Electrophilic Substitution at Saturated Carbon. XLVII. Conducted Tour Mechanisms around the Cyano Group[1]

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Abstract: The stereochemical course of the base-catalyzed hydrogen–deuterium exchange reactions of (−)-2-methyl-3,3,3-triphenylpropionitrile ((−)-I-*h*) in various solvent–base systems has been examined. Values of k_e/k_α (one point rate constant for isotopic exchange over that for racemization) were used as criteria of steric course, and were found to range from 1 (steric course, racemization) to 0.22 (isoinversion). Representative values are: 1.02 at 75° in CH_3OD–CH_3OK; 0.98 at 40° in $(CD_3)_2SO$–4 *M* CH_3OD–CH_3OK; 0.68 at 25° in $(CH_3)_3COD$–$(CH_3)_3COK$; 0.50 at 25° in *c*-C_6H_{12} (0.53 *M*) in $(CH_3)_3COD$–$(CH_3)_3COK$; 0.50 at 125° in $(CD_3)_2SO$–1.0 *M* CH_3OD–$N(CH_2CH_2)_3NN(CH_2CH_2)_3{}^+NDI^-$; 0.22 at 150° in $(CH_3)_3COD$–$[(CH_3)_2N]_2C{=}NCH_3$–$[(CH_3)_2N]_2C{=}NDCH_3I$. The mechanistic components contributing to these overall results were dissected by the *reresolution method*, in which (−)-I-*h* in four deuterated media was submitted to partial isotopic exchange and reisolated, racemate and enantiomer were separated, and each was analyzed for deuterium. The rate constants at which (−)-2-deuterio-2-methyl-3,3,3-triphenylpropionitrile ((−)-I-*d*) racemized in the same four media were also determined. These data provided *second-order* rate constants for isotopic exchange of (−)-I-*h* with retention, for isotopic exchange with inversion, and for inversion without isotopic exchange or *isoinversion*. From these rate constants at time equals zero it was calculated that in *tert*-butyl alcohol–potassium *tert*-butoxide, racemization accounted for 84% and isoinversion for 16% of the steric course for reaction. Crown ether (dicyclohexyl-18-crown-6 cyclic polyether) added to the same medium essentially destroyed the isoinversion component and increased the racemization–exchange rate by about two powers of 10. The isoinversion component appears dependent on the presence of potassium carbanide contact ion pair. In dimethyl sulfoxide–methanol–triethylenediamine at zero time, racemization accounted for 75% of the total reaction, and isoinversion for 25%. Even in this polar medium, ammonium carbanide ion pairs reorganize at rates competitive with dissociation. In *tert*-butyl alcohol–pentamethylguanidine at zero time, racemization accounted for 39% of the total reaction, net exchange with retention for 9%, and isoinversion for 52%. The retention component is interpreted as involving pentamethylguanidinium *tert*-butoxide ion pairs as catalyst. All isoinversion results are interpreted in terms of a conducted tour mechanism in which cations bound to the proton abstracted from carbon and migrate from the front face of the carbanion around nitrogen and to the back face of the carbanion, where collapse to the covalent state occurs. This contact ion pair reorganization reaction is competitive with ion pair dissociation, as is the reaction of collapse of the contact ion pair to the covalent state. When crown ether was added to the run in *tert*-butyl alcohol-*O*-*d*–potassium *tert*-butoxide, the kinetic isotope effect for racemization at 25° decreased from ~15 to ~5.

Isoinversion was first detected[2a] in the base-catalyzed isotopic exchange and racemization reactions of carbon acids II and III when k_e/k_α values (rate constant for isotopic exchange over rate constant for racemization) lower than 0.5 were observed.[2a,b] Further survey of carbon acids V–VII also revealed that under appropriate conditions k_e/k_α values of less than 0.5 could be obtained.[2d]

Determination of crude k_e/k_α values provides a qualitative measure of the *overall* stereochemical course of base-catalyzed isotopic exchange reactions of optically active carbon acids with isotopic reservoirs of the same acidity as the conjugate acid of the base used as catalyst. However, the overall stereochemical outcome is usually a blend of specific mechanistic paths, each with its own stereochemical course. Two methods were developed to dissect the overall outcome into its stereochemical components, the first being purely kinetic in character, the second depending on reresolution (in effect) and isotopic analysis of the component parts of a partially racemized–partially exchanged carbon acid.[2c] The latter is referred to as the *reresolution method.* Its use provides values for k_1, the rate constant for isotopic exchange with retention, k_2, the rate constant for isotopic exchange with inversion, and k_3, the rate constant for inversion without isotopic exchange (isoinversion[2h]). When $k_1 = k_2$, then $2k_1$ or $2k_2$ equals the rate constant for racemization (k_α). If H and D refer to the isotopic labels of the carbon acid and the plus or minus signs to their signs of rotation, then these components can be formulated. In this scheme, k_4 is the rate constant for total inversion of material that has already undergone isotopic exchange, and is a directly measured rate constant in which deuterated carbon acid is racemized in deuterated media.

$$H_- \xrightarrow{k_1} D_- \quad \text{retention}$$

$$H_- \xrightarrow{k_2} D_+ \quad \text{inversion}$$

$$H_- \xrightarrow{k_3} H_+ \quad \text{isoinversion}$$

$$D_- \xrightarrow{k_4} D_+ \quad \text{total inversion of material already exchanged}$$

With the reresolution technique, carbon acids IV[2c] and VIII[2g] have been shown under appropriate con-

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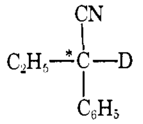
(1) This research was supported by the U. S. Research Office, Durham, N. C.

(2) (a) D. J. Cram and L. Gosser, *J. Amer. Chem. Soc.*, **86**, 2950 (1964); (b) D. J. Cram and L. Gosser, *ibid.*, **86**, 5457 (1964); (c) W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 4661 (1967); (d) D. J. Cram, W. T. Ford, and L. Gosser, *ibid.*, **90**, 2598 (1968); (e) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968); (f) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2612 (1968); (g) J. N. Roitman and D. J. Cram, *ibid.*, **93**, 2225 (1971); (h) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 98.

ditions to react to give isoinversion components blended with racemization, and net inversion with exchange. In general, tertiary amines as basic catalysts, nonpolar solvents, and carbon acids carrying functional groups capable of distributing the negative charge of derived carbanions have favored the isoinversion pathway. Carbon acid II with phenyl and cyano as anion-stabilizing groups gave the lowest k_e/k_α values obtained (0.05),[2b] and was acidic enough to allow a variety of conditions to be examined. However, the reresolution method could not be applied to the system because no direct means was available of separating racemate and enantiomer (both are oils).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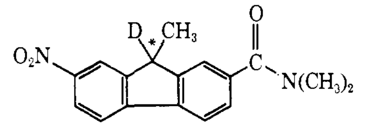
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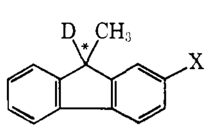
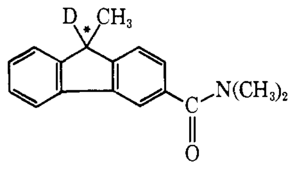

IV, X = CON(CH$_3$)$_2$
V, X = CN
VI, X = NO$_2$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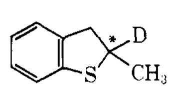
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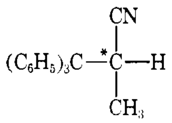
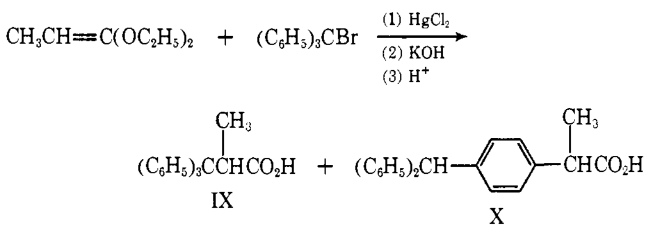

I

Accordingly, cyano compound I was examined, and was found to possess the following advantages. (1) It can be prepared in an optically pure and deuterated state. (2) Both racemate and enantiomers are crystalline, and can be separated from one another. (3) The compound is a strong enough acid (estimated pK_a of 25) to allow a variety of conditions to be studied.

