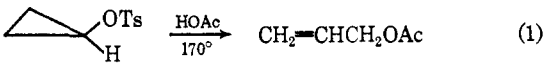
Solvolysis of Cyclopropyl Halides. 2-Phenylcyclopropyl Chlorides[1,2]

Jack W. Hausser and Norman J. Pinkowski[3]

Contribution from the Department of Chemistry, Duquesne University, Pittsburgh, Pennsylvania 15219. *Received July 31, 1967*

Abstract: *cis*- and *trans*-2-phenylcyclopropyl chloride and 2,2-diphenylcyclopropyl chloride have been solvolyzed in acetic acid. The products of solvolysis in all cases are the corresponding ring-opened allylic acetates. The relative rates at 150° and the activation parameters are presented. These results are considered in terms of the electronic and steric requirements of electrocyclic ring-opening processes. Two alternative interpretations are presented.

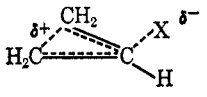
Cyclopropyl compounds have shown a remarkable lack of reactivity toward nucleophilic substitution. In most instances the product of solvolysis is the ring-opened allylic derivative as indicated by the reaction of cyclopropyl tosylate in acetic acid in eq 1.[4] The



(1)

lack of reactivity is attributed to the greater electronegativity of the carbon atom in the strained ring, the conjugative delocalization of the electrons in the C–X bond, and the increased internal strain in going to a planar transition state.

The concerted nature of the solvolysis and ring-opening process has been demonstrated by substituent effect studies.[5–7] Marked increases in rate are observed when β-aryl or β-alkyl groups are present, whereas the effect of α substitution seems to be smaller than expected. This suggests partial ring-opening in the transition state with stabilization of the developing positive charge at the β-carbon atom as indicated in I.



I

In most instances the exclusive product of solvolysis is the ring-opened allylic derivative. However, in recent reports,[8] through carefully chosen conditions or structures, cyclopropyl products have been obtained.

Considerable interest in this highly strained system has been stimulated by theoretical predictions concerning the stereochemistry of the ring-opening process.[9] The geometric requirements for a concerted process include twisting the bonds to the β-carbon atoms through approximately 90° to the coplanar allylic system, allowing the electrons of the 2–3 bond to assist the leaving group. This process requiring a reorientation of the bonding orbitals has been treated as an electrocyclic process by Woodward and Hoffmann.[9] Assuming that the highest energy occupied molecular orbital of the carbonium ion will determine the symmetry requirements, the carbonium ion may be approached by a disrotatory process with the group *trans* to the leaving group rotating outward and the group *cis* to the leaving group rotating inward as in Figure 1. This mode of disrotatory opening would be preferred since the electron density of the σ bond being broken can assist the leaving group from the backside.

DePuy, *et al.*,[6] presented the first evidence bearing on the stereochemical course of the ring opening. The relative rates of reaction of β-phenyl-substituted cyclopropyl tosylates are in agreement with the predictions. Further support has been reported with other substituents[7] and in fused and polycyclic structures.[10] An empirical incorporation of steric and electronic effects into the Woodward–Hoffmann postulates for alkyl-substituted cyclopropyl tosylates has produced surprisingly good correlations with the rates of solvolysis.[7]

Our efforts have concerned themselves with the solvolysis of phenyl-substituted cyclopropyl chlorides in acetic acid. This system utilizing a relatively poor leaving group in a relatively poor solvolyzing medium was chosen in order to increase the demands on the reactant for stabilization through increased ring opening, thus emphasizing the steric and electronic influence of the phenyl groups.

Results

cis- and *trans*-2-phenylcyclopropyl chloride and 2,2-diphenylcyclopropyl chloride were prepared by the addition of dichlorocarbene generated from chloroform

(1) Support of this research by a grant from the National Science Foundation is gratefully acknowledged.

(2) A portion of this work has been presented: J. W. Hausser, N. J. Pinkowski, and J. O. Frohliger, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p 124K.

(3) Taken from the Ph.D. Thesis of N. J. P., Duquesne University, 1967.

(4) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

(5) J. A. Landgrebe and D. E. Applequist, *ibid.*, **86**, 1536 (1964).

