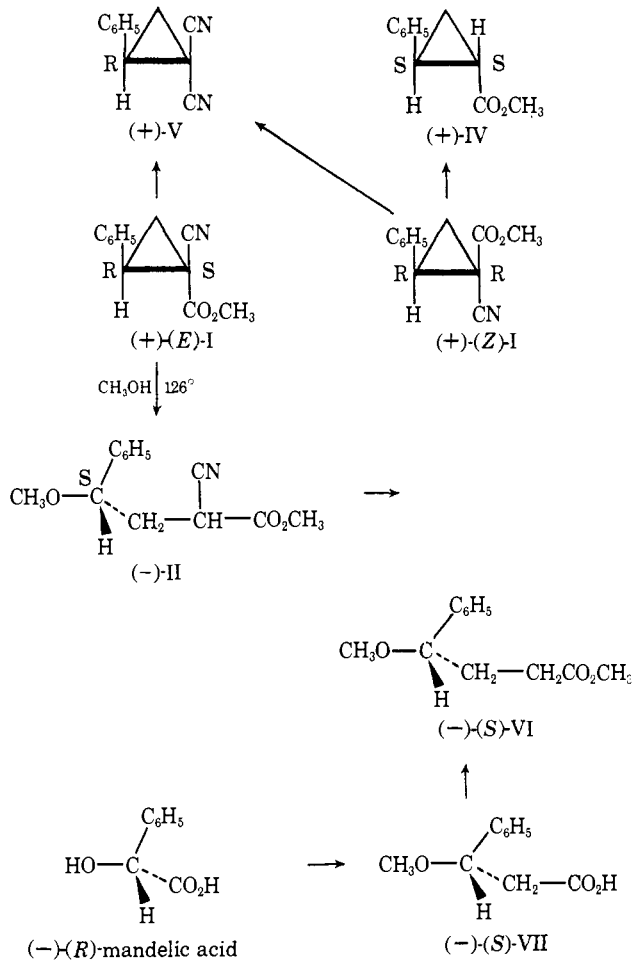
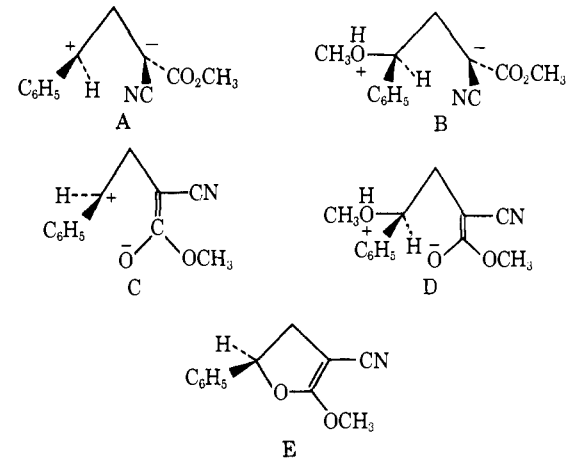
thoxy-3-phenylpropanoic acid, (+)-(*R*)-VII (prepared[11] from (+)-(*S*)-mandelic acid), was brought to optical purity by fractional crystallization of its brucine salt from acetone to give (+)-(*R*)-VII:[4a] mp 65–66°; $[\alpha]^{25}_{546}$ +72.3°; and $[\alpha]^{25}_{D}$ +58.3° (*c* 0.23, ethyl acetate). Arndt–Eistert homologation[12] of 95.2% optically pure (+)-(*R*)-VII gave (22%) (+)-(*R*)-VI[6a] (bp 85–95° (0.12 mm); $[\alpha]^{25}_{546}$ +90.5° (*c* 0.74, ethyl acetate)), whose nmr and ir spectra were identical with (−)-VI prepared above. These data demonstrate that (−)-(*S*)-VI of 99% optical purity was produced from the sample of II, which in turn was the methanolysis product of (+)-(*E*)-I. *Clearly the nucleophilic substitution reaction at the benzyl carbon of (+)-(E)-I (run 1) proceeded with essentially complete inversion of configuration.* In some cases to save space, the structural formulas have configurations opposite to those used.