Results

Synthesis of (−)-2-Methyl-3,3,3-triphenylpropionitrile ((−)-I-*h*) and Its 2-Deuterio Derivative ((−)-I-*d*). Treatment of methylketene diethyl acetal[3a] with trityl bromide in the presence of mercuric chloride gave an inseparable mixture of esters (90%) which was hydrolyzed to their corresponding acids, which were poorly separated by fractional recrystallization to give 2-methyl-3,3,3-triphenylpropionic acid (IX) and 2-(*p*-benzhydrylphenyl)propionic acid (X). The fact that both the α-carbon and the para position of the trityl cation were attacked by the ketene acetal must reflect a balance of charge distribution and steric effects. With dimethylketene dimethyl acetal and trityl bromide, the para position was essentially the only one involved.[4] Acid IX was resolved through its quinine salt to give (+)-IX of maximum rotation, and (−)-IX of the same rotational magnitude and melting point was separated by fractional crystallization of enantiomer from racemate. Both (+)-IX and (−)-IX of maximum rotation were converted by conventional reactions to their amides, whose melting points and rotational magnitudes were the same. By ordinary reactions these amides were converted to their nitriles, (−)-I-*h* and (+)-I-*h*, whose melting points and rotational magnitudes were identical. The same melting points and rotations of these nitriles could be reached by fractional crystallization of partially racemic I.



The methyl ester of (±)-IX was deuterated to 0.98 atom excess deuterium (mass spectrometry) with potassium methoxide and methanol-*O-d;* the ester was hydrolyzed with acid without deuterium loss, and partially resolved. The resulting (−)-IX-*d* was converted to (−)-I-*d* of about 21% optical purity that contained 0.97 atom excess deuterium (mass spectrometry).

Survey of Effect of Media on the Overall Steric Course of Isotopic Exchange. Fifteen runs were made in which optically pure nitrile (−)-I-*h* was submitted to isotopic exchange–racemization in various deuterated media containing catalytic amounts of base. The reactions were interrupted after from 10 to 68% isotopic exchange and from 19 to 90% racemization had occurred. The total sample of nitrile was recovered, and its rotation and deuterium content were determined (mass spectrometry). From the results, the ratios of one-point rate constants, k_e/k_α, were determined through the use of eq 1. Table I records the conditions for the experiments and the results. Values of

$$k_e/k_\alpha = \frac{\log(1 - \text{fraction exchanged material})}{\log(1 - \text{fraction racemized material})} \qquad (1)$$

k_e/k_α ranged from 1.03 to 0.20.

The conjugate acid of the basic catalyst served as the deuterium pool except in runs 10, 12, 13, and 14. Run 11 catalyzed by triethylenediamine was carried out in the presence of triethylenediamine dideuterium iodide and gave essentially the same k_e/k_α value as run 10 made without added salt. Similarly, run 15 with pentamethylguanidine as catalyst was carried out in the presence of pentamethylguanidinium iodide and gave about the same result as run 14 carried out in the presence of tetrabutylammonium iodide, or runs 12 and 13 made without added salt. In runs 11 and 15, the salts as deuterium reservoirs were backed by much larger alcoholic deuterium reservoirs, and the two types of deuterium pools were undoubtedly equilibrating much faster than the carbon acid was losing its proton to either of them. The added salts increased both the exchange and racemization rates by small amounts in runs 14 and 15. The deuterium reservoirs were not diluted with protium enough to change k_e/k_α values much except possibly in runs 7–9. A crude estimate of the effect of protium dilution in these runs suggests

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[3] (a) S. M. McElvain and W. R. Davie, *J. Amer. Chem. Soc.*, 73, 1400 (1951); (b) S. M. McElvain and C. L. Aldridge, *ibid.*, 75, 3987 (1953).

[4] (a) R. Heck, P. S. Magee, and S. Winstein, *Tetrahedron Lett.*, 2033 (1964); (b) D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *J. Amer. Chem. Soc.*, **88**, 2759 (1966).

Table I. Results of Survey of Overall Stereochemical Course of Isotopic Exchange and Racemization Reactions of Nitrile (−)-I-*h* in Various Deuterated Media

Run no.	Substrate concn, M	Base		Solvent	Deuteron pool		Time, min	Temp,[a] °C	% rac[b]	% exch[c]	k_e/k_α
		Nature	Concn, M		Nature	Concn, M					
1	0.1	CH_3OK	0.0244	CH_3OD^d	CH_3OD^d		180	75.2	41.3	42	1.02
2	0.1	CH_3OK	0.57	CH_3OD^d	CH_3OD^d		60	40	24.5	25	1.03
3	0.08	CH_3OK	0.0044	$(CD_3)_2SO^e$	CH_3OD^d	4.7	15	25	18.9	18	0.98
4	0.1	$(CH_3)_3COK$	0.019	$(CH_3)_3COD^f$	$(CH_3)_3COD^f$		10	25	44.8	33	0.68
5	0.09	$(CH_3)_3COK$	0.017	$(CH_3)_3COD^f$	$(CH_3)_3COD^f$		20	25	70.0	61	0.78
6	0.1	$(CH_3)_3COK$	0.009	$(CH_3)_3COD^f$	$(CH_3)_3COD^f$		17	25	65.7	51.5	0.68
7	0.086	$(CH_3)_3COK$	0.0054	$(CH_2)_4O$	$(CH_3)_3COD^f$	1.06	3	25	81	51	0.44
8	0.1	$(CH_3)_3COK$	0.0059	C_6H_6	$(CH_3)_3COD^f$	1.18	82	25	85.8	54	0.40
9	0.05	$(CH_3)_3COK$	0.003	C_6H_{12}	$(CH_3)_3COD^f$	0.53	150	25	95.1	68	0.38
10	0.1	$N(CH_2CH_2)_3N$	0.9	$(CD_3)_2SO^e$	CH_3OD^d	1.0	600	125	49.8	30.0	0.51
11	0.1	$N(CH_2CH_2)_3N$	0.7	$(CD_3)_2SO^e$	$CH_3OD^{d,g}$	1.0	480	125	19.4	10.2	0.50
12	0.1	$[(CH_3)_2N]_2C{=}NCH_3$	0.20	$(CH_3)_3COD^f$	$(CH_3)_3COD^f$		3855	150	94	37.8	0.17
13	0.1	$[(CH_3)_2N]_2C{=}NCH_3$	0.20	$(CH_3)_3COD^f$	$(CH_3)_3COD^f$		3020	150	88.4	35.5	0.20
14	0.1	$[(CH_3)_2N]_2C{=}NCH_3$	0.18	$(CH_3)_3COD^{f,h}$	$(CH_3)_3COD^f$		2400	150	86.6	38.5[i]	0.24
15	0.1	$[(CH_3)_2N]_2C{=}NCH_3$	0.17	$(CH_3)_3COD^f$	$[(CH_3)_2N]_2C{=}NDCH_3I$	0.01	2400	150	90.1	40.0[i]	0.22

[a] 25° bath is ±0.1°; 40°, 75°, 125°, and 150° baths were ±1°. [b] Starting material gave $[\alpha]^{25}_D$ −73.5° (*c* 1.0, CHCl$_3$); −74.2° (*c* 1.84, CHCl$_3$). [c] Infrared analysis, +3%. [d] >0.98 atom excess of deuterium. [e] >97% fully deuterated. [f] >0.98 atom excess of deuterium. [g] 0.001 *M* in $^-IDN^+(CH_2CH_2)_3{}^+NDI^-$. [h] 0.01 *M* in tetrabutylammonium iodide. [i] Analyzed by mass spectroscopy.

Table II. Kinetics of Racemization of (−)-I-*d*

Run no.	Subst concn, M	Base		Solvent	T,[a] °C	No. of points	k_4, l. mol^{-1} sec^{-1}
		Nature	Concn, M				
16	0.05	$(CH_3)_3COK$	0.00477	$(CH_3)_3COD^b$	25	12[c]	$2.24 \pm 0.07 \times 10^{-3}$
17	0.05	$(CH_3)_3COK$	0.00212	$(CH_3)_3COD^{b,d}$	25	20[c]	$300 \pm 8 \times 10^{-3}$
18	0.10	$N(CH_2CH_2)_3N$	0.9643	$(CD_3)_2SO^e$	125	3[f]	$2.78 \pm 0.21 \times 10^{-6}$
19	0.10	$[(CH_3)_2N]_2C{=}NCH_3$	0.1944	$(CH_3)_3COD^b$	150	3[f]	$2.63 \pm 0.11 \times 10^{-5}$

[a] 25° bath was ±0.1°; 125° and 150° baths were ±0.2°. [b] >0.98 atom excess deuterium. [c] Followed in polarimeter tube. [d] Was 0.0025 *M* in 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,24}]hexacosane (cyclic ether XI). [e] >97% deuterated, and was 1 *M* in CH$_3$OD containing 0.98 atom excess of deuterium. [f] Ampoule technique—total product was isolated for each point and its rotation taken.