(6) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965); C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(7) P. von R. Schleyer, G. W. V. Dine, V. Schöllkopf, and J. Paust, *ibid.*, **88**, 2868 (1966); P. von R. Schleyer, Abstracts, 20th National Organic Symposium of the American Chemical Society, Burlington, Vt., June 1967, p 8.

(8) W. Kirmse and H. Schütte, *J. Am. Chem. Soc.*, **89**, 1284 (1967); J. A. Landgrebe and L. W. Becker, *ibid.*, **89**, 2505 (1967); see also P. Lipp and C. Padberg, *Chem. Ber.*, 54B, 1316 (1921); R. Pettit, *J. Am. Chem. Soc.*, **82**, 1972 (1960); H. Hart and R. H. Martin, *ibid.*, **82**, 6362 (1960).

(9) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); also see H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965).

(10) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *ibid.*, **87**, 4007 (1965).

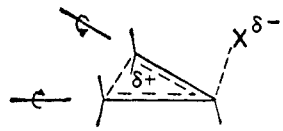
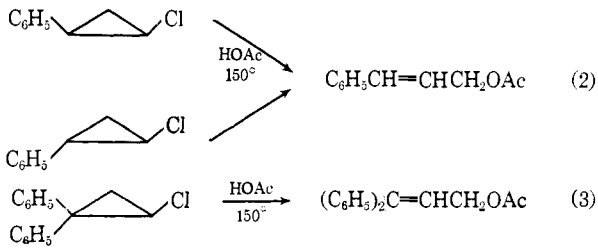


Figure 1.

and potassium *t*-butoxide to the corresponding olefin[11] followed by reduction of the geminal dichloride with tri-*n*-butyltin hydride.[12] The isomeric chlorides obtained on the reduction of 1,1-dichloro-2-phenylcyclopropane were separated by fractional distillation and the isomer purity checked by gas chromatography. The structural assignments based on spectral and physical properties were in agreement with those presented in the literature.[13]

Preliminary studies of the solvolysis by nmr and gas chromatography showed single products from each reaction. Both *cis*- and *trans*-2-phenylcyclopropyl chloride afforded the thermodynamically stable *trans*-cinnamyl acetate (eq 2). 2,2-Diphenylcyclopropyl chloride afforded solely the α-phenylcinnamyl acetate (eq 3). Under the conditions of solvolysis, the unreacted *cis* and *trans* isomers of 2-phenylcyclopropyl chloride could be recovered unchanged. The corresponding cyclopropyl acetates were shown to be stable to the reaction conditions and would have been detected if formed. *cis*- and *trans*-cinnamyl acetates equilibrate under the reaction conditions.[14]



$$C_6H_5CH{=}CHCH_2OAc \quad (2)$$

$$(C_6H_5)_2C{=}CHCH_2OAc \quad (3)$$

The method of analysis used for kinetics was the potentiometric determination of chloride ion formed. An electrode plated with a layer of silver and a layer of silver chloride used with a standard calomel electrode was shown to be sensitive to chloride ion in acetic acid–water mixtures. The use of standard solutions of known chloride ion concentration allowed the determination of chloride ion concentration in the unknown samples. This method proved to be accurate and convenient and allowed utilization of smaller sample sizes.

The rates of solvolysis were shown to follow a first-order kinetic dependence on the cyclopropyl chloride. The results of the rate determinations are presented in Table I. Table II lists the relative rates at 150° and the calculated activation parameters along with some comparative literature results.

(11) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954); P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956); E. Bergman, *J. Org. Chem.*, **28**, 2210 (1963).

(12) D. Seyferth, H. Yamazaki, and D. L. Alleston, *ibid.*, **28**, 703 (1963).

(13) W. L. Dilling, *ibid.*, **29**, 960 (1964).

(14) F. A. Braude, D. W. Turner, and E. S. Waight, *J. Chem. Soc.*, 2396 (1958).