The rate of methanolysis of (*Z*)-I in runs 2 and 3 exceeded the rates of isomerization of (*Z*)-I to (*E*)-I by a factor of $>10^2$. The factor by which the rate of inversion at benzyl carbon exceeded that of retention in the methanolysis of (+)-(*E*)-I is also $>10^2$. No retention or isomerization components were detectable in this system, unlike (+)-methyl 1-cyano-2,2-diphenylcyclopropanecarboxylate which isomerized $>10^2$ faster



than it methanolyzed.[7b] Another comparison involves methanolysis of optically active α-phenylethyl chloride[13] at 70°, which was reported to have occurred with 32% net inversion. This figure is minimal since racemization of starting material might have been a competing reaction.

Several possible mechanisms explain the high inversion in the methanolysis of (+)-(*E*)-I to give (−)-II, the possible intermediates being A–E. Sequences I → B → II and I → A → B → II are the simplest, but I →



A → C → D → II, and I → A → C → E → D → II also are possible. Probably once formed, B and D would undergo proton transfers faster than other covalent bonds are made or broken. Mechanisms

$$\mathrm{I} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{E} \xrightarrow{k_2} \mathrm{C \text{ or } D} \rightarrow \mathrm{II}$$

definitely are compatible with rate-determining ionization and nonaccumulation of E only if $k_{-1} \gg k_1 > k_2$. The fact that no epimerization accompanied methanolysis of (*Z*)-I (racemization of the benzhydryl analog occurred 10^2 times as fast as methanolysis)[7b] eliminates this possibility. Strong evidence that the rate-determining stage involves ionization is found in the adjacent paper.[7a]

(11) K. Balenovic, B. Urbas, and A. Deljac, *Croat. Chem. Acta*, **31**, 153 (1959).

(12) T. D. Hoffman and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1000 (1969).

(13) (a) E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1201 (1937); (b) H. M. R. Hoffman and E. D. Hughes, *ibid.*, 1244 (1964).

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The Question of Zwitterionic *vs.* Singlet Diradical Intermediates in Epimerization Reactions of Substituted Cyclopropanes[1]

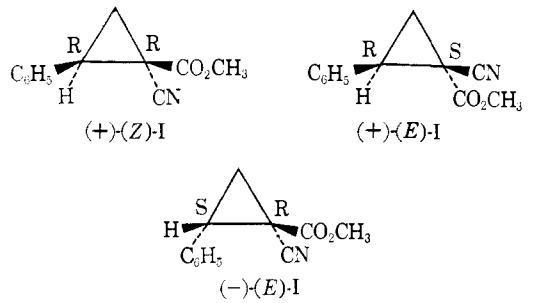
Sir:

In the preceding communication,[2a] the absolute configurations of (+)-(*E*)-I and (+)-(*Z*)-I were established. In cleavage of a cyclopropane ring, the answer to the question of whether the bond breaks homolytically to give a singlet diradical or heterolytically to give a zwitterion is elusive, since the sites of charge and spin

(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) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6328 (1970); (b) E. W. Yankee and D. J. Cram, *ibid.*, **92**, 6329 (1970).

are close enough in face-to-face conformations of opened structure to accommodate orbital overlap. The two chiral centers of I allow monitoring of the relative rates at which the two centers invert during isomerization in various solvents. Epimerization at each center provides a separate reaction whose structural coordinate provides a conformation in which bonding orbitals of the starting state pass through an orthogonal (face-to-edge) state in which overlap is poor. Here



differentiation between singlet diradical and zwitterion might be possible. These epimerizations might also be distinguished from a racemization reaction whose structural coordinate involved an edge-to-edge structure.

$$(+)\text{-}(Z)\text{-I} \xrightarrow{k_c} (\pm)\text{-}(E)\text{-I} \qquad (+)\text{-}(Z)\text{-I} \xrightarrow{k_b} (-)\text{-}(E)\text{-I}$$

$$(+)\text{-}(Z)\text{-I} \xrightarrow{k_r} (\pm)\text{-}(Z)\text{-I} \qquad (Z)\text{-I} \xrightarrow{k_i} (E)\text{-I}$$

Changes in rates and products with changes in solvent polarity served as criteria for differentiating between zwitterion-like and radical-like mechanisms. Reactions of 0.01 *M* solutions of ester in either dimethylformamide (DMF) or benzene (ampoules) gave diastereomeric mixtures analyzed by glc (complete separation, ±1%) at 160°, 2 ft × 0.25 in. column, 20% SE 30 on Firebrick with helium in the isolation (thermal conductivity), and a 10 ft × 0.125 in. column of 1% Epon 1001 on Anakrom SD with nitrogen in analytical (flame ionization) runs. Control runs proved (−)-(*E*)-I and (+)-(*Z*)-I completely optically stable to preparative glc and completely separable. In product isolation runs, >90% starting material was accounted for, and no side reaction detected. The (longer time) equilibration runs [(*E*)-I ⇄ (*Z*)-I] gave ~5% by-products.