Table III. Rate Constants for Stereochemical Components of Isotopic Exchange–Racemization of 0.1 *M* Solutions of Optically Pure (−)-I-*h*

Run no.	Base		Solvent	T,[a] °C	Time, min	k_e/k_α	Second-order rate constants, l. mol^{-1} sec^{-1}		
	Nature	Concn. M					Exchange ret (k_1)	Exchange inv (k_2)	Isoinversion (k_3)
20	$(CH_3)_3COK$	0.00477	$(CH_3)_3COD^b$	25	37	0.7	$(2.41 \pm 0.08) \times 10^{-2}$	$(2.42 \pm 0.08) \times 10^{-2}$	$(0.87 \pm 0.6) \times 10^{-2}$
21	$(CH_3)_3COK$	0.00233	$(CH_3)_3COD^{b,c}$	25	2	0.96	1.52 ± 0.05	1.52 ± 0.05	0.037 ± 0.023
22	$N(CH_2CH_2)_3N$	0.9643	$(CD_3)_2SO^d$	125	720	0.59	$(6.31 \pm 0.21) \times 10^{-6}$	$(6.71 \pm 0.25) \times 10^{-6}$	$(4.45 \pm 0.25) \times 10^{-6}$
23	$[(CH_3)_2N)_2$-$C{=}NCH_3$	0.1944	$(CH_3)_3COD^b$	150	570	0.27	$(1.28 \pm 0.08) \times 10^{-5}$	$(0.87 \pm 0.06) \times 10^{-5}$	$(2.36 \pm 0.09) \times 10^{-5}$

[a] 25° bath was ±0.1°; 125 and 150° baths were ±0.2°. [b] >0.98 atom excess of deuterium. [c] Was 0.0025 *M* in 18-crown-6 cyclic polyether XI. [d] >0.98 atom excess of deuterium.

that k_e/k_α values of not higher than 0.5 would have been obtained had dilution not occurred.

Dissection of Reactions into Their Component Stereochemical Pathways. The reresolution technique was applied to four sets of reaction conditions: *tert*-butyl alcohol-*O*-*d*–potassium *tert*-butoxide with and without an equimolar amount of the 18-crown-6 cyclic polyether (XI);[5] deuterated dimethyl sulfoxide (1 *M*) in methanol-*O*-*d* with triethylenediamine as base; *tert*-butyl alcohol-*O*-*d* with pentamethylguanidine as base. The pseudo-first-order rate constants of the racemization of (−)-I-*d* were measured in each of these media. The reactions were followed polarimetrically through from about 50 to 80% reaction, and good first-order rate constants were calculated from the data. By definition, $k_\alpha = 2k_4$. The reaction conditions and k_4 values as second-order rate constants are recorded in Table II.

Runs 20–23 were made under the same conditions as those for determination of k_4 except that optically pure (−)-I-*h* served as substrate, and the runs were interrupted after 35–61% racemization had occurred. The total sample was recovered, its rotation was taken, and the deuterium content was determined by mass spectrometry. Racemate and the (−)-enantiomer were separated by a combination of fractional crystallization and manual separation of the crystals. The rotations of each were taken and deuterium content measured. From these data and the equations developed earlier[2c] were calculated k_1, k_2, and k_3. Table III records these results calculated as second-order rate constants. The probable errors reported include those in the deuterium analyses (±1 standard deviation) and in the base concentration (±2%). The difference in k_1 and k_2

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(5) (a) C. J. Pederson, *J. Amer. Chem. Soc.*, **89**, 2495 (1967). (b) We are grateful to Dr. E. K. Gladding of the Elastomers Department of E. I. du Pont for a supply of this material.

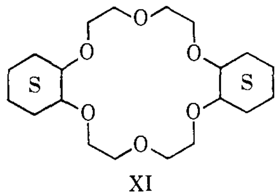
in run 23 is considered real. Runs 20, 22, and 23 all contain sizable isoinversion components whereas that of run 21 is negligible.

Discussion

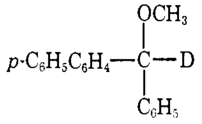
The pattern of k_e/k_α values of Table I indicates a blend of stereochemical pathways for reaction of nitrile I. The close proximity of these values to unity in runs 1–3 with potassium methoxide as base in methanol or dimethyl sulfoxide (1.03–0.98) indicates the exchange reaction proceeded with essentially total racemization. The very low concentration of potassium methoxide in runs 1 and 3 (0.024 and 0.0044 M) suggests that methoxide ion was the probable catalyst, but the same result was obtained when 0.57 M base was employed, and some was probably ion paired. An increase in net inversion components was observed as the solvent became less polar on the one hand, and amine catalysts were substituted for potassium alkoxides on the other.

In the four media selected for closer examination in runs 20–23, in no case did isotopic exchange with inversion (k_2) exceed in rate isotopic exchange with retention (k_1). All the inversion visible in the depression of k_e/k_α values below unity was due entirely to an isoinversion (k_3) component. The same is also probably true for runs 4–15 of Table I. The validity of the use of k_e/k_α values obtained from single points for purposes of surveying overall stereochemical reaction course is confirmed by the results of runs 20–23 (Table III). Examination of the k_e/k_α value of run 20 (0.7) indicates the presence of a net inversion component. At time equals zero, isoinversion (k_3) contributed 16% to the overall sum of reaction components [$100\% k_3/(k_1 + k_2 + k_3)$]. In run 21, k_e/k_α = 0.96, which indicated the reaction went with essentially total racemization. At time zero, isoinversion (k_3) contributed ~1% (if at all) to the overall reaction. In run 22, k_e/k_α = 0.59, which indicated that some of the reaction went with net inversion. Actually at time zero, isoinversion contributed 25% and racemization 75% to the overall reaction. In run 23, k_e/k_α = 0.27, a value which indicates the presence of a very substantial isoinversion component. Dissection of the mechanistic components indicated that at time zero isoinversion contributed 52%, racemization 39%, and *net retention* 9% to the overall reaction. The two qualitative pieces of information the reresolution method uniquely provided were that no exchange with net inversion contributed ($k_2 \overset{=}{<} k_1$), and that in run 23, a small exchange with net retention component was present ($k_1 > k_2$).

Dependence of Isoinversion Mechanism on Potassium Ion in *tert*-Butyl Alcohol–Potassium *tert*-Butoxide. In run 20 carried out in *tert*-butyl alcohol-*O-d*-0.00477 M potassium *tert*-butoxide, $k_3/(k_1 + k_2 + k_3) = 0.16$ and $k_1 = k_2$. In run 21, the same solvent was used, the potassium *tert*-butoxide concentration was 0.00233, and the medium was 0.00233 M in 18-crown-6 cyclic polyether XI. This crown ether is capable of filling the coordination sites of potassium ion[5a] and of turning contact ion pairs into what behave like solvent-separated ion pairs.[6] The presence of the crown ether caused a rate *increase* in isotopic exchange ($k_1 + k_2$) by a factor of 63, and virtually eliminated the isoinversion component, although its absolute rate (k_3) increased by a factor between 1.5 and 7. In prior work,[2g] carbon acid XII was found to give k_e/k_α = 46 in *tert*-butyl alcohol–potassium *tert*-butoxide. Addition of crown ether to the medium increased the rates of exchange and racemization by several powers of 10, and reduced k_e/k_α to unity. Thus both the retention and isoinversion components being competitive with racemization mechanisms appear to depend on the presence of potassium ion in a form capable of coordinating with the alcohol molecule formed by proton abstraction by the alkoxide.



XI



$$p\text{-}C_6H_5C_6H_4\text{—}\overset{\overset{\textstyle OCH_3}{|}}{\underset{\underset{\textstyle C_6H_5}{|}}{C}}\text{—}D$$

XII

The blend of isoinversion and racemization mechanisms visualized is outlined in Chart I. It makes use of contact ion pair reorganization in such a way that both anion and cation rotate at rates competitive with ion pair dissociation, which also probably contributes to the racemization mechanism (not included). The specific manner in which the carbanion turns over involves the potassium ion with its ligands of leaving group ($(CH_3)_3COH$) and solvent molecules ($(CH_3)_3COD$) going on a conducted tour of the π system of the cyanocarbanion, plus charge following minus charge in the process. The tour starts at the front face of the carbanion and goes out to nitrogen, where it partitions, part going back to the front face and part to the back face. Rotation of potassium ion is a competitive process, and when deuterium is rotated into hydrogen bonding position, isotopic exchange results, both on the front and back faces. Return of protium to the front face and collapse to the covalent state gives starting material. Conduction of protium to the back face and collapse to the covalent state gives isoinversion. Although hydrogen or deuterium might be donated to nitrogen on this conducted tour to form an azaketene, the proton would be removed again by the basic catalyst and continue on its way to give the more stable carbon acid. Ligand exchange with bulk solvent also undoubtedly occurs, and contributes to the exchange.