Table I. Rate Constants for the Solvolysis of β-Phenyl-Substituted Cyclopropyl Chlorides[a]

Compound	Temp, °C	k_1, sec^{-1} [b]
cis-2-Phenylcyclopropyl chloride	139.9	$2.43 \pm 0.11 \times 10^{-6}$
	150.1	$5.91 \pm 0.61 \times 10^{-6}$
	160.3	$1.44 \pm 0.01 \times 10^{-5}$
trans-2-Phenylcyclopropyl chloride	139.9	$1.09 \pm 0.10 \times 10^{-5}$
	150.1	$3.01 \pm 0.17 \times 10^{-5}$
	160.3	$6.92 \pm 0.44 \times 10^{-5}$
2,2-Diphenylcyclopropyl chloride	139.9	$2.66 \pm 0.19 \times 10^{-5}$
	150.1	$8.47 \pm 0.39 \times 10^{-5}$
	160.3	$2.03 \pm 0.04 \times 10^{-4}$

[a] In 0.04 *M* sodium acetate in anhydrous acetic acid, cyclopropyl chloride concentrations approximately 5×10^{-3} *M*. [b] Rate constants determined by least-squares calculation.

Table II. Solvolysis of Phenyl-Substituted Cyclopropyl Chlorides and Tosylates at 150.1° in Acetic Acid

Compound	k_1, sec^{-1}	k_{rel}	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
Cyclopropyl chloride[a]	5.5×10^{-10}	10^{-4}		
cis-2-Phenylcyclopropyl chloride	5.91×10^{-6}	1	30.2	−11.8
trans-2-Phenylcyclopropyl chloride	3.01×10^{-5}	5	31.4	−5.7
2,2-Diphenylcyclopropyl chloride	8.47×10^{-5}	14	34.6	+4.0
Cyclopropyl tosylate[b]	6.3×10^{-6}	1	33.8	−2.9
cis-2-Phenylcyclopropyl tosylate[c]	1.22×10^{-4}	20	32.7	0
trans-2-Phenylcyclopropyl tosylate[c]	1.75×10^{-3}	280	30.6	−0.9

[a] The rate of acetolysis of cyclopropyl chloride was estimated by extrapolation of the data for cyclopropyl tosylate, assuming the same relative rates for chloride to tosylate as for isopropyl. [b] Extrapolated from the data given in ref 4. [c] Extrapolated and calculated from the data in ref 6.

Experimental Section

1,1-Dichloro-2-phenylcyclopropane. Dichlorocarbene prepared from chloroform and potassium *t*-butoxide was added to styrene to prepare 1,1-dichloro-2-phenylcyclopropane according to standard procedures.[11]

***cis*- and *trans*-2-Phenylcyclopropyl Chloride.** In a 250-ml, one-necked flask equipped with a condenser was placed 32 g (0.17 mole) of 1,1-dichloro-2-phenylcyclopropane and 55 g (0.19 mole) of tri-*n*-butyltin hydride.[15] The mixture was heated at 160° for 21 hr. The mixture was then distilled directly giving 19 g (75% yield) of *cis*- and *trans*-2-phenylcyclopropyl chloride, bp 68–75° (4.0 mm), ratio of *cis* to *trans* 1.5 to 1 by vapor phase chromatography. Redistillation through an 18-in. Nester-Faust semimicro spinning-band column gave 3.0 g of *trans*-2-phenylcyclopropyl chloride, bp 77.2–78.2° (5.4 mm), n^{25}D 1.5391, and 2.5 g of *cis*-2-phenylcyclopropyl chloride, bp 83.0–84.0° (5.4 mm), n^{25}D 1.5507. Vapor phase chromatography indicated 95.3% purity for the *trans* isomer and 98.0% purity for the *cis* isomer.

The nmr spectrum of the *trans* isomer showed absorption at 1.36 ppm (two protons) for the cyclopropyl methylene hydrogens, at 2.31 ppm (one proton) for the benzylic cyclopropyl proton, at 3.04 ppm (one proton) for the proton on the chlorine-bearing carbon, and at 6.87–7.48 ppm (five protons) for the aromatic protons. The nmr spectrum of the *cis* isomer showed absorption at 1.36 ppm (two protons), at 2.28 ppm (one proton), at 3.30 ppm (one proton), and at 7.27 ppm (five protons). These absorptions were assigned to the cyclopropyl methylene protons, to the benzylic cyclopropyl proton, to the proton attached to the chlorine-bearing carbon, and to the aromatic protons, respectively.

