Electrophilic Substitution at Saturated Carbon. XLVIII. High Stereospecificity in a Transamination Reaction[1,2]

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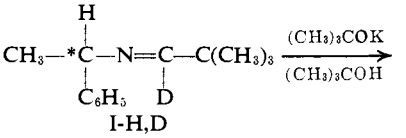
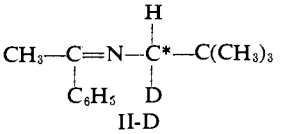
Abstract: Pivalaldehyde-*1-d* and optically pure α-phenylethylamine were condensed to their imine derivative, *N*-(neopentylidene-*1-d*)-α-phenylethylamine (I-H,D). This material when heated at 75° with potassium *tert*-butoxide in *tert*-butyl alcohol, isomerized through an azaallylic anion to give 97% optically pure *N*-(α-methylbenzylidene)neopentylamine-*1-d* (II-D), which was hydrolyzed to optically active neopentylamine-*1-d* and then converted back to II-D. The optical purity of II-D was demonstrated by its reduction with lithium aluminum hydride to *N*-(neopentyl-*1-d*)-α-phenylethylamine, which was resolved. The enantiomers were examined for stereochemical purity by nmr measurements. The absolute configurations of neopentylamine-*1-d* and α-phenylethylamine have been previously established. These data demonstrated that a base-catalyzed transamination occurred with essentially complete stereospecificity, and the reaction involved only one of eight theoretically possible reaction paths. Rates of isomerization at 75° were examined with all combinations of isotopic labels (deuterium and protium) in the benzyl position of optically pure starting material and in the *tert*-butyl alcohol. Both starting imine and rearranged imine were isolated before complete reaction and were examined for optical purity and deuterium. Equilibrium constants between starting and rearranged imine were determined at 75° in dimethyl sulfoxide–methanol–potassium methoxide and were found to favor product by a factor of 23. Kinetic analysis provided the following facts. Starting imine underwent isotopic exchange 21–36 times as fast as it racemized. The intramolecularity for the rearrangement varied from 46% when protium was transferred to 8% when deuterium was transferred. The higher value involved protonated substrate and deuterated medium, and the lower value, deuterated substrate and protonated medium. The ratio of the rate constant for isotopic exchange that gave starting imine to that for isotopic exchange that gave rearranged imine, termed the collapse ratio, was found to be dependent on the original positions of the isotopic labels. The collapse ratio favored starting imine over rearranged imine by factors of 3.0 and 5.7. The lower value involved deuterated substrate and protonated medium, and the higher value, protonated substrate and deuterated medium. Use of an average collapse ratio of 4.4 ± 1.3 and an isotope effect free model allowed calculation of the rate constants for the *invisible* reaction of formation of ion pair and return to starting material and the rate constants for total ionization. In all cases, the rate constants for the invisible reaction were lower valued than those for isotopic exchange of starting material. Isotope effects for all processes were calculated. The results are interpreted in terms of asymmetric ion pair intermediates and their reorganization and collapse to product as a process that competes favorably with ion pair dissociation.

Although the importance of the methylene–azomethine rearrangement as a prototype of the biochemical transamination reaction has been recognized for many years,[4] the mechanism of the reaction was shown to involve azaallylic anions as intermediates only recently.[5] We now report the results of an investigation designed to reveal the stereochemical course of the transformation, the configuration of the intermediate azaallylic anion, the intramolecularity of the isomerization, and other mechanistic details of this rearrangement.

The conversion of I to II was selected for study for the following reasons. (1) The two imines proved stable to and easily separable by glc. (2) Both I and deuterium-labeled II are capable of optical activity. (3) The maximum rotation and absolute configuration of α-phenylethylamine are known,[6] and therefore that of I could be determined. (4) The absolute configuration of neopentylamine-*1-d* could be inferred from its sign of rotation with the use of "Brewster's rules,"[2c,7] and therefore the configuration of II-D deduced. (5) The maximum rotation of II-D was determinable by an nmr method (see below). (6) Preliminary experiments established that the anticipated rearrangement occurred with the equilibrium lying well on the side of product, and that the reaction could be conducted under conditions that left the product, once formed, intact. (7) The large sizes of the phenyl and *tert*-butyl



I-H,D



II-D

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(2) Some of these results have been published in preliminary form: (a) D. J. Cram and R. D. Guthrie, *J. Amer. Chem. Soc.*, 87, 397 (1965); (b) R. D. Guthrie, W. Meister, and D. J. Cram, *ibid.*, 89, 5288 (1967); (c) W. Meister, R. D. Guthrie, J. L. Maxwell, D. A. Jaeger, and D. J. Cram, *ibid.*, 91, 4452 (1969).

(3) NATO Postdoctoral Fellow at the University of California at Los Angeles, 1965–1967, sponsored by Deutscher Akademischer Austauschdienst, Bad Godesberg, Germany.

(4) For example, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 572.

(5) D. J. Cram and R. D. Guthrie, *J. Amer. Chem. Soc.*, 88, 5760 (1966).

(6) (a) W. Theilacker and H. G. Winkler, *Chem. Ber.*, 87, 690 (1954); (b) W. Leithe, *ibid.*, 64, 2827 (1931).

(7) J. H. Brewster, *Tetrahedron Lett.*, 20, 23 (1959).

Table I. Rate Constants for Isomerization of 0.311 *M* Solutions of Imine I in Potassium *tert*-Butoxide–*tert*-Butyl Alcohol at 75 ± 0.02°

Run no.	Substrate	Solvent	Base concn, *M*	$(k_i + k_{-i}) \times 10^6$ sec^{-1} Initial	Final	Av
1	(−)-I-H,H	*tert*-BuOD[a]	0.468	6.3[b]	2.4[c]	
2	(−)-I-D,H	*tert*-BuOD[a]	0.468			2.15 ± 0.02
3	(−)-I-D,H	*tert*-BuOH	0.472	1.25[d]	2.7[e]	
4	(−)-I-H,D	*tert*-BuOH	0.472			3.71 ± 0.04

[a] 0.989 atom of deuterium/molecule by nmr analysis. [b] Calculated assuming first-order kinetics for the first 2.5% of reaction (one-point rate constant). [c] Calculated as slope between points at 33.5 and 39.6% reaction. [d] Calculated assuming first-order kinetics for the first 0.91% of reaction (one-point rate constant). [e] Calculated as slope between points at 35.3 and 42.0% reaction.

groups of the system were anticipated to provide a high degree of conformational purity for the azaallylic anion intermediate, and therefore, the reaction had a reasonable chance of occurring stereospecifically.

Results

Starting Materials. Nondeuterated imines I and II were prepared by conventional methods (see Experimental Section) from the corresponding amines and carbonyl-containing compounds. Deuterated α-phenylethylamine was prepared by two methods. Reduction of acetophenone oxime-*O*-*d* in ether with sodium and acetic acid-*O*-*d* gave material with 0.94 atom of deuterium (nmr analysis) in the α position (51% yield). The Curtius reaction with α-phenylpropionic-α-*d* acid yielded material with 0.995 atom of deuterium (mass spectral analysis) in the α position (58% yield). Reduction of pivalonitrile with lithium aluminum deuteride[8] gave pivalaldehyde-*1*-*d* which when converted to I-H,D gave material that contained 0.996 atom of excess deuterium per molecule (combustion and falling drop analysis).

Equilibria. When imine I was heated at 100° for about 50 hr in *tert*-butyl alcohol 0.43 *M* in potassium *tert*-butoxide, equilibrium between the two imines was reached as shown by the lack of change of the relative amounts of each with time, and K = II/I = 15. A similar experiment carried out with II in a solution of 0.30 *M* potassium methoxide in methanol–dimethyl sulfoxide at 75° gave K = II/I = 23. The same experiment performed with I as starting material under the same conditions gave K = II/I = 21. The two values are within experimental error of one another, and the value of 23 is used in subsequent calculations because it was the more accurately measured. In all measurements the relative amounts of I and II in the mixtures were determined by the averaging of at least three glc determinations which differed from one another by less than 3%.

Kinetics. The kinetics of potassium *tert*-butoxide catalyzed reaction for I → II (k_i is the rate constant for the forward and k_{-i} that for the back reaction) were studied with both I-H,H and I-D,H in both *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d* at 75° (Table I). First-order rate constants (the base concentration remained constant) were determined by following the rates of disappearance of starting material and appearance of product by glc. Use of an internal standard in the glc measurements established that *ca.* 98% of the starting material could be accounted for in the form of either I or II.

(8) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 86, 1085 (1964).