Difference in Stereochemical Course When Tertiary Amine and Potassium Methoxide Served as Catalyst in Dimethyl Sulfoxide–Methanol. In run 3 made with potassium methoxide in dimethyl sulfoxide–methanol-*O-d*, racemization accounted for the whole reaction. In this medium, dissociated methoxide ion was probably the catalytic species, and the carbanion lasted long enough to pass into an isotopically symmetrical environment. When triethylenediamine was substituted as base in runs 10 and 11 in the same medium both in the presence and absence of added deuterium iodide salt of the base, a sizable inversion component was visible in the k_e/k_α values (~0.5). Run 22 demonstrated that this was due entirely to isoinversion (k_3), and that $k_3/[k_1 + k_2 + k_3] = 0.25$. Again contact ion pair reorganization and collapse to the covalent state appear to be reactions competitive with ion pair dissociation,

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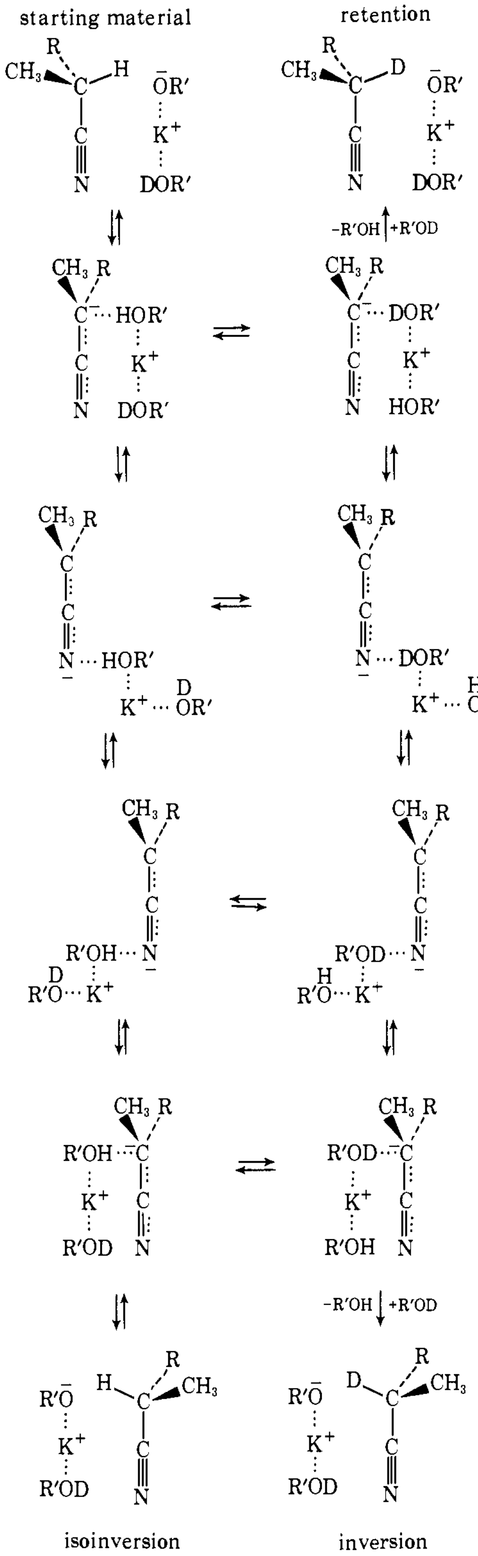
[6] L. L. Chan, K. H. Wong, and J. Smid, *J. Amer. Chem. Soc.*, **92**, 1955 (1970), and prior papers.

Chart I

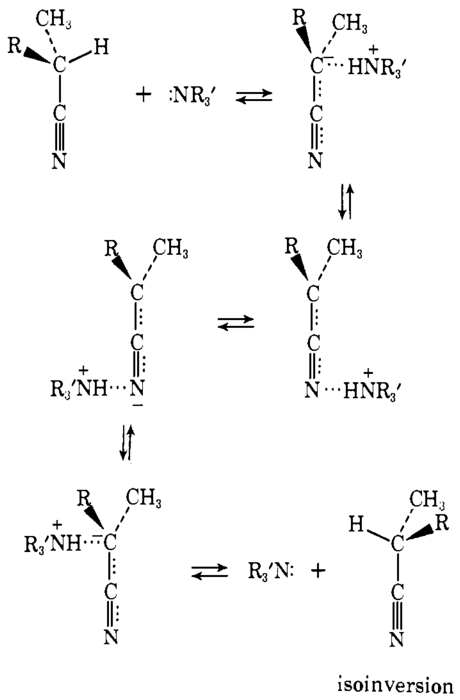


which would lead to exchange. This polar medium was required for the reaction to be observed at reasonable temperatures. Had nonpolar media been usable, isoinversion would undoubtedly have dominated over the racemizing isotopic exchange reaction. Again a conducted tour mechanism is visualized in which the trialkylammonium ion transports a proton from the front to the back face of the carbanion out around nitrogen, which carries much of the negative charge of the anion (Chart II). This result coupled with those of runs 20 and 21 suggests that the presence of an appreciable isoinversion component in the nitrile system is dependent on ion-pair intermediates. This same medium had previously been shown[4b] to provide >85% intramolecularity in the isomerization of 3-deuterio-1,3,3-triphenylpropyne to 1-deuterio-1,3,3-triphenylallene. However, small isoinversion components have been observed in potassium methoxide–methanol in both amide system IV[2c] and sulfone system VIII.[2g]

Blend of Net Retention, Isoinversion, and Racemization When Pentamethylguanidine Served as Catalyst. Runs 12–15 and 23 all involved pentamethylguanidine as base and *tert*-butyl alcohol-*O-d* as solvent. The k_e/k_α values were between 0.17 and 0.27, and were not affected by the presence of either tetrabutylammonium iodide or deuterated pentamethylguanidinium iodide. Run 23 demonstrated that the contribution of isoinversion to the detectable processes $[k_3/(k_1 + k_2 + k_3)]$ was 0.52, racemization $[2k_2/(k_1 + k_2 + k_3)]$ was 0.39, and net retention $[(k_1 - k_2)/(k_1 + k_2 + k_3)]$ was 0.09. This is the first example of a blend of isoinversion with net retention, although a blend of isoinversion and net inversion has been encountered.[2g]

An attractive explanation for the presence of both an isoinversion and retention mechanism invokes the existence of two catalytic species, each being responsible for one of the two components. Pentamethylguanidinium ion possesses a pK_a of about 15.6[7] and *tert*-butyl alcohol one of about 19.[8] Thus small amounts of pentamethylguanidinium *tert*-butoxide should be present in the reaction mixture. It is postulated that pentamethylguanidine in acting as a catalyst provides the conducted tour mechanism for isoinversion similar to that envisioned when triethylenediamine served as base (Chart II). Pentamethylguanidinium *tert*-butoxide is regarded as providing the net retention component (Chart III). The competing racemization

Chart II



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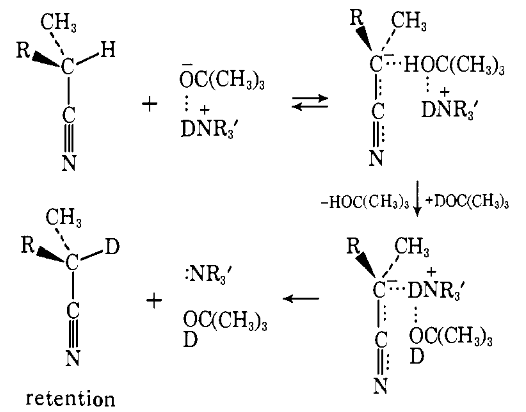
(7) K. G. Flynn and D. R. Nenortas, *J. Org. Chem.*, **28**, 3527 (1963).
(8) W. K. McEwen, *J. Amer. Chem. Soc.*, **58**, 1124 (1936).

Chart III



component probably reflects dissociation of the contact ion pairs visualized as responsible for the two stereospecific components.

$$[(CH_3)_2N]_2C{=}NCH_3 + DOC(CH_3)_3 \rightleftarrows$$

pentamethylguanidine

$$[(CH_3)_2N]_2C{=}\overset{+}{N}DCH_3\overset{-}{O}C(CH_3)_3$$

pentamethylguanidinium *tert*-butoxide

These suggestions are not without precedent. Fluorene system IV with an amido group in the 2 position gave $k_e/k_\alpha \sim 6$ in *tert*-butyl alcohol and tripropylamine. A tripropylammonium *tert*-butoxide ion pair was thought responsible. The competing abstraction of deuterium by tripropylamine was interpreted as being an invisible reaction, starting material being the only product.[2d] In contrast, fluorene system VII with the amido group in the 3 position where it could better distribute negative charge in the derived anion gave $k_e/k_\alpha \sim 0.1$. In this system, the deuterium abstraction by the tertiary amine was rendered visible by the conducted tour mechanism out around the amido group to give isoinversion. In the present system, both the retention and isoinversion mechanisms appear to operate side by side.