(15) H. G. Kuivila and O. F. Beumerl, Jr., *J. Am. Chem. Soc.*, **83**, 1248 (1961).

Anal. Calcd for C_9H_9Cl (*trans*-2-phenylcyclopropyl chloride): C, 70.81; H, 5.95; Cl, 23.25. Found: C, 70.69; H, 5.80; Cl, 23.22.

Anal. Calcd for C_9H_9Cl (*cis*-2-phenylcyclopropyl chloride): C, 70.81; H, 5.95; Cl, 23.25. Found: C, 70.65; H, 6.04; Cl, 23.14.

1,1-Dichloro-2,2-diphenylcyclopropane. Dichlorocarbene prepared from chloroform and potassium *t*-butoxide was added to 1,1-diphenylethylene to prepare 1,1-dichloro-2,2-diphenylcyclopropane according to standard procedures.[11]

2,2-Diphenylcyclopropyl Chloride. In a one-necked, 250-ml flask equipped with a condenser and a nitrogen inlet tube was placed 17.0 g (0.07 mole) of 1,1-dichloro-2,2-diphenylcyclopropane and 28.0 g (0.10 mole) of tri-*n*-butyltin hydride.[15] The mixture was heated at 150–160° for 9 hr. The mixture was then allowed to cool and added dropwise to 1.9 g (0.05 mole) of lithium aluminum hydride in 150 ml of ether in a three-necked flask, which was cooled by an ice bath and equipped with a stirrer, a condenser, and a dropping funnel. The mixture was then stirred for 8 hr. At this time the mixture was hydrolyzed with 75 ml of water. The ether layer was separated and treated in the usual manner. After the ether was removed, vacuum distillation gave 3.0 g (7% yield), bp 115–120° (0.6 mm), of 1-chloro-2,2-diphenylcyclopropane which crystallized on standing. Three recrystallizations from petroleum ether (bp 30–69°) gave 1.5 g of product, mp 71.0–72.0°. The nmr spectrum showed a doublet at 1.62 ppm (two protons), a triplet at 3.59 ppm (one proton), and complex absorption from 7.10 ppm to 7.50 ppm (ten protons).

Anal. Calcd for $C_{15}H_{13}Cl$: C, 78.75; H, 5.73; Cl, 15.51. Found: C, 78.78; H, 5.69; Cl, 15.39.

Kinetic Procedure. All kinetic determinations were obtained for approximately 5×10^{-3} *M* cyclopropyl chloride concentrations in anhydrous acetic acid containing 0.0401 *M* sodium acetate. Samples of 6 ml were sealed in ampoules and placed in a constant temperature bath regulated to ±0.1°. The ampoules were removed at the appropriate intervals and opened. A 5-ml aliquot of the solution was added to 10 ml of water. The potential of a silver–silver chloride electrode[16] to a standard calomel electrode of the solution was measured on a Beckman Research pH meter. The chloride ion concentration was then determined from a standard curve which had been obtained by measuring the potential of solutions of known chloride ion concentrations in 10 ml of water and 5 ml of acetic acid containing 0.0401 *M* sodium acetate. The first-order rate constants were determined by the method of least squares.

Discussion

Two alternative interpretations of the solvolysis results seem possible from consideration of the concerted nature of the reaction, the extent of ring opening in the transition state, the inductive, resonance, and steric effects of substituents, and the effect of the leaving group. The very large rate acceleration observed for a β-phenyl group over the estimated rate for cyclopropyl chloride supports a concerted process with considerable positive charge being developed at the β-carbon atom. A process that is totally stereoselective or a process with only steric preference can account for the results.

In considering the reaction as being stereoselective as outlined by Woodward and Hoffmann[9] and DePuy, *et al.*,[6] one must account for the effect of substitution. The inductive effect of the phenyl group should slow the reaction but be greatly overcome by the resonance stabilization of the developing positive charge at the β-carbon atom. If the predicted directions of rotation are correct, very large steric differences should be seen. The *cis*-phenyl group must rotate inward with a large steric compression causing interference with the resonance stabilization, while the *trans*-phenyl group rotates away from the ring.