In run 2, benzyl-deuterated starting material (I-D,H) in deuterated *tert*-butyl alcohol was employed, and in run 4, imino-deuterated starting material (I-H,D) in ordinary *tert*-butyl alcohol was used. In these two runs (seven points each covering about the first half-life) good first-order kinetics were observed for the approach of I to equilibrium between I and II. In runs 1 and 3, the benzyl position of I and the hydroxyl group of the solvent differed isotopically. In run 1 (I-H,H in *tert*-butyl alcohol-*O*-*d*) the instantaneous rate constant decreased with six data points taken over about a half-life. In run 3 (I-D,H in *tert*-butyl alcohol-*O*-*h*) the instantaneous rate constant increased with eight data points taken over about a half-life. Clearly, the benzyl position of imine I exchanges faster than the substance isomerizes. The reduction of the first-order rate constant for isomerization in run I is due to a primary isotope effect, with $(k_H/k_D)_{OD}^{75°}$ = 2.9 (calculated from initial rate constant of run 1 and average rate constant of run 2). As I approached complete deuteration, the slope of the curve in run 1 approached that observed throughout run 2. Indeed, in another run equivalent to 1, the plot between 40 and 60% isomerization (four points) was nearly linear with an average slope of 2.21×10^{-6} sec^{-1}, which agrees well with the rate constant observed for run 2 ($k = 2.15 \pm 0.02 \times 10^{-6}$ sec^{-1}). In run 3, the increase in value of the instantaneous rate constant with time reflected the incorporation of protium into the benzyl position of I. The slope was still changing after 40% isomerization, a fact which indicates that I-H,H in deuterated solvent isomerizes relatively faster than it exchanges as compared to I-D,H in protonated solvent. The primary isotope effect for isomerization in protonated solvent was calculated from runs 3 and 4 to be $(k_H/k_D)_{OH}^{75°}$ = 3.0 (calculated from initial rate constant of run 3 and average rate constant of run 4). Thus, the primary isotope effect for isomerization was independent within experimental error of the isotopic label of solvent. The solvent isotope effects for benzyl-protonated I can be calculated from the initial rate constant of run 1 and the average rate constant of run 4, and $(k_{OH}/k_{OD})_{CH}^{75°}$ = 0.59. Likewise, from runs 2 and 3 with benzyl-deuterated material, $(k_{OH}/k_{OD})_{CD}^{75°}$ = 0.58. Thus, the solvent isotope effect is independent of the isotope transferred in the isomerization.

Product Analysis. After 40–44% isomerization the reactions in runs 1–4 were quenched; the starting material I and product II were isolated in a pure state by preparative glc and analyzed polarimetrically and for deuterium content. Table II reports these results and those of run 5, which empolyed fully deuterated (+)-I-D,H in *tert*-butyl alcohol.

The conclusion that starting material underwent iso-

Table II. Starting Material and Product Analyses for Runs 1–5[a] for the Isomerization of Imine I to II at 75 ± 0.02° Catalyzed by Potassium *tert*-Butoxide

	Run 1	Run 2	Run 3	Run 4	Run 5
Initial starting material					
Nature	(−)-I-H,H	(−)-I-D,H	(−)-I-D,H	(−)-I-H,D	(±)-I-D,H
α^{25}D (neat),[b] deg	−42.24	−43.84	−43.84	−42.30	
% of 1 atom of D[c]	0	94[d]	94[d]	0	99.5[e]
Solvent	*tert*-BuOD[f]	*tert*-BuOD[f]	*tert*-BuOH	*tert*-BuOH	*tert*-BuOH
Base concn, *M*	0.468	0.468	0.472	0.472	0.483
T, sec × 10^{-4}	15.97	25.84	25.80	16.27	26.10
% isomerization	39.6	40.8	42.0	44.0	45.6
Recovered starting material					
α^{25}D (neat),[b] deg	−40.68	−40.28	−41.68	−41.34	
% racem	6.8[g]	8.1	2.6[g]	2.3	
% of 1 atom of D[c]	90[d]	>90[d]	33,[d] 42[h]		39.8[e]
Product, α^{25}D (neat),[b] deg	−3.64	−4.60	−0.18	+5.62[i]	
Product, % of 1 atom of D[i]	75[d,k]	91[l,m]	4.3[l]	~100[d]	3.94[e]

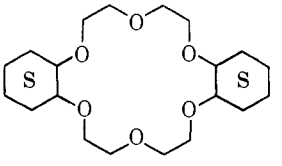
[a] See Table I for rates for runs 1–4. [b] *l* = 1 dm. [c] Per cent of one atom of deuterium per benzyl position. [d] Nmr analysis. [e] Mass spectral analysis of *N*-*p*-toluenesulfonamide derivative. [f] 0.989 atom of deuterium per molecule by nmr analysis. [g] Calculated taking into account the difference in maximum rotation between deuterated and nondeuterated material and extent of isotopic exchange. [h] Analysis by combustion and falling drop method. [i] The maximum rotation of II-D is calculated below to be α^{25}D +5.40° (neat, 1 dm); difficulties in polarimetry led to this greater value. [j] Per cent of one atom of deuterium in neopentyl methylene position. [k] In good agreement with value calculated from rate constants of Table VIII. [l] Combustion analysis of derived neopentylamine hydrochloride. [m] Combustion analysis on II was unsuitable because recovered II had undergone some exchange in the α-methyl group (nmr spectrum).

Table III. Starting Material and Product Analyses and Controls for Isomerizations of Imine I to II and for Accompanying Racemization and Isotopic Exchange Reactions at 75 ± 0.03° in *tert*-Butyl Alcohol-*O*-*d*[a] 0.44 *M* in Potassium *tert*-Butoxide

Run no.	Substrate		Time, sec × 10^{-4}	Product		Starting material	
	Nature	Concn, *M*		%[b]	% exch[c]	% exch[c]	% rac
6	(−)-I-H,H[d]	0.28	1.17	6.57		20.5	
7	(−)-I-H,H[d]	0.43	3.60	15.3	58.8	49.1	2.2[e]
8	(−)-I-H,H[d]	0.43	4.30	16.9	61.8		
9[f]	(−)-I-H,H[d]	0.28	8.80	<0.1		<2	<0.1
10	II-H	0.28	4.45	1.38[g]		<2[h]	

[a] 0.989 atom of deuterium per molecule by nmr analysis. [b] Average of at least three glc determinations that differed from one another by less than 3%. [c] Combustion and falling drop analysis, represented as per cent of one atom of deuterium per molecule. [d] α^{25}_{546} −50.45° (neat, 1 dm). [e] Calculated taking into account the difference in maximum rotation between deuterated and nondeuterated material and extent of isotopic exchange. [f] Base was omitted in this run. [g] Product was I in this run. [h] Starting material was II in this run.

topic exchange faster than it isomerized is borne out by the presence of 90% of one atom of deuterium incorporated from the solvent into the benzyl position of recovered starting material in run 1 (Table II), and the 60% of one atom of protium incorporated from the solvent into the benzyl position of recovered starting material in run 5 (Table II). Further evidence for this conclusion is found in the results of runs 6 and 7 of Table III, in which (−)-I-H,H in *tert*-butyl alcohol-*O*-*d*–potassium *tert*-butoxide at 75° was caused to isomerize 6.6 and 15%, respectively, before products and starting materials were isolated and analyzed. In run 6 the starting material had undergone 21% and, in run 7, 49% isotopic exchange in the benzyl position. In run 7 recovered starting material had undergone only 2.2% racemization, confirming the fact apparent in runs 1–4 that isotopic exchange of starting material is a process considerably faster than racemization. In run 7 the isolated product II was found to have incorporated 59% of one atom of deuterium into the methylene position. Run 8 (Table III), carried to 17% reaction (*vs.* 15% in run 7), gave product containing 62% of one atom of deuterium in the methylene position (*vs.* 59% in run 7). Thus, the results of runs 7 and 8 are consistent with one another. In a control run (9, Table III) base was omitted, and the product was found to be stable to the three reactions, isomerization, isotopic exchange, and racemization. Control run 10 (Table III) was carried out under essentially the same conditions as runs 6–8 except for the slightly longer time and the use of II-H as starting material. Only 1.4% of I was produced, and recovered II contained less than 2% of one atom of deuterium. Thus, compound II, once formed in runs 6–8, incorporated essentially no deuterium from solvent in the neopentyl position. Table IV reports the results of potassium *tert*-butoxide catalyzed reactions of I-H,H in *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d* containing 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane (crown ether III).[9] The addition of III effected increases in the rates of racemization, exchange, and isomerization by factors of ~5.5 × 10^3, ~56, and ~54, respectively. Analysis of recovered starting material in run 13 indicated that it racemized a little faster than it underwent isotopic exchange.