At 200° in benzene for 15 days, (*E*)-I and (*Z*)-I each gave $K = [(E)\text{-I}/(Z)\text{-I}] = 7.3$. In benzene 7 days at 200° and 21 days at 175°, each isomer gave $K = 8.1$. In DMF at 126 and 100°, K so favored (*E*)-I and side reactions became so important with extended times that K's were estimated from kinetic data. Qualitatively (*E*)-I at 126° for 1.0 hr gave 1% (*Z*)-I. At 126° for 1.0 hr (*Z*)-I gave 36% (*E*)-I. The isomerization rate of (+)-(*Z*)-I at 126° in DMF was followed (four polarimetric points through 47% and two glc points through 97% reaction). To these six points were fitted the best values for k_i ($160 \pm 10 \times 10^{-6}$ sec^{-1}) and for K (40 ± 30). The isomerization rate of (+)-(*Z*)-I in DMF at 100° (four polarimetric points) gave $k_i = 22 \pm 1 \times 10^{-6}$ sec^{-1} and $K = 40 \pm 30$. The k_i values were only slightly sensitive to $K > 10$. These k_i's and those from runs 3 and 4 provide $E_a \sim 23$ in DMF and ≈37 kcal/mol in benzene. Thus at 150°, (*Z*)-I → (*E*)-I in DMF occurs ~10^4 as fast as in benzene. In contrast at 125°, racemization of the benzhydryl system, (+)-methyl 1-cyano-2,2-diphenylcyclopropanecarboxylate, was only about four times as fast in DMF as in benzene.[2b]

In runs made to estimate each epimerization and the racemization rate constants, optically pure (+)-(*Z*)-I was used, the diastereomeric products were separated by glc, and the rotation of each was taken. In run 1 at 100° in DMF, 17 hr gave 75% isomerization, recovered (+)-(*Z*)-I was 100% optically pure, and the (+)-(*E*)-I produced was 97.7 ± 0.3% optically pure. In run 2 at 126° in DMF, 1 hr gave 37% isomerization, recovered (+)-(*Z*)-I was 100% optically pure, and the (+)-(*E*)-I produced was 92.8 ± 0.4% optically pure. In run 3 at 175° in benzene, 11 days gave 61% isomerization, recovered (+)-(*Z*)-I was 80% optically pure, and the (+)-(*E*)-I produced was 21.9 ± 0.3% optically pure. In run 4 at 200° in benzene, 24 hr gave 57% isomerization, recovered (+)-(*Z*)-I was 80% optically pure, and the (+)-(*E*)-I produced was 15.7 ± 0.3% optically pure. A control run with (−)-(*E*)-I at 126° proved it stable to run 2 (and therefore run 1) conditions.

First-order one-point rate constants were estimated from the equilibrium constants and product data.[3] In runs 1 and 2, the (+)-(*E*)-I and (−)-(*E*)-I once formed were stable. In runs 3 and 4, the relatively small amounts of (+)-(*E*)-I and (−)-(*E*)-I that came from (±)-(*Z*)-I concurrently formed are neglected in calculation of k_c and k_b. Thus $k_i = k_c + k_b$, $k_c = k_i[(+)\text{-}(E)\text{-I}]/[(+)\text{-}(E)\text{-I} + (-)\text{-}(E)\text{-I}]$, and $k_b = k_i[(-)\text{-}(E)\text{-I}]/[(+)\text{-}(E)\text{-I} + (-)\text{-}(E)\text{-I}]$. Values × 10^6 sec^{-1} are: run 1 (DMF, 100°), $k_r \sim 0$, $k_i \sim 21$, $k_c \sim 21$, $k_b \sim 0.24$; run 2 (DMF, 126°), $k_r \sim 0$, $k_i \sim 160$, $k_c \sim 154$, $k_b \sim 5.7$; run 3 (benzene, 175°), $k_r \sim 0.23$, $k_i \sim 1.1$, $k_c \sim 0.67$, $k_b \sim 0.43$; run 4 (benzene, 200°), $k_r \sim 2.6$, $k_i \sim 10$, $k_c \sim 5.8$, $k_b \sim 4.2$. Interesting rate factors emerge: $(k_c/k_b)_{DMF}^{100°} \sim 90$, $(k_c/k_b)_{DMF}^{126°} \sim 27$, $(k_c/k_b)_{benzene}^{175°} \sim 1.6$; $(k_c/k_b)_{benzene}^{200°} \sim 1.4$; ($k_c$, DMF, 126°)/$k_c$, benzene, 175°) ~ 230; (k_b, DMF, 126°)/(k_b, benzene, 175°) ~ 13; $[(k_i, \text{DMF})/(k_i, \text{benzene})]^{150°} \sim 10^4$; $(k_i/k_r)_{DMF}^{100-126°} > 10^2$; $(k_i/k_r)_{benzene}^{175-200°} \sim 4$.