Isotope Effects. The data of Tables II and III allow calculation of kinetic isotope effects for racemization of carbon acids (−)-I-*h* and (−)-I-*d* in the deuterated media of runs 20–23 through use of eq 2.[2c] Thus in

$$(k_H/k_D)_{ROD}{}^{\alpha} = (k_2 + k_3)/k_4 \qquad (2)$$

$(CH_3)_3COD–(CH_3)_3COK$ at 25°, the isotope effect was ~15 (run 20). Addition of crown ether XI reduced the isotope effect by a factor of 3 to ~5 (run 21). Of these two isotope effects, that obtained without crown ether present appears the more unusual, being considerably higher than has been observed before in our studies. However, others[9] have observed very large (k_H/k_D = 24) kinetic isotope effects in the 2,4,6-trimethylpyridine-catalyzed carbanion formation from 2-nitropropane in *tert*-butyl alcohol (60%)–water (40% by volume) at 25°. These authors also found that the isotope effect increased with increasing steric hindrance of the pyridine, the isotope effect being 10 with pyridine itself. They interpreted the increase in isotope effect with increased hindrance to possible proton tunneling and loss of zero-point energy with the highly hindered bases.

The three phenyl groups of system I coupled with the three methyl groups of the *tert*-butoxide anion and the potassium ion with its solvent ligands provide a sterically compressed transition state for proton transfer in our system. Some of this compression is probably relieved by removal of the potassium ion with its ligands from the transition state by turning the active base from a contact ion pair (run 20) into (in effect) a solvent-separated ion pair (run 21) by the addition of crown ether XI. This interpretation allows analogy to be drawn between our and Lewis and Funderburk's results. We have no new interpretation.

In run 22 in dimethyl sulfoxide–methanol–triethylenediamine at 125°, an isotope effect of 4.0 was observed. In run 23 in *tert*-butyl alcohol–pentamethylguanidine at 150°, the isotope effect decreased to 1.2. Although both of these isotope effects would be substantially higher at 25°, both would be in the normal range.

Experimental Section

Ethyl 2-Methyl-3,3,3-triphenylpropionate and Ethyl 2-(*p*-Benzhydrylphenyl)propionate Mixture. From 56 g (0.318 mol) of triethyl orthopropionate and 80 g (0.325 mol) of sublimed aluminum *tert*-butoxide by the procedure of McElvain and Davie[3a] was prepared 28 g (0.215 mol) of methylketene diethyl acetal, bp 62° (62 mm). This material with 32 g of trityl bromide and 0.265 g of mercuric chloride was converted by the McElvain and Aldridge procedure[3b] to a mixture of 45 g of the title esters. These materials were identified by their hydrolysis products (see below).

2-Methyl-3,3,3-triphenylpropionic Acid (IX) and 2-(*p*-Benzhydrylphenyl)propionic Acid (X). The above ester mixture was dissolved in 400 ml of absolute ethanol. To this solution, 125 g of potassium hydroxide in 100 ml of water was added, and the solution was refluxed for 64 hr. The alcohol was removed on a rotatory evaporator, and the residue was poured into an ice–hydrochloric acid mixture to give a white gummy solid. The acid mixture was extracted with dichloromethane and dried. After removal of solvent, the remaining light yellow viscous oil solidified upon standing to give a mixture of the two acids, 30 g (90% based on trityl bromide), mp 140–180°. This mixture was dissolved in 100 ml of hot benzene. From the cooled solution, 12 g of IX crystallized, mp 184–190°. Further recrystallization of this material from benzene yielded 9 g of pure IX: mp 192–193°; ir (CH_2Cl_2) 3–3.5 μ (acid OH) and 5.84 (acid C=O); nmr ($CDCl_3$) δ 7.23 (m, 15, aromatic), 4.37 (q, 1, J = 7 Hz, CH), 1.16 (d, 3, J = 7 Hz, CH_3). *Anal.* Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.59; H, 6.62.

The benzene filtrate was concentrated to 50 ml and 50 ml of pentane was added. A mixture of the two acids crystallized. Recrystallizations of the material from benzene gave further 3 g of pure IX (40% yield overall).

The mother liquors were combined, the solvent was evaporated, and the oily residue dissolved in a little acetone. After standing at −10°, 2 g of X separated. Recrystallization of this material from acetone gave 1.5 g of pure acid X: mp 153–154°; nmr (CCl_4) δ 7.22 (m, 14, aromatic), 5.54 (s, 1, Ar_3CH), 3.71 (q, 1, J = 7 Hz, ArCH), 1.44 (d, 3, J = 7 Hz, CH_3). *Anal.* Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.59; H, 6.62.

Resolution of 2-Methyl-3,3,3-triphenylpropionic Acid (IX). A mixture of 100 g of racemic IX and 100 g of quinine was dissolved in 306 ml of absolute ethanol. The ethanol was evaporated under reduced pressure and the oily residue was dissolved in 4280 ml of dry ether. After 48 hr at −18°, 46 g of quinine salt was obtained. After five crystallizations of this salt from absolute ethanol, a total of 19 g of optically pure salt was obtained. The salt was converted to the acid, and the acid was recrystallized from benzene to give white solid, 8 g: mp 172–173°; $[\alpha]^{25}_{546}$ +8.1° (*c* 3.69, $CHCl_3$), $[\alpha]^{25}_{436}$ +18.0° (*c* 3.69, $CHCl_3$), mp 173–174°. *Anal.* Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.68; H, 6.38.

The filtrate of the quinine salt was concentrated to 1200 ml and was allowed to stand at −25° for 48 hr. A further 50 g of salt was obtained whose acid showed no optical activity. The mother liquor of the second crop was concentrated, and 40 g of (−)-IX was isolated from the oily quinine salt, $[\alpha]^{25}_{546}$ −2.43° (*c* 3.88,

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(9) E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, **89**, 2322 (1967).

$CHCl_3$), $[\alpha]^{25}_{436}$ −5.86° (*c* 3.9, $CHCl_3$). This (−)-acid was dissolved in 160 ml of benzene. After addition of 60 ml of pentane to the benzene solution, 30.3 g of racemic acid crystallized. By adding 160 ml of pentane to the filtrate, another 1.3 g of racemic acid was obtained. The mother liquor was evaporated, and 13 g of (−)-IX, $[\alpha]^{25}_{546}$ −7.1° (*c* 3.7, $CHCl_3$), was recovered. This 90% optically pure acid was recrystallized from benzene–pentane mixture. A total of 10.5 g of pure (−)-IX, $[\alpha]^{25}_{546}$ −8.2° (*c* 3.7, $CHCl_3$) was obtained, mp 172–173°. *Anal.* Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.34; H, 6.30.

2-Methyl-3,3,3-triphenylpropionamide. The procedure was an adaptation of one in the literature.[10] A mixture of 10 g (0.0318 mol) of racemic acid IX, 33 ml (0.46 mol) of thionyl chloride, and 3.3 ml of *N*,*N*-dimethylformamide in 170 ml of benzene was stirred at room temperature for 2 hr. The volatile material was evaporated under reduced pressure, and the last trace of thionyl chloride was removed by codistillation with added benzene at low pressure. The residue was evacuated for 2.5 hr and dissolved in 150 ml of dry dichloromethane (distilled over phosphorus pentoxide). The solution was stirred for 1 hr with 60 ml of dry ammonia in 40 ml of dichloromethane, and was warmed to room temperature, washed with 2 *N* hydrochloric acid, 2 *N* sodium carbonate, and water, dried, and concentrated. About 10 g of residue was obtained, which solidified upon addition of a small amount of ether. Recrystallization of the material from 100 ml of benzene gave white needles, 7.5 g (76%): mp 183–184°; ir ($CHCl_3$) 2.87 and 2.97 μ (NH_2), 6.0 (amide C=O); the nmr spectrum was very similar to that of acid IX. *Anal.* Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.62; H, 6.65; N, 4.49.

By the above procedure, 20 g of optically pure (+)-IX gave 15.6 g (80%) of (+)-amide: mp 216–217°, $[\alpha]^{25}_{546}$ + 55.0° (*c* 2.4, dimethyl sulfoxide), $[\alpha]^{25}_{436}$ +100.0° (*c* 2.4, dimethyl sulfoxide). *Anal.* Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.96; H, 6.76; N, 4.18.

By the same procedure, 20 g of optically pure (−)-IX gave 16 g (80%) of (−)-amide: mp 216–217°; $[\alpha]^{25}_{546}$ −54.9° (*c* 2.4, dimethyl sulfoxide), $[\alpha]^{25}_{436}$ −100° (*c* 2.4, dimethyl sulfoxide). *Anal.* Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 84.02; H, 6.72; N, 4.25.

2-Methyl-3,3,3-triphenylpropionitrile (I). An adaptation of the procedure of Fischer and Grob[10] was employed. A mixture of 10.4 g (0.073 mol) of phosphorus pentoxide and 30 g of purified sand was mixed intensively.