III

(9) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967). We warmly thank Dr. E. K. Gladding of the Elastomers Department of E. I. du Pont for a supply of this material.

Table IV. Potassium *tert*-Butoxide Catalyzed Isomerizations of Imine I to II in *tert*-Butyl Alcohol and *tert*-Butyl Alcohol-*O*-*d* with Crown Ether III at 75 ± 0.05°

Run no.	Substrate: Nature	Substrate: Concn, *M*	Solvent	Base concn, *M*	III concn, *M*	Time, sec × 10^{-3}	% II[a]	Starting material: % rac	Starting material: % exch[b]
11	(−)-I-H,H[c]	0.36	*tert*-BuOH	0.483	0.50	0.600	9.26	38	
12	(−)-I-H,H[c]	0.36	*tert*-BuOH	0.483	0.49	5.34	63.9	100	
13	(−)-I-H,H[c]	0.36	*tert*-BuOD[d]	0.481	0.51	0.600	12.7	56	48
14	(±)-I-H,H	0.33	*tert*-BuOH	0.48	0.51	8.46	97		

[a] Average of at least three glc analyses that differed from one another by less than 3%. [b] Nmr analysis, represented as per cent of one atom of deuterium at the benzyl position. [c] $[\alpha]^{25}_{5461}$ −80.2 ± 0.7° (*c* 0.739, chloroform). [d] 0.975 atom of deuterium per molecule by nmr analysis.

Table V. Starting Material and Product Analyses and Controls for Isomerizations of Imine I to II and for Accompanying Racemization and Isotopic Exchange Reactions at 25 ± 0.03° and at 75 ± 0.03° in Dimethyl-d_6 Sulfoxide[a] 3.06 *M* in Methanol-*O*-*d*[b] and 0.304 *M* in Potassium Methoxide

Run no.	Substrate: Nature	Substrate: Concn, *M*	*T*, °C	Time, sec × 10^{-4}	Product: %[c]	Product: % exch[d]	Starting material: % exch[d]	Starting material: % rac
15	(−)-I-H,H[e]	0.28	25	8.67	13.5		16.5	18.0
16	(−)-I-H,H[e]	0.28	25	17.2	23.1		28.8	33.2
17	(−)-I-H,H[e]	0.42	25	17.4	22.6	80.0		31.9
18	II-H	0.28	25	17.9	0.45[f]		<2[g]	
19	(−)-I-H,H[e]	0.28	75	0.059	25.5		32.7	35.8
20	(−)-I-H,H[e]	0.28	75	0.030	13.6	83.7	15.6	17.7
21	(−)-I-H,H[e]	0.28	25	17.4	13.1			18.7

[a] 5.97 atoms of deuterium per molecule by combustion and falling drop analysis. [b] 0.995 atom of deuterium per molecule by combustion and falling drop analysis. [c] Average of at least three glc determinations that differed from one another by less than 3%. [d] Combustion and falling drop analysis, represented as per cent of one atom of deuterium per molecule. [e] α^{25}_{5461} −50.46° (neat, 1 dm). [f] Product was I in this run. [g] Starting material was II in this run.

Table VI. Results of Isomerizations of (−)-(*S*)-I-H,D[a] to (+)-(*R*)-II-D[b] in Potassium *tert*-Butoxide–*tert*-Butyl Alcohol at 75 ± 0.1°

Run no.	Starting material concn, *M*	Base concn, *M*	Time, hr	Recovered starting material: %	Recovered starting material: $\alpha^{25}D$,[c] deg	Recovered starting material: % dec in α	Product: Yield, %	Product: $\alpha^{25}D$,[c] deg
22	0.28	0.45	10	90	−42.22	0.6	10	5.40
22	0.28	0.45	25	69	−41.86	1.2	31	5.24
22	0.28	0.45	75	35	−40.53	4.6	65	5.22
22	0.28	0.45	125	19	−38.30	10.0	81	5.16
23	0.28	0.45	78	35	−40.22	4.9	65	5.24
24	0.27	0.45	79	35	−40.44	4.8	65	5.36
25	0.30	0.472	166	13	−36.30	14.2	87	5.36

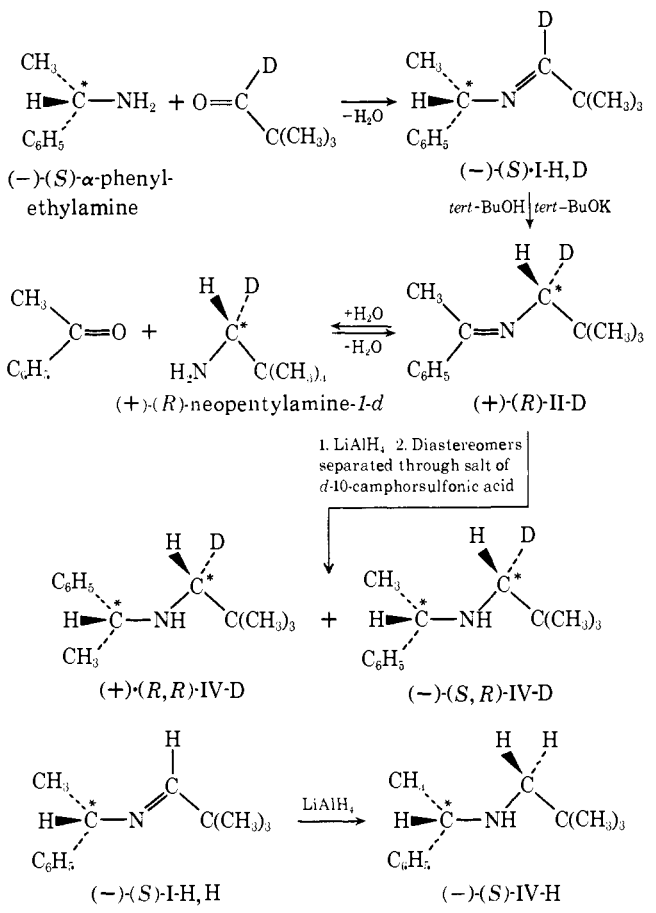
[a] $\alpha^{25}D$ −42.46° (except run 25, in which material with $\alpha^{25}D$ −42.30° was used), neat, 1 dm, 0.996 atom of deuterium per molecule by combustion and falling drop analysis. [b] 0.992 atom of deuterium per molecule by combustion and falling drop analysis. [c] Neat, 1 dm. Rotations were taken after two glc purifications and a vacuum distillation.

Table V reports results obtained when (−)-I-H,H was allowed to isomerize, racemize, and undergo isotopic exchange catalyzed by potassium methoxide in a 3.06 *M* solution of methanol-*O*-*d* in dimethyl-d_6 sulfoxide. Analyses of the recovered starting materials in runs 15, 16, 19, and 20 indicate that it racemized a little faster than it underwent isotopic exchange. Analysis of the products in runs 17 and 20 demonstrated that about 80% of one atom of deuterium had been introduced in the product from solvent under conditions that the product once formed, II, incorporated a negligible amount of deuterium (control run 18).

Stereochemical Course and Specificity of Proton Transfer. To examine the stereochemical course and stereospecificity of the proton transfer during isomerization, (−)-(*S*)-I-H,D (0.996 atom of deuterium per molecule) of maximum rotation ($\alpha^{25}D$ −42.46°, neat, 1 dm) formed from (−)-(*S*)-α-phenylethylamine ($\alpha^{25}D$ −38.20°, neat, 1 dm) of maximum rotation,[6a] was subjected to a series of potassium *tert*-butoxide catalyzed isomerizations in *tert*-butyl alcohol-*O*-*h* at 75°. The products (II) and starting materials (I) were separated by glc, and their rotations examined. The results are found in Table VI. In these reactions, protium was transferred in protio solvent, and any isotopic exchange between substrate and solvent was invisible. In runs 22–25, optically active (+)-(*R*)-II-D was obtained with rotations that varied from $\alpha^{25}D$ 5.16 to 5.40° (neat, 1 dm).[2c] The sign of rotation of II-D in these runs where protium migrated (see also run 4 of Table II) was always positive, but those of runs 1, 2, and 3, in which deuterium migrated to produce optically active II-D, were always negative (see Table II). Furthermore, the magnitudes of the rotations of II-D in runs 1–3 were approximately proportional to the amount of deuterium in the methylene position of II-D. These facts establish beyond reasonable doubt that the rotations of II-D have their origin in the asymmetrically substituted neopentyl methylene group. Substantiation of this conclusion was obtained through hydrolysis of optically active imine from run 25, $\alpha^{25}D$ 5.36° (neat, 1 dm), to form after purification as its hydrochloride, (+)-neopentylamine-*1*-*d*, $\alpha^{25}D$ 0.25 ± 0.05° (neat, 1 dm). Conversion of this material back to its imine II-D gave ma-

terial, $\alpha^{25}D$ 5.40° (neat, 1 dm). The absolute configurations of (+)-neopentylamine-*1-d* and (+)-II-D can be assigned as *R*.[2c] The configurational relationships and interconversions are summarized in Chart I.[10]