For (+)-(*Z*)-I, cyanoacetate center epimerization (k_c) and benzyl center epimerization rate constants (k_b) are *dramatically and similarly* dependent on solvent polarity, the former being slightly more sensitive. This fact provides strong evidence for *epimerization at both centers involving a similar rate-determining ionization step*, and strong evidence against a triplet diradical or singlet diradical-like mechanism for either of the two epimerizations. Irrespective of mechanism, each epimerization passes through a different orthogonal orbital arrangement (face-to-edge structure) where differentiation of ion pair and singlet diradical is possible, although an electron migration with an activation energy is still possible.

For the three reactions of (+)-(*Z*)-I, the rates of cyanoacetate center epimerization (k_c) > benzyl center epimerization (k_b) > racemization (inversion at both centers, k_r) for both solvents and all temperatures. This order indicates the π-cyclopropane mechanism for simultaneous inversion at both centers[4] makes little or no contribution to these reactions.[4] Lower tem-

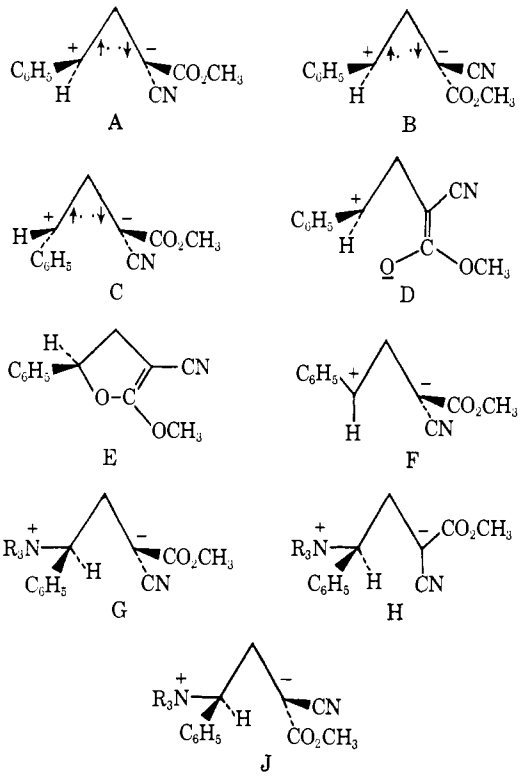
(3) For equations used, see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 186.
(4) R. Hoffmann, *J. Amer. Chem. Soc.*, 90, 1475 (1968).

peratures and the more polar solvent favor larger spreads in rates of the three reactions. In DMF, in going from 100 to 126°, k_c/k_b decreased by 3.3 for a 26° temperature rise. Extrapolation to 175° gives only a factor of 2.7, not far from benzene at 175° (1.6). Possibly temperature differences are mainly responsible for changes in k_c/k_b, not solvent polarity or nucleophilicity.