A solution of 5.2 g (0.0165 mol) of the above racemic amide in 28.3 ml of triethylamine and 57 ml of dry chloroform (distilled over phosphorus pentoxide) was added to the sand mixture. The mixture was vigorously stirred and refluxed for 2 hr. After the mixture was cooled, 475 ml of ether and 475 ml of water were added to dissolve the excess phosphorus pentoxide. The sand was filtered, and the ether layer was washed successively with 2 *N* hydrochloric acid, 2 *N* sodium carbonate and water, and dried. After the solvent was removed, 5 g of oily residue was obtained. It was chromatographed on 350 g of silica gel. The column was eluted with ether–pentane mixtures, and 450-ml fractions were collected. A total of 4.1 g (84%) of nitrile was obtained from fractions 6–8. Recrystallization of this material from methanol gave pure I: mp 126–127°; ir ($CHCl_3$) 4.5 μ (C≡N); nmr ($CDCl_3$) δ 7.3 (m, 15, aromatic), 4.35 (q, 1, *J* = 7 Hz, CHCN), 1.15 (d, 3, *J* = 7 Hz, CH_3). *Anal.* Calcd for $C_{22}H_{19}N$: C, 88.84; H, 6.44. Found: C, 88.98; H, 6.44.

Under the same conditions, 5.5 g of optically pure (+)-amide gave 4.5 g (80%) of (+)-I: mp 118–119°; $[\alpha]^{25}_{546}$ +74.5° (*c* 2.0, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{19}N$: C, 88.84; H, 6.44. Found: C, 89.03; H, 6.63.

Under the same conditions, 10 g of optically pure (−)-amide gave 8 g (80%) of (−)-I: mp 108–109°; $[\alpha]^{25}_{546}$ −74.8° (*c* 2.0, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{19}N$: C, 88.84; H, 6.44. Found: C, 88.47; H, 6.42.

Methyl 2-Methyl-3,3,3-triphenylpropionate and Its 2-Deuterio Derivative. A mixture of racemic acid IX (20 g), 750 ml of absolute methanol, and 15 ml of concentrated sulfuric acid (added dropwise) was heated at reflux for 96 hr. Part of the methanol was evaporated, and the residue was shaken with ether and water. The ether solution was washed with sodium carbonate solution, with water, and was dried and evaporated. The residue was chromatographed on a 200-g silica gel column. The column was eluted with 5% ether–pentane mixture, and 19 g of ester was collected. Recrystallization of the ester from dry hexane (dried over sodium) gave 18 g (87%) of crystalline solid: mp 97.5–98.5°; ir ($CHCl_3$) 5.77 μ (ester C=O); nmr ($CDCl_3$) δ 7.30 (m, 15, aromatic), 4.40 (q, 1, *J* = 7 Hz, $CHCO_2$), 3.40 (s, 3, CO_2CH_3), 1.17 (d, 3, *J* = 7 Hz, CCH_3). *Anal.* Calcd for $C_{23}H_{22}O_2$: C, 83.61; H, 6.71. Found: C, 83.68; H, 6.71.

The above ester was deuterated by exchange with methyl alcohol-*O-d* with potassium methoxide as catalyst. The ester, 16 g (0.05 mol), was refluxed for 24 hr with 200 ml of 0.1 *M* potassium methoxide in methyl alcohol-*O-d* (97% atom excess of deuterium). The solvent was removed by distillation. The recovered solid was dissolved in 100 ml of methyl alcohol-*O-d* (99% atom of deuterium) for 24 hr before the solvent was again removed by distillation. The progress of deuteration was followed by comparing the nmr signal of the hydroxyl proton in the distillate with the ^{13}C satellite. By this method, the distillate contained more than 0.98 atom of deuterium in the hydroxyl position after four exchanges. The dry solid was extracted with 2 *N* hydrochloric acid and ether. The ether solution was washed with water, dried, and chromatographed to obtain 13 g of ester. Recrystallization of the ester from hexane gave 12 g (75%): mp 97.5–98.5°; nmr ($CDCl_3$) δ 7.20 (m, 15, aromatic), 3.38 (s, 3, CO_2CH_3), 1.14 (s, 3, CCH_3). The deuterium content at the 2 position was determined by the ratio of the P + 1 peak in the mass spectrum at 20 eV. The amount of deuterium was found to be 0.982 atom excess of deuterium per molecule.

(−)-2-Deuterio-2-methyl-3,3,3-triphenylpropionitrile ((−)-I-*d*). The above deuterated methyl ester (9 g) was dissolved in a mixture of 120 ml of glacial acetic acid and 30 ml of concentrated hydrochloric acid, which was heated at reflux for 12 days. The resulting solution was shaken with ice–water and dichloromethane. The organic layer was washed with water, dried, and evaporated. The residue was recrystallized from benzene to give 7 g (86%) of IX-*d*: mp 191–192°; nmr ($CDCl_3$) δ 7.30 (m, 15, aromatic), 1.14 (s, 3, CH_3).

This material was partially resolved as before to give optically active (+)-IX-*d* ($[\alpha]^{25}_{546}$ +3.87° (*c* 3.4, $CHCl_3$) and (−)-IX-*d* ($[\alpha]^{25}_{546}$ −2.78° (*c* 3.4, $CHCl_3$)). From 1 g of (−)-IX-*d* was obtained 0.7 g of the deuterated amide: mp 182–205°; $[\alpha]^{25}_{546}$ −15.2 (*c* 1.8, dimethyl sulfoxide). From 0.66 g of this amide was obtained 0.50 g of chromatographed nitrile, (−)-I-*d*: $[\alpha]^{25}_{546}$ −15.6° (*c* 2.1, $CHCl_3$); nmr ($CDCl_3$) δ 7.30 (m, 15, aromatic), 1.15 (s, 3, CH_3). The deuterium content was found to be 0.972 atom excess by mass spectrometry at 15 eV.

(±)-2-Deuterio-2-methyl-3,3,3-triphenylpropionitrile (I-*d*). A sample of 1.2 g of I-*h* was refluxed for 41 hr with a 10-ml solution of 1.22 *M* potassium methoxide in methanol-O-*d* (>0.98 atom excess of deuterium). The nitrile was recovered and submitted to the same procedure, chromatographed, and recrystallized to give 0.80 g of I-*d*, mp 126–127°. The deuterium content of this material was determined by comparing the relative areas of its residual proton quartet at δ 4.35 and methine proton singlet of an internal standard (Ar_2CH) of *p*-biphenylylphenylmethoxymethane[11] at δ 5.2. A solution of 0.505 mmol of I-*d* and 0.0113 mmol of standard in $CDCl_3$ (>0.99 atom excess of deuterium) was scanned with a Varian computer of average transients on a Varian A-60 spectrometer to obtain a time-averaged spectrum. By this method, I-*d* contained 0.985 atom of deuterium per molecule at the 2 position.

Pentamethylguanidine Hydriodide. Hydriodic acid (Merck reagent, with preservative) was added to 0.4 ml of pentamethylguanidine[12] (90% pure) until the solution was acidic. The water was removed with an oil pump, while the last trace of it was removed by codistillation with benzene. The residue was evacuated for 14 hr. It was dissolved in absolute ethanol, dried over Drierite, allowed to stand for 1 hr, and filtered. The ethanol was concentrated under nitrogen to a volume of 2 ml. The ethanol solution was placed in a freezer, and solid appeared. The solvent was decanted, and the solid (very hygroscopic) was quickly washed twice with ice-cold ethanol and placed in an evacuated desiccator for 24 hr. About 300 mg of the iodide salt was obtained, mp 127–129° (sealed tube). *Anal.* Calcd for $C_6H_{16}N_3I$: C, 28.02; H, 6.27; I, 49.36. Found: C, 27.90; H, 6.22; I, 49.43.

Preparation of Triethylenediamine Dihydriodide. Hydriodic acid (Merck reagent, with preservative) was added to a solution of 290 mg of sublimed amine in 1 ml of absolute ethanol until the

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[10] H. P. Fischer and C. A. Grob, *Helv. Chim. Acta*, **47**, 564 (1964).

[11] W. D. Kollmeyer and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 1779 (1968).

[12] H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1232 (1964).

solution was acidic (pH 1). During the course of addition, white solid precipitated. The heterogeneous solution was stirred for 0.5 hr and the volatile material was removed under vacuum. The residue was washed three times with absolute ethanol and filtered. Attempts to recrystallize the salt from ethanol failed due to its extremely slight solubility. Thus, the salt was finally washed with ether and dried in an evacuated desiccator for 15 hr. The product, 800 mg, had mp 198–200° dec. *Anal.* Calcd for $C_6H_{14}N_2I_2$: C, 19.58; H, 3.83; I, 68.98. Found: C, 19.54; H, 4.09; I, 69.08.