Chart I



The maximum rotation of (+)-(*R*)-II-D was required before the stereospecificity of its formation could be established. This was determined as follows. Racemic imine I-H,H was reduced with lithium aluminum hydride to give *N*-(neopentyl)-α-phenylethylamine, or racemic IV-H. The hydrochloride of this material in deuterium oxide exhibited an nmr spectrum in which the protons of the methylene group were nonequivalent and appeared as an AB pattern with doublets at δ 2.99 and 3.20, with J_{AB} = 12 Hz. The maximum rotation of (−)-(*S*)-IV-H was determined by its preparation from (−)-(*S*)-α-phenylethylamine of maximum rotation *via* (−)-(*S*)-I-H,H. The hydrochloride of (−)-(*S*)-IV-H gave $[\alpha]^{25}D$ −22.8° (*c* 3.1, water). Imine (+)-(*R*)-II-D obtained in run 23 (Table VI) was reduced likewise, but gave a diastereomeric mixture, (*R,R*)-IV-D and (*S,R*)-IV-D, which exhibited $\alpha^{25}D$ 1.51° (neat, 1 dm).

Mass spectral analysis of this mixture established the presence of greater than 0.99 atom of excess deuterium per molecule. The methylene region of the nmr spectrum of the hydrochloride of this mixture in deuterium oxide gave two *singlets* of equal intensity (areas 0.5 each relative to 5.0 for aromatic protons), one at δ 3.20 and one at 2.96. As expected, the two diastereomers were formed in about equal amounts, and no asymmetric induction, due to the deuterioneopentyl group, was observed. The two diastereomers were separated by fractional crystallization of their *d*-10-camphorsulfonic acid salts from water, and their hydrochlorides from methanol–ether. The hydrochloride of the (+)-(*R,R*)-IV-D isomer gave $[\alpha]^{25}D$ 23.0° (*c* 2.7, water), and a singlet of relative area 1.0 at δ 3.20 in the methylene region of its nmr spectrum. The hydrochloride of the (−)-(*S,R*)-IV-D isomer could only be brought to about 90% purity, $[\alpha]^{25}D$ −20.6° (*c* 2.1, water), and this material also exhibited a singlet of relative area of about 1.0 but at δ 2.96 in the methylene region of its nmr spectrum. Under the applied conditions, bands with relative area <0.1 could not be detected. More refined analyses of the two isomers were obtained through use of a time averaging computer. To determine the sensitivity of the method, the analysis was also applied to prepared mixtures of the hydrochloride of (+)-(*R,R*)-IV-D that contained 2, 6, and 10% of added hydrochloride prepared from the 1:1 diastereomeric mixture of (+)-(*R,R*)-IV-D and (−)-(*S,R*)-IV-D. Table VII records the results. These data demonstrate that as little as 3% of salt of diastereomers of (+)-(*R,R*)-IV-D could be detected in this analysis, and that the methylene carbon of the sample of (+)-(*R,R*)-IV-D was at least 97% configurationally homogeneous. It follows that (+)-(*R*)-II-D from run 23 was at least 97% optically pure, and therefore that the maximum rotation of II-D is not greater than $\alpha^{25}D$ ±5.40° (neat, 1 dm), taken immediately after glc purification.[11]

Table VII. Analysis for Methylene Protons in Nmr Spectra Obtained with a Time Averaging Computer Attached to a Varian A-60 Spectrometer of Solutions of the Hydrochloride Salts of IV-D, 10% by Weight in Deuterium Oxide Solution

Hydrochloride salt of	% added diaster mixt[a]	Rel intensity of signal δ 3.20	δ 2.96
(+)-(*R,R*)-IV-D[b]	0	1.00	0[c]
(+)-(*R,R*)-IV-D	2	1.00	0.03
(+)-(*R,R*)-IV-D	6	1.00	0.06
(+)-(*R,R*)-IV-D	10	1.00	0.08
(−)-(*S,R*)-IV-D[d]	10	0.07	1.00

[a] Hydrochloride of 1:1 mixture of (+)-(*R,R*)-IV-D and (−)-(*S,R*)-IV-D. [b] Rotation indicated the absence of (−)-(*S,R*)-IV-D, and mass spectral analysis indicated <1% IV-H. Traces of (+)-(*R,S*)-IV-D might have been present which resulted from nonstereospecific isomerization, and which should give a signal at δ 2.96. [c] No signal detectable. [d] Since this material was incompletely resolved (rotation was 90% of the magnitude of maximum), it must have contained about 5% of (+)-(*R,R*)-IV-D.

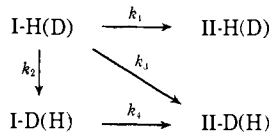
Kinetic Calculations

Rate Constants for Isotopic Exchange of Starting Imine, and for Isomerization with and without Accompanying Exchange. In the following kinetic scheme (independent of whether isotopic label is in substrate or medium) outlined in Chart II, I-H(D) is starting imine with either hydrogen or deuterium in the benzyl position, I-D(H) is starting imine that has undergone isotopic exchange with the medium at the benzyl posi-

(10) Dr. H. S. Mosher kindly informed us in advance of publication of an independently determined rotation of >98% optically pure (+)-(*R*)-neopentylamine-*1-d* of $\alpha^{23}D$ 0.25 ± 0.01° (neat, 1 dm).

(11) M. Raban and K. Mislow [*Tetrahedron Lett.*, 4249 (1965); 3961 (1966)] first applied this nmr method for determining the optical purity of neopentyl alcohol-*1-d* by preparing derivatives of this alcohol that contained additional asymmetric centers.

Chart II



tion, II-H(D) is rearranged imine that contains only the isotope present in the initial starting material, and II-D(H) is rearranged imine that contains only the isotope present in isotopically exchanged starting material. Under the conditions of all the experiments used in the kinetic calculations, II-H(D) and II-D(H) once formed underwent negligible isotopic exchange or return to I-H(D) or I-D(H) (see runs 10 and 18).

The values of k_4 are equal to k_i, which can be calculated from $K = (k_i/k_{-i})^{75°} = 23$ and $k_i + k_{-i}$ values measured in runs 2 and 4 in which imine I and the solvent contained the same isotopic label. The value of the sum, $k_1 + k_2 + k_3$, can be calculated since the disappearance of I-H(D) is a first-order process as indicated in eq 1, and the amount of I-H(D) left after a given amount of time was measured in runs 1, 3, 5, and 7. The concentrations of II-H(D) were also measured in these runs, and use of the values, coupled with the

$$[\text{I-H(D)}] = [\text{I-H(D)}]_0 e^{-(k_1 + k_2 + k_3)t} \quad (1)$$

values of $(k_1 + k_2 + k_3)$ and eq 2 and 3, allows values of k_1 to be calculated. The concentrations of I-D(H) were also known in these runs, and the values for k_2 were extracted from values of [I-D(H)], of $(k_1 + k_2 + k_3)$,

$$\frac{d[\text{II-H(D)}]}{dt} = k_1[\text{I-H(D)}] = k_1[\text{I-H(D)}]_0 e^{-(k_1 + k_2 + k_3)t} \quad (2)$$

$$[\text{II-H(D)}] = \frac{-k_1[\text{I-H(D)}]_0}{(k_1 + k_2 + k_3)} e^{-(k_1 + k_2 + k_3)t} + \frac{k_1[\text{I-H(D)}]_0}{(k_1 + k_2 + k_3)} \quad (3)$$

of k_4, and eq 5, derived from eq 4. Values of k_3 were then obtained by difference. Values of k_1, k_2, k_3, and k_4 for runs made in *tert*-butyl alcohol (deuterated and undeuterated)–potassium *tert*-butoxide are listed in Table VIII. The constants, k_1, k_2, and k_3, each depend upon single points, and therefore are approximate.

$$\frac{d[\text{I-D(H)}]}{dt} = k_2[\text{I-H(D)}] - k_4[\text{I-D(H)}] \quad (4)$$

$$[\text{I-D(H)}] = \frac{k_2[\text{I-H(D)}]_0}{k_4 - (k_1 + k_2 + k_3)}[e^{-(k_1 + k_2 + k_3)t} - e^{-k_4 t}] \quad (5)$$

