol or C would give III in any solvent. The second-order bromide ion catalysis of racemization is probably an SN2 reaction in its first stage, followed by rotational equilibration of the carbanion and ring closure by expulsion of bromide by C$^-$.

(8) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 615, for references.
(9) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2780 (1956).
(10) R. Hoffmann, *ibid.*, **90**, 1475 (1968).
(11) (a) H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 147 (1966); (b) E. S. Huyser and R. M. Van Scoy, *J. Org. Chem.*, **33**, 3524 (1968).

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Stereochemistry of the Methanolysis of a System with Carbon as Leaving Group[1]

Sir:

We have examined the stereochemical course of the methanolysis with ring opening of the substituted cyclopropane derivative, (+)-methyl 1-(*S*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate [(+)-(*S*),(*R*)-I], and demonstrated that the reaction occurs with 99 ± 2% stereospecificity and inversion at the center (C-2) that underwent nucleophilic substitution. The preparation of all four stereomers of I of maximum rotation was accomplished, and their absolute configurations were assigned. The methanolysis product, methyl 2-cyano-4-methoxy-4-phenylbutanoate (II), was converted to (−)-(*S*)-methyl 4-methoxy-4-phenylbutanoate, whose absolute configuration and maximum rotation were also determined.

Treatment of (*E*)-ethyl 2-cyanocinnamate[2] with di-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) (a) J. Zabicky, *J. Chem. Soc.*, 683 (1961). (b) For nomenclature, see J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).