Mechanisms of the three reactions might involve intermediates A–J. Of these only E is not an ion pair.[5] Mechanism (+)-(Z) → E → (+)-(E) is incompatible with the dramatic and similar response of k_c and k_b to solvent polarity. Epimerization at benzyl (k_b) cannot involve E as an intermediate. Mechanisms

$$(+)\text{-}(Z) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{E} \xrightarrow{k_2} \text{D or G} \longrightarrow (+)\text{-}(E)$$

definitely are compatible with the solvent effects and nonaccumulation of E only if $k_{-1} \gg k_1 > k_2$. This scheme would make fortuitous the similar response of k_c and k_b to solvent polarity. An analogous mechanism for the I ⇄ E → D or G stages was found not to occur in methanol,[2a] although k_c and k (methanolysis) are not far from one another in value. These facts make such a scheme highly improbable. Mechanisms that involve G, H, and J are not possible in benzene, and yet epimerization occurs.



Mechanisms (+)-(Z) → A $\xrightarrow{D}$ B → (+)-(E), (+)-(Z) → A → D → B → (+)-(E), and (+)-(Z) → A → D ⇄ E → B → (+)-(E), with the first stage rate determining, are consistent with the solvent effect on k_c. Mechanisms

$$(+)\text{-}(Z) \longrightarrow \text{A} \xrightarrow{F} \text{C} \longrightarrow (-)\text{-}(E)$$

and (+)-(Z) → A → F → C → (−)-(E) are consistent with the solvent effect on k_b. Structure D either as a transition state or intermediate might provide less charge separation than F, and could be used to explain why $k_c > k_b$. A rapidly reversible D ⇄ E stage is equally attractive. In effect, inclusion of such stages in epimerization at cyanoacetate provides a path for a *conducted tour of C^+ of benzyl from C^- to O^-, to inverted C^-*, to product inverted at the cyanoacetate center, and resembles ionic conducted tour mechanisms suggested in other connections.[6] Intervention of intermediates G, H, and J in the epimerization at the cyanoacetate center in DMF also might explain $k_c > k_b$ in this medium. No such structures are available for epimerization at the benzyl center. Racemization rates appear equally sensitive to solvent character, and probably the same intermediates are involved as in the two epimerization reactions. For example, (+)-(Z) → A → B or C → enantiomer of A → (−)-(Z) are the simplest processes.

(5) Intervention of ketene acetal in (+)-(Z)-I → (+)-(E)-I would nicely correlate this particular epimerization reaction with the well-known aldehydo or acylcyclopropane ⇄ dihydrofuran rearrangement [*e.g.*, see C. L. Wilson, *J. Amer. Chem. Soc.*, 69, 3002 (1947); D. W. Boykin and R. E. Lutz, *ibid.*, 86, 5046 (1964); E. Vogel, *Angew. Chem., Int. Ed. Engl.*, 2, 1 (1963)].

(6) (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 102; (b) T. D. Hoffman and D. J. Cram, *J. Amer. Chem. Soc.*, 91, 1009 (1969).

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Photosensitive Protecting Groups

Sir:

The use of *o*-nitrobenzyl derivatives as photosensitive blocking reagents for amino and carboxyl functions in peptides has been described.[1-3] In this communication we describe some new photosensitive blocking groups, and conditions required for achieving photoremoval in quantitative yields.

Amino acid derivatives, in which the amino function was blocked with photosensitive protecting groups of two kinds, namely, 6-nitroveratryloxycarbonyl (NVOC) and 2-nitrobenzyloxycarbonyl (NBOC), were prepared and characterized (Table I). These blocking groups could be removed by irradiation with light of wavelength longer than 3200 Å. Under these conditions, even the most light-sensitive amino acid, tryptophan, was not affected when deblocked. Irradiations were done in an RPR-100 apparatus (Rayonet, the Southern Co., Middletown, Conn.) The amino acid and peptide derivatives were irradiated at concentrations of 10^{-2}–10^{-3} *M*. Irradiation times were 1–24 hr. Solvents used were dioxane, chloroform, tetrahydrofuran, dimethoxyethane, alcohols, and mixtures of alcohol–water, ether–water. Removal of the blocking groups was quantitative in all cases, as judged by the quantitative release of CO_2, which was determined titrimetrically.[4] The yield of the released amino function was

(1) J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Commun.*, 822 (1966).

(2) A. Patchornik in "Pharmacology of Hormonal Polypeptides and Proteins," Plenum Publishing Co., New York, N. Y., 1968, p 11.

(3) A. Patchornik, B. Amit, and R. B. Woodward, presented at the Tenth European Peptide Symposium, Abano-Terme, Italy, Sept 1969.

(4) A. Patchornik and Y. Shalitin, *Anal. Chem.*, 33, 1887 (1961).