The availability of k_1, k_2, k_3, and k_4 values, coupled with eq 6 derived from eq 1 and 5, allowed calculation of the change in concentration of I-H(D) + I-D(H) with time for runs 1 and 3 in which solvent and the benzyl position of substrate contained different isotopes. Then with these values the change of the integrated one-point rate constant for isomerization with time was calculated for runs 1 and 3. In Table IX these calculated values are compared with those observed in the runs themselves. The correspondence between calculated and observed values is excellent, and points to the general validity of the method.

$$\frac{[\text{I-H(D)}] + [\text{I-D(H)}]}{[\text{I-H(D)}]_0} = e^{-(k_1 + k_2 + k_3)t} + \frac{k_2[e^{-(k_1 + k_2 + k_3)t} - e^{-k_4 t}]}{k_4 - (k_1 + k_2 + k_3)} \quad (6)$$

The data of run 20 (Table V) provide a basis for estimating k_1, k_2, and k_3 values for I → II in dimethyl sulfoxide–methyl alcohol. Assumptions of kinetic isotope effects that ranged from 1.8 to 4.1 for I → II and application of eq 1, 3, and 5 to the data of run 20 indicated that k_2 and k_3 were very insensitive to the value of the kinetic isotope effect assumed. For example, at

Table VIII. First-Order Rate Constants for Potassium *tert*-Butoxide Catalyzed Isomerization (I → II) and Accompanying Isotopic Exchange at 75 ± 0.02° in *tert*-Butyl Alcohol

Process	Schematic designation	$k \times 10^6$ sec^{-1} for I-D,H in *tert*-BuOH[a]	$k \times 10^6$ sec^{-1} for I-H,H in *tert*-BuOD[b]
Isom without exchange	k_1	0.13	2.6
Exchange starting material	k_2	4.18	17.8
Isom with exchange	k_3	1.41	3.1
Isom exchanged starting material	k_4	3.56 ± 0.04[c]	1.92 ± 0.02[d]

[a] Calculated from runs 4 and 5 (0.472 and 0.483 *M* potassium *tert*-butoxide, respectively; rate constants are for the former base concentration): time, 26.1 × 10⁴ sec; 45.6% isomerization; 60.2% exchange of starting material; 3.94% of one atom of deuterium in product. [b] Calculated from runs 2 and 7 (0.44 *M* potassium *tert*-butoxide): time, 3.60 × 10⁴ sec; 15.3% isomerization; 49.1% exchange of starting material; 58.8% of one atom of deuterium in product. [c] $k_4 = k_i$, calculated from $K = (\text{II}/\text{I})_{\text{equil}}^{75°} = 23$ and $k_i + k_{-i} = 3.71 \pm 0.04 \times 10^{-6}$ sec^{-1}, run 4, I-H,D in *tert*-BuOH. [d] $k_4 = k_i$, calculated from $K = (\text{II}/\text{I})_{\text{equil}}^{75°} = 23$ and $k_i + k_{-i} = 2.15 \pm 0.03 \times 10^{-6}$ from run 2, corrected from 0.468 to 0.44 *M* base concentration, I-D,H in *tert*-BuOD.

Table IX. Comparison between Observed and Calculated Values of One-Point Integrated Rate Constants (k_i) for I[a] → II[b] at Various Times in Runs Where Substrate and Solvent Have Different Isotopic Labels

Time, sec × 10⁻⁴	At times *t*: k_i (sec^{-1}) × 10⁵ obsd[c]	k_i (sec^{-1}) × 10⁵ calcd[c]
Run 1, I-H,H in *tert*-BuOD		
0.417	0.60	0.59
1.113	0.58	0.57
2.649	0.54	0.52
7.125	0.41	0.42
11.78	0.35	0.36
15.97	0.32	0.32
Run 3, I-D,H in *tert*-BuOH		
0.756	0.107[d]	0.103
1.788	0.112[d]	0.109
4.128	0.128[d]	0.123
8.48	0.150[d]	0.144
12.87	0.168[d]	0.163
17.42	0.183[d]	0.179
21.47	0.195[d]	0.191
25.80	0.204[d]	0.203

[a] I = I-H,H + I-D,H. [b] II = II-H + II-D. [c] $k_i = (1/t)(\ln [I_0/I_t])$. [d] Corrected for 6.1% I-H,H impurity in I-D,H. For I-H,H in *tert*-BuOH, k_i was time independent and known from run 4. The concentration of I-H,H originating from the starting impurity was calculated at each time and subtracted from the total concentration of I observed by glc.

Table X. One-Point Rate Constants for Reactions of (−)-I-H,H in Dimethyl-d_6 Sulfoxide, 3.06 *M* in Methanol-*O*-*d* and 0.304 *M* in Potassium Methoxide at 75 ± 0.03° (Run 20)

Process	Schematic designation	k's × 10^4 sec^{-1} for assumed $(k^H/k^D)^a$ of 1.8	4.1
Isom without exchange	k_1	0.86	0.86
Exchange starting material	k_2	5.5	5.4
Isom with exchange	k_3	4.1	4.2
Isom exchanged starting material[b]	k_4	2.8	1.2

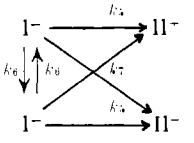
[a] Substrate primary kinetic isotope effect. [b] Values for k_4 that arise from the assumed isotope effects.

the extremes of isotope effect variation assumed, k_2 and k_3 varied by only about 2%. Thus, estimates of k_1, k_2, and k_3 for run 20 were made and are found in Table X.[12]

Rate Constants for Stereospecific and Nonstereospecific Isomerization and for Inversion of Starting Material. In the conversion of I-H,D to II-D in *tert*-butyl alcohol (Table VI), it was concluded that the reaction occurred with 97% stereospecificity. This value is minimal since slow racemization of starting material was concomitant with isomerization. Likewise, in the conversion of I-D,H to II-D in *tert*-butyl alcohol-*O*-*d* (Table II), the reaction occurred with a minimal stereospecificity of 85%. Calculations of the rate constants for stereospecific and nonstereospecific isomerization and for inversion of starting imine in runs 23 and 2 were made as follows.

In the following kinetic scheme of Chart III the minus and plus superscripts of I and II represent the signs of rotation of these materials when hydrogen was trans-

Chart III



ferred, and k_5, k_6, and k_7, the first-order rate constants. When deuterium was transferred as in run 2, the signs of II should be inverted. In cases where the benzylic position of I and the solvent carry the same isotopic label (*e.g.*, runs 24 and 2), exchange becomes a kinetically invisible reaction and is disregarded. The return of II to I becomes important only at high conversions of I to II and is also disregarded. Equations 7–10 were derived by integrating four simultaneous differential equations representing the rates of change in concentration of I^-, I^+, II^+, and II^- with time. The initial conditions of $[I^-] = 1$ and $[I^+]$, $[II^-]$, and $[II^+] = 0$ were incorporated in the equations. In eq 7–10, $\phi = k_5 + k_7$ and $\beta = k_5 + 2k_6 + k_7 = \phi + 2k_6$. In runs 23 and 2 at time t, the concentrations $[I^-]$, $[I^+]$, $[II^+]$, and $[II^-]$ were all measured. One-point rate constants for isomerization of I → II (k_i) and for racemization of I (k_α)

(12) In other investigations, k^H/k^D for isotopic exchange or racemization in dimethyl sulfoxide has ranged from 0.6 to 3.0 [(a) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 3688 (1961); (b) A. I. Shatenshtein, I. O. Shapiro, F. S. Iakushin, A. A. Isaewa, and Yu. I. Ranneva, *Kinet. Catal. (USSR)*, **5**, 752 (1963); (c) J. E. Hofmann, A. Schriesheim, and R. E. Nickols, *Tetrahedron Lett.*, 1745 (1965)].

$$[I^-] = {}^1/_2[e^{-\phi t} + e^{-\beta t}] \quad (7)$$

$$[II^+] = \frac{k_5 + k_6}{\beta} - {}^1/_2\left[e^{-\phi t} + \frac{k_5 - k_7}{\beta} e^{-\beta t}\right] \quad (8)$$

$$[II^-] = \frac{k_6 + k_7}{\beta} - {}^1/_2\left[e^{-\phi t} - \frac{k_5 - k_7}{\beta} e^{-\beta t}\right] \quad (9)$$

$$[I^+] = {}^1/_2[e^{-\phi t} - e^{-\beta t}] \quad (10)$$

were calculated directly from the per cent conversion of I → II and the rotation of recovered I. Since $k_i = k_5 + k_7$ and $k_\alpha = 2k_6$, ϕ and β were calculated. Combination of eq 8 and 9 gave eq 11, which provided the

$$k_5 - k_7 = \frac{([II^+] - [II^-])\beta}{1 - e^{-\beta t}} \quad (11)$$

value of $k_5 - k_7$, which when combined with $\phi = k_5 + k_7$ gave k_5 and k_7. Thus, k_5, k_6, and k_7 were all calculated for runs 23 and 2, and are recorded in Table XI.