The relative rates are in qualitative agreement with this picture; however, the acceleration of only a factor of five for the *trans* to the *cis* isomer seems to be too small. A somewhat better correlation is possible by considering that the *cis* isomer is very likely experiencing a steric acceleration due to the eclipsing effect of the phenyl group and the chloro group that raises the energy of the ground state.

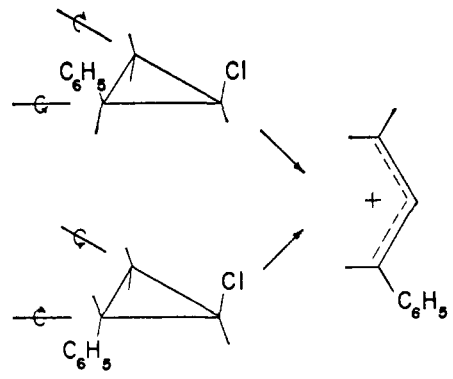


Figure 2.

2,2-Diphenylcyclopropyl chloride solvolyzes faster than either *cis*- or *trans*-2-phenylcyclopropyl chloride; however, again the magnitude of the acceleration is surprisingly small. One would anticipate comparable steric effects to that of the *cis* isomer, but a much greater degree of resonance stabilization in the transition state due to the added phenyl group. The small acceleration observed suggests a lesser degree of ring opening in the transition state of the stereoselective process, possibly due to the difficulty in solvating a more bulky carbonium ion.[17]

A look at the activation enthalpies and entropies listed in Table II raises additional questions as to the validity of the stereoselective process. When taking into account the experimental uncertainties,[18] it may be seen that the variations in these quantities are small, and do not provide for the expected differences based on the stereochemical requirements.

The alternative interpretation of the relative rates and the activation parameters still accepts the process as being a preferred disrotatory process as specified, but allows for the alternative rotational direction when steric effects make the preferred direction unfavorable. The phenyl group of *trans*-2-phenylcyclopropyl chloride on solvolysis would be normal and rotate outward proceeding to a *trans*-cinnamyl cation. The phenyl group of *cis*-2-phenyl cyclopropyl chloride rather than rotating inward with a large steric compression rotates outward reducing the eclipsing in the ground state and eventually producing the same *trans*-cinnamyl cation in what now becomes a more favorable pathway. These two processes are shown in Figure 2. The relative rates and the activation parameters now are more reasonable. As the ring opening increases in the transition state, the isomeric transition states become more similar and therefore the ground-state energy becomes more important. An analogy for this behavior might be the concerted *cis* and *trans* E2 elimination

(16) J. O. Frohliger and R. T. Pflaum, *Talanta*, 9, 755 (1962).

(17) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. McC. Duggleby, *J. Am. Chem. Soc.*, 87, 1541 (1965); K. T. Leffek, R. E. Robertson, and S. Sugamori, *ibid.*, 87, 2097 (1965).

(18) See K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, pp 377–379.

reactions[19] in which the preferred course of reaction is *trans* coplanar except in cases where this geometry cannot be achieved. In these cases a coplanar *cis* elimination becomes preferred.

A consideration of the solvolysis of 2,2-diphenylcyclopropyl chloride lends additional support to this alternative approach. Since one phenyl group must rotate inward regardless of the direction of rotation, then the steric compression cannot be avoided. This steric compression may prevent extensive ring opening in the transition state thereby cancelling the expected stabilization from the added phenyl group.

It is difficult to make a clear distinction between the two pathways based on literature examples. Most alkyl-substituted cyclopropyl derivatives seem to behave as predicted,[7] showing large rate effects. However, at least one exception is the apparently anomalous behavior of the *exo*- and *endo*-norcaranyl chlorides[7] and tosylates.[10] Our system, utilizing aromatic substituents, strongly suggests the alternative type of behavior. The large resonance stabilization capabilities and the sensitive steric requirements of the phenyl group in the *cis* position may be sufficient to favor the alternate mode of ring opening over the predicted mode which is sterically less favorable and must necessarily sacrifice some of the resonance stabilization. A decision between the two alternatives should be possible through investigation of additional substituent effects designed to emphasize the stereoselective properties of the ring-opening reaction.