Solvents, Bases, and Equipment for Kinetics. Tetrahydrofuran was distilled in a nitrogen atmosphere from lithium aluminum hydride immediately before use. Methanol-*O-d* (>0.98 atom excess of deuterium) was prepared by hydrolysis of dimethyl carbonate in deuterium oxide,[13] and purified by the method of Fieser.[14] The preparation of *tert*-butyl alcohol-*O-d* has been described.[15] Benzene was purified by distillation from lithium aluminum hydride. Dimethyl-d_6 sulfoxide (>97% deuterated) was prepared by a series of facile exchanges in deuterium oxide.[16] Cyclohexane was purified by distillation. The tertiary amine, triethylenediamine, was purified by sublimation at 35° under vacuum.

All glassware used in these experiments, except the polarimeter cell, was cleaned with chromic acid, rinsed with water and dilute ammonium hydroxide solution, and dried in an oven at 120° for at least 12 hr. The polarimeter cell was thoroughly rinsed with solvent and purged with dry nitrogen before use.

General Procedure for One-Point Kinetic Runs for Determination of k_e/k_α Values. Reactions were carried out in stoppered volumetric flasks at room temperature, or in heavy-walled Pyrex tubes at elevated temperature. The substrate, solvent, and base were placed in the tube under nitrogen. The tube and contents were degassed and sealed under vacuum. After the tube or the flask had been placed in a constant-temperature bath for a required time, it was cooled and opened, and its contents were shaken with a mixture of dilute hydrochloric acid and ether. The organic layer was washed with water, dried, and evaporated. The residue was purified by silica gel chromatography and the whole sample submitted to polarimetric and isotopic analyses. The rotations of the recovered substrate and the starting material were measured in solutions of the same concentration at similar temperature.

Runs 3–9 were carried out in a similar fashion. Run 6 will serve as an example. The substrate, 60 mg (0.2 mmol), was dissolved in about 1 ml of solvent in a 2-ml volumetric flask. This solution and a 0.018 *M* base solution were thermostated at 25° for 30 min. Then, 1 ml of the base solution was added to the substrate solution, and more solvent was added to the 2-ml mark. The kinetic solution was vigorously shaken and placed in a 25° bath. The solution was quenched with dilute acid after 17 min and worked up in the same manner as previously described. The recovered nitrile was submitted to analyses.

Runs 1–2 and 10–15 were carried out in sealed tubes. The substrate was dissolved in the base solution before it was transferred to the tube. Run 13 was typical. A sample of 90 mg (0.3 mmol) of substrate was dissolved in 3 ml of a 0.196 *M* pentamethylguanidine solution. The solution was transferred to a rate tube with a syringe. The tube was degassed three times and sealed under vacuum. It was placed in a 150° bath for 50.33 hr. The tube was removed, cooled, opened, and poured into dilute hydrochloric acid. The product was recovered by the standard procedure and analyzed.

Racemization Kinetics of Nitrile (−)-I-*d*. Determination of k_4. The substrate used in the kinetic runs had 0.970 atom of excess deuterium per molecule and a rotation $[\alpha]^{25}{}_{546}$ −15.6° (*c* 2.07, $CHCl_3$). Rotations for racemization runs were observed at 546 nm.

Racemization of (−)-I-*d* with 0.00477 *M* Potassium *tert*-Butoxide in *tert*-Butyl Alcohol-*O-d* at 25° (Run 16). In a 2-ml volumetric flask was placed 30 mg of (−)-I-*d* and 1.3 ml of *tert*-butyl alcohol-*O-d*. After the substrate dissolved, the solution was placed in a 25° bath for 30 min. To the flask was added 0.6 ml of thermostated 0.0159 *M* potassium *tert*-butoxide solution. Solvent was added to fill the flask to the mark, and the flask was vigorously shaken. The thermostated polarimeter cell was immediately filled and rotations were taken on the polarimeter, the first reading at time 2 min. The starting observed rotation was −0.201° and the final was −0.098. Twelve points were taken during the reaction. The logarithms of the rotations were plotted against time, and the slope of the line was determined by the least-squares method to be $2.15 \pm 0.02 \times 10^{-5}$ sec^{-1}.

Racemization of (−)-I-*d* at 25° with 0.00212 *M* Potassium *tert*-Butoxide in *tert*-Butyl Alcohol-*O-d*, 0.0025 *M* in 2,5,8,15,18,21-Hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane (Run 17). The racemization run was conducted in the same manner as run 16: 30 mg of substrate and 1.6 ml of *tert*-butyl alcohol-*O-d* were added to a 2-ml volumetric flask which was then thermostated at 25°. After 30 min, 0.3 ml of a 0.0155 *M* base solution containing the cyclic polyether was added to the flask containing the substrate. The racemization was followed the same way as previously described. Twenty points were taken during the first 75% of the reaction. After the run, the kinetic solution was titrated. A least-squares plot gave a straight line with a slope of $1.27 \pm 0.01 \times 10^{-3}$ sec^{-1}.

Racemization of (−)-I-*d* with 0.9643 *M* Triethylenediamine in Dimethyl-d_6 Sulfoxide, 1 *M* in Methanol-*O-d* (Run 18). The base solution was prepared by adding 2.7 g of sublimed amine and 0.63 ml of methanol-*O-d* to enough dimethyl-d_6 sulfoxide to make a 25-ml solution. The base concentration was determined by stoichiometric calculation rather than by titration. To 210 mg of the substrate was added 7.5 ml of the above base. After mixing, the initial rotation of the kinetic solution was taken (the rotation remained unchanged at room temperature after 5 days). Aliquots of 1.4 ml were pipetted into each of the three rate tubes. After the tubes were degassed and sealed under vacuum, they were placed in a 125° bath. Tubes were removed at designated times and quenched with dilute hydrochloric acid and ether. The rotations of the recovered material were measured after purification. The observed rotation at the beginning was −15.66° and at the end was −6.42°. A least-squares plot gave a racemization rate constant of $5.35 \pm 0.30 \times 10^{-6}$ sec^{-1}.

Racemization of (−)-I-*d* at 150° with 0.1944 *M* Pentamethylguanidine in *tert*-Butyl Alcohol-*O-d* (Run 19). The base solution was prepared by adding about 0.7 ml of pentamethylguanidine to 21 ml of *tert*-butyl alcohol-*O-d*. The base was titrated with standard acid to a phenolphthalein end point. To 180 mg of substrate was added 6 ml of the above base solution. After mixing, a homogeneous solution was obtained, and the initial rotation was taken. Aliquots of 1.5 ml were pipeted into each of the three constricted heavy-walled Pyrex tubes. The tubes were degassed and sealed under vacuum. They were placed in a 150° oil bath. Tubes were removed from the bath at appropriate times, cooled, opened, and allowed to warm to room temperature. The rotation of each solution was measured at 25° less than 10 min after the solution reached room temperature. The beginning observed rotation was 0.470° and the final was 0.097°. The data provided a least-squares rate constant of $1.024 \pm 0.023 \times 10^{-5}$ sec^{-1}.

Reresolution Experiments of (−)-I-*h*. The bases used for the following exchange reactions are from the same stock base solutions used for racemization runs of (−)-I-*d*. All fractional crystallizations were carried out in ether–pentane. Rotations were taken in chloroform at 546 nm and 25°.

Partial Exchange of (−)-I-*h* with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol-*O-d* and Reresolution (Run 20). A solution containing 300 mg of substrate in 4.9 ml of *tert*-butyl alcohol-*O-d* was thermostated at 25°. After 30 min, 3 ml of a 0.0159 *M* potassium *tert*-butoxide solution and more *tert*-butyl alcohol-*O-d* were added to the 10-ml mark. After thorough mixing, 1 ml of the kinetic solution was transferred to a thermostated polarimeter cell, and the rest of the solution was placed in a 25° bath. When observed rotation reached −1.1450 at 546 nm (which required 37 min), the solution was quenched with dilute hydrochloric acid. The mixture was extracted with five 25-ml portions of ether. The combined ether extracts were washed with water, dried, and evaporated. The residue was chromatographed on a 40-g silica gel column. The column was eluted with ether–pentane mixtures. The isolated product, 280 mg of white solid A_1, displayed $[\alpha]^{25}{}_{546}$ −36.56° (*c* 2.1, $CHCl_3$), was 50.25% racemized, and contained 0.397 atom of excess deuterium per molecule by mass spectrometry.

Recrystallization of 220 mg of solid A_1 gave 76 mg of solid B_1. Solid B_1 gave 56 mg of solid C_1. Solid C_1 gave 44.5 mg of solid D_1, having $[\alpha]^{25}{}_{546}$ −1.86° (*c* 1.94). Solid D_1 gave 26 mg of solid E_1, having $[\alpha]^{25}{}_{546}$ −0.69° (*c* 1.30). From the mother liquor of B_1, 29 mg of solid F_1, having $[\alpha]^{25}{}_{546}$ −71.2° (*c* 1.47), was recovered.