Table XI. One-Point Rate Constants That Represent the Stereochemical Courses for Potassium *tert*-Butoxide Catalyzed Conversion of I to II at 75°

Run 23 (−)-I-H,D to II-D in *tert*-BuOH			Run 2 (−)-I-D,H to II-D in *tert*-BuOD[a]		
Process	Rate const	$k \times 10^6$ sec^{-1}	Process	Rate const	$k \times 10^6$ sec^{-1}
$I^- \rightarrow II^+$	k_5	3.72[b]	$I^- \rightarrow II^-$	k_5	1.92
$I^- \rightarrow I^+$	k_6	0.974	$I^- \rightarrow I^+$	k_6	0.163
$I^- \rightarrow II^-$	k_7	0.015	$I^- \rightarrow II^+$	k_7	0.11

[a] No correction was made in these calculations for the presence of the 6% (−)-I-H,H impurity in the starting material. Isotopic exchange occurred at a faster rate than isomerization. [b] This value is the same within probable error of $(k_i + k_{-i})$ value for run 4 (see Table I). The small difference in base concentration was not corrected for in the comparison.

Rate Constants for Racemization of Starting Imine in the Presence of Competing Isotopic Exchange and Isomerization. The data provide a means of estimating the relative rates of isotopic exchange and of racemization of the starting imine (rate constants k_e and k_α, respectively). Thus, $k_\alpha = 2k_6$ (see Chart III). Although k_6 for (−)-I-H,D in *tert*-butyl alcohol-*O*-*h* (run 23) and k_6 for (−)-I-D,H in *tert*-butyl alcohol-*O*-*d* (run 2) are in Table XI, in each case the medium and substrate (benzyl position) both had the same isotopic label, and isotopic exchange of I could not be observed. Furthermore, $k_e = k_2$ of Chart II, so the task remains for developing a kinetic scheme that allows calculation of k_α when I and medium contain different isotopic labels, and with the concurrent competing reactions of isomerization of labeled, unlabeled, optically pure, and racemized starting material. In these calculations, the reasonable assumption is made that imine I does not undergo appreciable isoinversion (inversion without exchange). Also taken into account is the small difference in rotation of deuterated and nondeuterated starting imine (I).

Equation 12 relates the rate constants of Chart IV to the fraction of isotopically exchanged–configurationally

Chart IV

$$(-)\text{-I-H(D)} \xrightarrow{k_x} (-)\text{-I-D(H)}$$

$$(-)\text{-I-H(D)} \xrightarrow{k_y} (+)\text{-I-D(H)}$$

$$(-)\text{-I-D(H)} \underset{}{\overset{k_z}{\rightleftharpoons}} (+)\text{-I-D(H)}$$

unchanged starting material [(−)-Ie] at time t.[13] The

$$(k_x - k_y) = \frac{2(2k_z - k_1 - k_2 - k_3 + k_4)}{[e^{-(k_1 + k_2 + k_3)t} - e^{-(2k_z + k_4)t}]}\left\{[(-)\text{-Ie}] - \frac{(k_x + k_y)}{2(k_4 - k_1 - k_2 - k_3)}[e^{-(k_1 + k_2 + k_3)t} - e^{-k_4 t}]\right\} \quad (12)$$

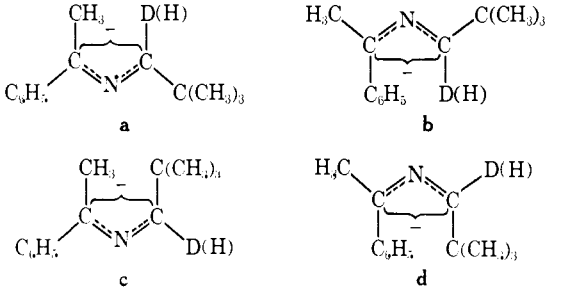
data of Tables II, III, and VIII applied to eq 12, coupled with $k_2 = k_x + k_y$ (by definition) and $k_z = 0$ (assumed), allows calculation of values for k_x and k_y for runs 3 and 7.

The racemization rate constant (k_α) for runs 3 and 7 in which substrate and solvent contained different isotopes equals $2k_y$, or $k_\alpha = 2k_y$. Thus, $k_\alpha = 0.84 \times 10^{-6}$ sec^{-1} for run 7, and $k_\alpha = 0.14 \times 10^{-6}$ sec^{-1} for run 3. Since $k_e = k_2$, and k_2 for runs 7 and 3 have been calculated (Table VIII), k_e/k_α for protio substrate in deuterio solvent is 21, and for deuterio substrate in protio solvent is 36.

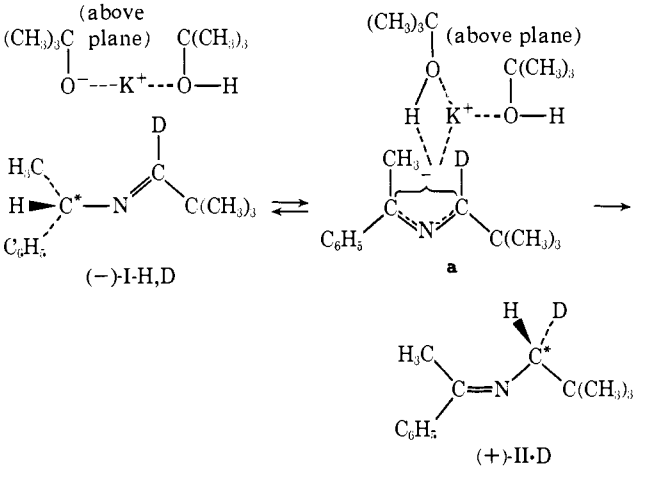
Discussion

Comparisons of the rate constants of the preceding section provide measures of these factors: (1) the stereospecificity of the isomerization of the benzyl to the neopentylimine; (2) the stereochemical character of the isotopic exchange of starting benzylimine; (3) the intramolecularity of the rearrangement; (4) the total ionization rate constants and the rate constants for the invisible reactions of collapse of intermediates to starting material; and (5) the substrate and solvent isotope effects. These factors are discussed in terms of a unifying mechanism in the succeeding sections.

Stereospecificity of Isomerization Reactions. The values for the ratio of rate constants $k_5/(k_5 + k_7)$ (Table XI) provide a measure of the stereospecificity of the isomerization reactions. In run 23, where (−)-I-H,D was isomerized to (+)-II-D in *tert*-butyl alcohol, $k_5/(k_5 + k_7) = 0.996$. The approach of this value to unity indicates that protium was transferred across the azaallylic system with essentially 100% stereospecificity. In run 2, where (−)-I-D,H was isomerized to (−)-II-D in *tert*-butyl alcohol-*O*-*d*, $k_5/(k_5 + k_7) = 0.946$. Thus, deuterium was transferred across the azaallylic system with only about 95% stereospecificity. Four azaallylic carbanions are envisioned as possible intermediates in the isomerizations, **a**, **b**, **c**, and **d**. These anions differ only in the relative positions of the phenyl, methyl, *tert*-butyl, and deuterium (protium) substituents. These carbanions are all intrinsically symmetrical, yet one or more of them must have intervened as intermediates in the base-catalyzed protium (deuterium) transfer from an asymmetric starting material to an asymmetric product. Clearly, an asymmetric element must be added in the form of a potassium ion and at least one *tert*-butyl alcohol (*tert*-butyl alcohol-*O*-*d*) molecule, which together occupy one face of the anion. Since **a**, **b**, **c**, and **d** each have two faces, eight structurally discrete intermediates are possible in principle.