(19) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Am. Chem. Soc.*, 87, 2421 (1965); J. L. Coke, and M. P. Cooke, Jr., *ibid.*, 89, 2779 (1967).

The Hydrolysis of Thioimidate Esters. Tetrahedral Intermediates and General Acid Catalysis[1]

Rama K. Chaturvedi, Andrew E. MacMahon, and Gaston L. Schmir

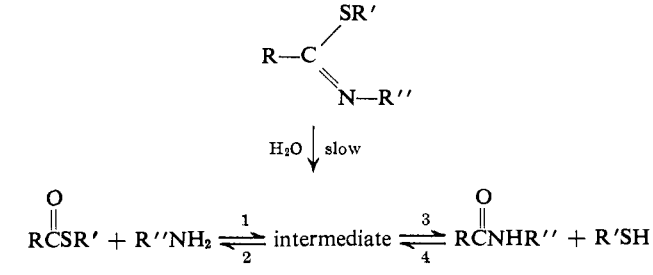
Contribution from the Department of Biochemistry, Yale University, New Haven, Connecticut 06510. *Received August 7, 1967*

Abstract: The hydrolysis of four acyclic thioimidate esters has been investigated in the pH range 0–10 at 30°. The pH–rate profiles exhibit the features characteristic of the hydrolysis of other imines (thiazolines, oxazolines, Schiff bases, iminolactones). The nature of the products of hydrolysis is influenced by pH and by the concentration of buffers. Hydrolysis yields thiol esters and amines at pH <2 and amides (and mercaptans) at higher pH. Increasing buffer concentration at pH 2–6 directs the breakdown of a tetrahedral intermediate from C–S to C–N bond cleavage. Buffer effects on the products are in quantitative agreement with a mechanism involving general acid catalysis of the breakdown of an anionic carbinolamine intermediate. Some conclusions concerning the mechanism of the aminolysis of thiol esters are presented.

The chemistry of the tetrahedral addition intermediates generated in nucleophilic reactions of carboxylic acid derivatives is the subject of continuing investigation.[2] The very existence of such intermediates has been convincingly demonstrated in relatively few instances.[2,3] Questions ancillary to the proof of existence of the intermediate deal with the nature of the rate-determining step, and with the mechanisms available for the catalysis of the several steps of the acyl transfer reaction.

A particularly simple approach to the mechanism of certain acyl transfer reactions consists of the detailed study of the factors influencing the nature of the products of hydrolysis of related imidates. The principle is illustrated in Scheme I. Evidence for the existence

Scheme I



of an intermediate in the hydrolysis of the imidate provides compelling support for the participation of the same intermediate in the acyl transfer reactions leading to interconversion of the products (*via* the sequences 1–3 or 4–2). Determination of the yields of the products formed *via* reactions 2 and 3 upon hydrolysis of the imidate immediately indicates which step is rate determining when the related acyl transfer reaction

(1) (a) This work is taken in part from a dissertation presented by A. E. M. in partial fulfillment of the requirements for the M.D. Degree, Yale University, 1964. (b) Financial support by the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged (Grant No. AM-04288).

(2) (a) M. L. Bender, *Chem. Rev.*, 60, 53 (1960); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

(3) (a) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, 83, 2267 (1961); (b) M. L. Bender and R. J. Thomas, *ibid.*, 83, 4183, 4189 (1961); (c) R. B. Martin and R. I. Hedrick, *ibid.*, 84, 106 (1962); (d) B. Hansen, *Acta Chem. Scand.*, 17, 1307 (1963); (e) R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Am. Chem. Soc.*, 86, 2406 (1964); (f) T. C. Bruice and L. R. Fedor, *ibid.*, 86, 4886 (1964); (g) W. P. Jencks and M. Gilchrist, *ibid.*, 86, 5616 (1964); (h) G. E. Lienhard and W. P. Jencks, *ibid.*, 87, 3855 (1965); (i) L. R. Fedor and T. C. Bruice, *ibid.*, 87, 4138 (1965); (j) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 20, 1892 (1966); (k) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, 89, 917 (1967).