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Solid E_1 and F_1 contained 0.530 and 0.270 atom of excess deuterium per molecule, respectively, by mass spectrometry.

Partial Exchange of (−)-I-*h* with Potassium *tert*-Butoxide (0.00233 *M*) in *tert*-Butyl Alcohol-*O-d*, 0.0025 *M* in 2,5,8,15,18,21-Hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane (Run 21). A solution of 300 mg of substrate in 8.3 ml of *tert*-butyl alcohol-*O-d* was thermostated at 25°. After 30 min, 1.5 ml of a 0.015 *M* potassium *tert*-butoxide solution containing the cyclic polyether and enough *tert*-butyl alcohol-*O-d* were added to the 10-ml mark. The base concentration in the kinetic solution was titrated with standard acid. The solution was quenched with dilute hydrochloric acid after 2 min. After purification by chromatography the recovered product, solid A_2, was 58.1% racemized and contained 0.570 atom of excess deuterium per molecule by mass spectrometry.

Recrystallization of 220 mg of A_2 gave 125 mg of solid B_2, having $[\alpha]^{25}_{546}$ −9.66° (*c* 2.08). Upon two recrystallizations of B_2, 70 mg of C_2 was obtained, having $[\alpha]^{25}_{546}$ −1.21° (*c* 2.14). Solid C_2 gave 30 mg of D_2, having $[\alpha]^{25}_{546}$ −0.00 (*c* 1.84). From the mother liquor of B_2, 44 mg of E_2 was recovered, having $[\alpha]^{25}_{546}$ −70.8° (*c* 2.15). Solid D_2 and E_2 contained 0.694 and 0.414 atom of excess deuterium per molecule, respectively, by mass spectrometry.

Partial Exchange of (−)-I-*h* with 0.9643 *M* Triethylenediamine in Dimethyl-d_6 Sulfoxide Containing 1 *M* Methanol-*O-d* (Run 22). A kinetic solution was prepared by dissolving 380 mg of substrate in 12.6 ml of the base solution. After the solution was well mixed, an 8-ml aliquot was introduced into a heavy-walled Pyrex tube with a syringe. The tube was degassed and sealed under vacuum. After the tube was placed in a 125° bath for 12 hr, it was cooled and opened. The content was quenched with dilute hydrochloric acid and extracted with ether. Purification of the product by silica gel chromatography with ether–pentane as elution solvent gave 230 mg of solid A_3 which was 60.8% racemized and contained 0.427 atom of excess deuterium per molecule by mass spectrometry.

Recrystallization of 200 mg of A_3 gave 93.4 mg of solid B_3. Upon three recrystallizations of B_3, 15 mg of solid C_3 was obtained, having $[\alpha]^{25}_{546}$ −0.74° (*c* 1.35). From the mother liquor of B_3, 30 mg of solid D_3 was recovered, having $[\alpha]^{25}_{546}$ −70.93° (*c* 2.26). Solids C_3 and D_3 contained 0.497 and 0.301 atom of excess deuterium per molecule, respectively, by mass spectrometry.

Partial Exchange of (−)-I-*h* with 0.1944 *M* Pentamethylguanidine in *tert*-Butyl Alcohol-*O-d* (Run 23). A 10-ml volumetric flask containing 300 mg of substrate was filled with a 0.1944 *M* pentamethylguanidine solution. The solution was vigorously shaken until all the solid was dissolved. It was transferred to a rate tube under a stream of nitrogen. The tube was degassed and sealed under vacuum. It was placed in a 150° bath for 9.5 hr. The tube was opened and quenched with dilute hydrochloric acid. About 270 mg of product was recovered after column chromatography. Polarimetric and isotopic analyses showed product A_4 with 34.9% racemization and 0.188 atom of excess deuterium per molecule.

Recrystallization of 220 mg of A_4 gave 85.2 mg of B_4. Upon three recrystallizations of B_4, 50 mg of C_4, having $[\alpha]^{25}_{546}$ −1.72° (*c* 2.09), was obtained. Solid C_4 gave 40 mg of D_4, having $[\alpha]^{25}_{546}$ −0.60° (*c* 2.16). From the mother liquor of B_4, 23 mg of E_4, having $[\alpha]^{25}_{546}$ − 70.04° (*c* 2.31), was recovered. Solid D_4 and E_4 contained 0.210 and 0.097 atom of excess deuterium per molecule, respectively, by mass spectrometry.

Deuterium Analysis of I by Mass Spectrometry. All measurements were performed on an Associated Electronics Industries Limited MS 9. Quantitative measurements were made at 15 eV. Since the intensity of the P − 2 peak (*m/e* 295) increases with time, samples were introduced into the system by direct insertion. Instrumental settings varied slightly from day to day. Typical conditions were multiplier 250–500, band width 6 (max), monitor 10 × 25, sample temperature, inlet temperature and source temperature 140 ± 5°, source inlet maximum, collector 0.015, ion repeller first maximum, beam centering varied. Because of the complexity of fragmentation, analyses were performed with a calibration curve. Standard mixtures were prepared by weighing amounts of racemic I-*h* and I-*d* (98.5% atom of deuterium by nmr) into flasks, dissolving the solid in ether, and evaporating the solvent on a rotatory evaporator. The last trace of solvent was removed by an oil pump. The amount of deuterium was calculated by use of eq 3

$$\%\text{ atom D calcd} = \frac{R_{\text{obsd}} - K}{R_{\text{obsd}} - K + 1} \qquad (3)$$

where R_{obsd} = ratio of intensity of (P + 1)/P observed and K = P + 1 contribution of $C_{22}H_{19}N$ (*m/e* 297).

Results were reproducible to +0.003 atom of deuterium per molecule when the same sample was run on two different days. Two standards prepared from (−)-I-*h* and (±)-I-*d* were submitted to mass spectral analysis. Their calculated deuterium contents were in agreement with the known deuterium contents within experimental error, demonstrating that the racemate and the antipode of I do not fractionate during sublimation into the system of the mass spectrometer.

A typical analytical procedure was as follows: the sample was introduced into the instrument by direct insertion. After a steady concentration of the sample was obtained in the source, the peaks P + 1 to P − 2 were scanned several times. Since the sample gave a strong memory effect, the analyses were carried out at a minimum of 24-hr intervals for each sample.

Samples of racemate and antipode from reresolution experiments and the recovered material from exchange reactions were analyzed by this method. The calculated fractions of deuterium were corrected by interpolation from the standard curve.

Deuterium Analysis of Methyl 2-Deuterio-2-methyl-3,3,3-triphenylpropionate by Mass Spectrometry. The deuterium content of the ester at the 2 position was determined at 20 eV by direct insertion. The source temperature was about 120° and the instrumental settings described above were used. Since the ester gave no P − 1 peak, the deuterium content was determined directly from eq 3. The ratios of the (P + 1)/P peak were determined by means of a decapot. The ester was found to contain 0.982 atom of excess deuterium per molecule by this method.

Deuterium Analysis of I by Infrared Spectrophotometry. Nitrile I recovered from exchange reactions was a gummy solid. Each sample was chromatographed over a silica gel column. The columns were prepared with 5% ether in pentane. Each sample was packed on the column with a minimum amount of silica gel. The nitrile was eluted with ether–pentane mixtures. The solvent from the combined fractions was evaporated to about 1 ml and transferred with a dropper to a clean, dry vial. The solvent was removed on a rotatory evaporator, and a powdery, light-weight solid remained. The vial and the contents were placed in an evacuated desiccator over Drierite for at least 12 hr. This procedure afforded 95% recovery of nitrile.

Standard mixtures of racemic I-*h* and I-*d* (98.5% atom of deuterium by nmr) were prepared by weighing amounts of the pure compounds totalling 65 mg into vials. Each standard was chromatographed by the procedure described above. About 20 mg of the chromatographed standard was dissolved in 0.100 ml of bromoform (Matheson reagent delivered by a syringe). Spectra were obtained in 0.1-mm sodium chloride cells. The difference in absorption (Δabs) between a peak at 973 cm^{-1}, which appeared in I-*d* but was absent in I-*h*, and base line of the 960-cm^{-1} peak was measured on a Perkin-Elmer Model 421 dual grating spectrophotometer with the following adjustments: slit program, 1 × 1000; amplifier gain, 5; attenuator speed, 1100; scan speed, 20 cm^{-1}/min; suppression, 0; scale, 1 ×; source current, 0.3 A.

The standards gave a linear plot of (100)Δabs/weight of sample in milligrams against % atom of deuterium. No point was located more than 1% atom of deuterium from the line. Unknown samples from kinetic runs were analyzed by the procedure used for standards. Deuterium contents were determined by interpolation from a calibration plot of standards made immediately before the unknown samples were analyzed.