Structure **a** is the least hindered sterically and places the large phenyl and *tert*-butyl groups in the least constrained positions. The size of the phenyl group in the anion is probably potentiated by its tendency to become coplanar with the azaallylic system, and thus maximize orbital overlap with resulting charge delocalization. The high stereospecificity in the protium (deuterium) transfer, coupled with the known configurations of starting material and product,[2c,6b] demonstrate that only one of the eight possible routes for reaction was used, namely, that based on structure **a**, in which protium (deuterium) was transferred only above the plane of the page. This corresponds to *suprafacial* protium (deuterium) transfer in contrast to an *antarafacial* transfer. Therefore, the stereospecific isomerization of (−)-I-H,D to (+)-II-D in *tert*-butyl alcohol can be envisioned as follows, and an analogous reaction sequence applies to the stereospecific isomerization of (−)-I-D,H to (−)-II-D in *tert*-butyl alcohol-*O*-*d*. Abstraction of the benzyl proton of (−)-I-H,D in the conformation formulated by potassium *tert*-butoxide contact ion pair yields anion **a**, solvated by *tert*-butyl alcohol and ion paired with potassium only on that side from which the proton was abstracted (above the plane of the paper). Collapse to the covalent state then occurs *within* this asymmetrically ion paired anion to give (+)-II-D, the product of stereospecific isomerization, and (−)-I-H,D, the product of an invisible reaction. The low dielectric constant of *tert*-butyl alcohol (11 at 19°[14]) probably results in



(13) D. A. Jaeger, Ph.D. Thesis, University of California at Los Angeles, Los Angeles, Calif., 1970, Appendix II.

(14) "International Critical Tables of Numerical Data, Physics, Chemistry, and Technology," E. W. Washburn, Ed., Vol. 6, McGraw-Hill, New York, N. Y., 1929, p 87.

potassium *tert*-butoxide existing as contact ion pairs. Likewise in this medium, carbanion **a** is expected to exist as part of a contact and/or solvent-separated ion pair with potassium as its counterion. Protonation (collapse) occurs only on that side ion paired to potassium, *i.e.*, only *within* the ion pair. Protonation by *tert*-butyl alcohol on the opposite face of **a** would leave potassium *tert*-butoxide as a *product-separated* ion pair, which is of higher energy in *tert*-butyl alcohol.

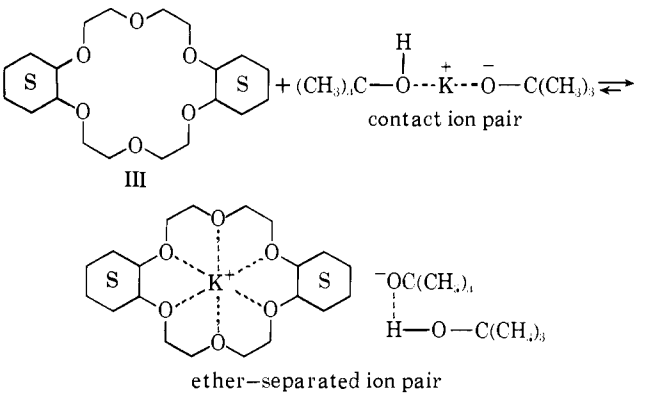
Stereospecificity of the Isotopic Exchange Reactions of Benzyl Imine I. The values of k_e/k_α (Results) provide a measure of the stereospecificity of the potassium *tert*-butoxide catalyzed isotopic exchange reactions of the starting benzyl imine I. The high values in *tert*-butyl alcohol indicate that isotopic exchange occurred

$$\left(\frac{k_e}{k_\alpha}\right)_{OD}^{CH} = 21 \qquad \left(\frac{k_e}{k_\alpha}\right)_{OH}^{CD} = 36$$

with high retention of configuration in this medium, as has been observed with other systems.[12a,15] The exchange is envisioned as occurring on the front face of a contact ion pair intermediate analogous to that formulated. The rotation of potassium and its ligands (the molecule of alcohol formed by abstraction of protium or deuterium from substrate and at least one molecule of alcohol of opposite isotope from the medium) is followed by collapse to isotopically exchanged I of retained configuration. In this low polarity solvent[14] these processes are faster than ion pair dissociation. In this picture of isotopic exchange with high retention of configuration, the contact ion pair formulated is an intermediate common to both isotopic exchange of starting material and generation of rearranged imine.

The addition of crown ether III had a profound effect on the potassium *tert*-butoxide catalyzed isotopic exchange of I-H in *tert*-butyl alcohol-*O*-*d*. Thus, k_e/k_α dropped to 0.8 in the presence of crown ether (run 13) from a value of 21 in its absence (run 7). Most likely, the fact that this k_e/k_α value was slightly less than unity is attributed to incomplete drowning in the *tert*-butyl alcohol-*O*-*d* pool of the *tert*-butyl alcohol molecule generated by ionization of I-H. Collapse of carbanion to the covalent state was faster than drowning, and as a result, the system exhibited a small isoinversion reaction component.

Crown ethers such as III are known to effectively fill the coordination sites of potassium ion[9] and convert contact ion pairs into ether-separated ion pairs.[16] Therefore, the addition of crown ether III probably converted potassium *tert*-butoxide contact ion pairs almost totally into ether-separated ion pairs as indicated. The loss of stereospecificity in the isotopic exchange of (−)-I-H in run 13 points to its dependence on asymmetric ion pairing of intermediate carbanion **a** with potassium ion. Crown ether III effectively removes potassium from the reaction site. The effect of crown ether III on the stereospecificity of the potassium *tert*-butoxide catalyzed isomerization was not investigated. However, since $k_e/k_\alpha = 0.8$ for I-H,H in *tert*-butyl alcohol-*O*-*d* with III, the isomerization of I-H,D in *tert*-butyl alcohol with III would almost certainly yield nearly if not totally racemic II-D. The stereospecificities of both isotopic exchange of starting imine and isomerization are dependent on asymmetric ion pairing with potassium ion.



Intramolecularity in the Rearrangement. Values of $k_1/(k_1 + k_3)$ can be calculated from the data of Table VIII. They provide a measure of the intramolecularity of the hydrogen migration. The value of 0.46 intramolecularity for protium migration for I-H,H in *tert*-butyl alcohol-*O*-*d* is not far from the value of 0.51 observed for protium migration in the potassium *tert*-butoxide catalyzed rearrangement of 3-phenyl-1-butene to *cis*-2-phenyl-2-butene in the same solvent.[17] The value of 0.08 intramolecularity for deuterium migration for I-D,H in *tert*-butyl alcohol is lower than the value of 0.23 observed for 3-phenyl-1-butene-*3*-*d* in the same solvent,[17] although in both systems intramolecularity was higher for protium transfer. Similar mechanisms probably apply to both systems. On the whole, the greater bulk of the *tert*-butyl group in I over the similarly placed hydrogen in 3-phenyl-1-butene appears to play a surprisingly small role in reducing intramolecularity.

$$\left(\frac{k_1}{k_1 + k_3}\right)_{t\text{-BuOD}}^{\text{I-H,H}} = 0.46$$

$$\left(\frac{k_1}{k_1 + k_3}\right)_{t\text{-BuOH}}^{\text{I-D,H}} = 0.08$$

$$\left(\frac{k_1}{k_1 + k_3}\right)_{\text{DMSO-}d_6\text{–CH}_3\text{OD}}^{\text{I-H,H}} = 0.17$$

Rate Constants for Total Ionization and for the Invisible Reaction of Ion Pair Formation and Collapse Back to Starting Material. The ratio of the rate constant for *isotopic exchange* that gives starting material (k_2) to that for *isotopic exchange* which gives product (k_3) is termed the *collapse ratio*, since it reflects two modes of collapse of the intermediate ion pair to the covalent state. The collapse ratios calculated from the rate constants of Tables VIII and X are listed.

$$\left(\frac{k_2}{k_3}\right)_{t\text{-BuOD}}^{\text{I-H,H}} = 5.7$$

$$\left(\frac{k_2}{k_3}\right)_{t\text{-BuOH}}^{\text{I-D,H}} = 3.0$$

$$\left(\frac{k_2}{k_3}\right)_{\text{DMSO-}d_6\text{–CH}_3\text{OD}}^{\text{I-H,H}} = 1.3$$

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

(16) K. H. Wong, G. Konizer, and J. Smid, *ibid.*, **92**, 666 (1970).

(17) D. J. Cram and R. T. Uyeda, *ibid.*, **86**, 5466 (1964).

Table XII. Approximate Rate Constants for Ionization (k_t), Return to Starting Material (k_r), Isomerization without Exchange (k_1), Exchange of Starting Material (k_2), and Isomerization with Exchange (k_3) for Imine I → Imine II at 75°

Run no.	Starting material	Solvent	$k \times 10^6$, sec^{-1}				
			k_t[a]	k_r	k_1	k_2	k_3
7	I-H,H	*tert*-BuOD	38 ± 6	12 ± 4[b]	2.8[c]	19.1[c]	3.3[c]
5	I-D,H	*tert*-BuOH	6.2 ± 0.2	0.56 ± 0.18[b]	0.13[c]	4.18[c]	1.41[c]
4	I-H,D	*tert*-BuOH	19 ± 5[d]	15 ± 5[b]	3.56		
2	I-D,H	*tert*-BuOD	11 ± 4[d]	9 ± 3[b]	2.06[c]		
20	I-H,H[e]	$(CD_3)_2SO$–CH_3OD	1160	115	86	550	410

[a] $k_t = k_r + k_1 + k_2 + k_3$. [b] Assumed $k_r = (4.4 \pm 1.3)k_1$. [c] Rate constants corrected from 0.44 (run 7), 0.483 (run 5), or 0.468 (run 2) to 0.472 *M* potassium *tert*-butoxide (run 4) assuming reaction to be first order in base. [d] Assumed $k_t = (5.4 \pm 1.3)k_1$. [e] Run 20, assumed $k_4/k_d = 1.8$. See Table X.

The collapse ratios obtained for I-H,H in *tert*-BuOD and for I-D,H in *tert*-BuOH clearly differ from one another. This difference is attributed to substrate and/or solvent isotope effects on the partitioning of ion pairs between *isotopically exchanged* starting material and product. Likewise, partitioning of ion pairs between *nonexchanged* starting material and product should also be subject to solvent and/or substrate isotope effects.

In previous investigations of potassium *tert*-butoxide catalyzed isomerizations of olefins in *tert*-butyl alcohol, the absence of substrate and solvent isotope effects on collapse ratios was assumed.[18] The above results indicate this assumption is not strictly correct. The results allow a quantitative determination of the deviation of the system at hand from a model in which the collapse ratio is assumed free of isotope effects.

In our isotope effect free model, the average collapse ratio of $k_2/k_3 = 4.4$ is employed with the two values observed (5.7 and 3.0) as limits of error. The values of k_1, k_2, and k_3 of Table VIII, coupled with a collapse ratio of 4.4 ± 1.3, provide a means of estimating the values of rate constants otherwise not accessible. If k_r is the rate constant for the invisible reaction of producing ion pair and the ion pair *returning* to starting material, then $k_r = k_1k_2/k_3$. If k_t is the total rate constant for ionization of I to produce ion pair, then $k_t = k_r + k_1 + k_2 + k_3$. In this model, k_r and k_t values can be calculated for runs with I-H in *tert*-BuOH as well as for I-D in *tert*-BuOD. Thus, $k_r/k_1 \sim 4.4$ for runs 2 and 4. The k_4's of Table VIII are the rate constants for isomerization of I-H,D in *tert*-BuOH (3.56×10^{-6} sec^{-1}) and for isomerization of I-D,H in *tert*-BuOD (1.92×10^{-6} sec^{-1}). Although exchange undoubtedly occurs in these runs, the same products and starting materials are produced with and without exchange. Therefore, the k_4's of these runs become the equivalent of the k_1's of the runs in which isotopes of substrate and solvent are different. Thus $k_r \sim 4.4k_1$, and $k_t \sim k_r + k_1 = 5.4k_1$ for such runs.

Based on this collapse ratio isotope effect free model, values for k_t, k_r, k_1, k_2, and k_3 are listed in Table XII for I-H in *tert*-BuOD and in *tert*-BuOH, and for I-D in *tert*-BuOH and *tert*-BuOD. Values also are listed for the rate constants of I-H,H in deuterated dimethyl sulfoxide–methanol. In this medium, too, the calculations involved the assumption that collapse ratio was independent of isotope effects. In Table XII, those rate constants dependent on the assumption of $k_2/k_3 = 4.4 \pm 1.3$ are assigned limits of error accordingly. Some of the limits of errors that result are quite large. Only gross comparisons and not fine distinctions will be made in those cases.

Values of $k_2/(k_2 + k_r)$ give a measure of the rate of isotopic exchange of starting material relative to the rate of ionization of material leading to exchanged and nonexchanged starting material. These numbers provide calibration for the use of isotopic exchange rates as measures of ionization rates of carbon acids. The

$$\left(\frac{k_2}{k_2 + k_r}\right)^{\text{I-H,H}}_{t\text{-BuOD}} = 0.62 \pm 0.08$$

$$\left(\frac{k_2}{k_2 + k_r}\right)^{\text{I-D,H}}_{t\text{-BuOH}} = 0.88 \pm 0.03$$

$$\left(\frac{k_2}{k_2 + k_r}\right)^{\text{I-H,H}}_{\text{DMSO-}d_6\text{-CH}_3\text{OD}} = 0.83$$

pK_a values of *tert*-butyl alcohol and I differ by approximately 10 units, and yet isotopic exchange accounted for from 0.62 to 0.88 of the total rate of return of intermediate ion pair to starting material. This fact suggests that rates of isotopic exchange in *tert*-butyl alcohol of nonrearranging carbon acids with pK_a's up to about 30 are not far from the rates of ionization, particularly when deuterium of the carbon acid is being exchanged for protium of *tert*-butyl alcohol. Information of this sort is important when correlations between kinetic and thermodynamic acidity are made for carbon acids.[19] Furthermore, correlations between isotope effects and the difference in pK_a of carbon acid and solvent depend on identification of the rate-determining step. In dimethyl sulfoxide–methanol, the indications are that even when carbon acid is exchanged with deuterated solvent, the rates of exchange and of ionization are not far from one another.

If the isomerization of I-H,D to II-D in *tert*-butyl alcohol (run 23) proceeded only through carbanion **a** as indicated previously, then k_6/k_7 (Table XI, ratio of rate constant for inversion of starting material to that for nonstereospecific isomerization) is the collapse ratio on the back face of the anion and that of the system as a whole. The same reasoning applies to the k_6/k_7 ratio for the isomerization of I-D,H to II-D in *tert*-butyl alcohol-*O*-*d* (run 2). Values of $k_6/k_7 = 6.5$ for run 23 and 1.5 for run 2 were obtained. Although limits of error are large for these numbers, the inequality is expected since the k_2/k_3 values calculated above are unequal (3.0 and 5.7). As with the k_2/k_3 ratios, the in-

(18) S. W. Ela and D. J. Cram, *J. Amer. Chem. Soc.*, **88**, 5777, 5791 (1966).

(19) For example, D. J. Cram and W. D. Kollmeyer, *ibid.*, **90**, 1791 (1968).

equality probably reflects substrate and/or solvent isotope effects on collapse ratio.

The small nonstereospecific components for the isomerization reactions must have involved rotation of the face of the azaallylic carbanion with respect to the potassium ion and its ligands. Such rotation could have occurred either by reorganization of a solvent-separated ion pair, or by complete ion pair dissociation.

The inequality of collapse ratios, k_2/k_3 (3.0 and 5.7), may reflect tunneling effects. Protonation of intermediate azaallylic anion by *tert*-butyl alcohol at the neopentyl position should be subject to severe steric effects, and such effects on proton transfer may induce proton tunneling.[20] If it is assumed that there is no isotope effect on collapse at the benzyl center, then a value of k_2/k_3 for I-D,H in *tert*-BuOH (3.0) which is lower valued than that for I-H,D in *tert*-BuOD (5.7) is consistent with tunneling in collapse at the neopentyl center.

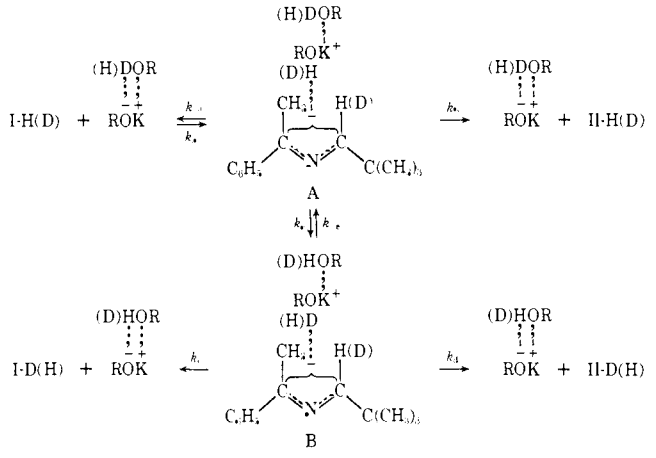
General Mechanistic Scheme. One *common* intermetiate, which formed in a slow step and gave the four possible products directly in fast steps, is incompatible with the data. Such an intermediate would contain carbanion **a**, potassium ion, and a molecule each of *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d*, and would require values of k_1/k_3 (rate constant for rearrangement without exchange to that with exchange) to be constant. Actually, this ratio varied by a factor of 9 when the positions of the isotopic label in substrate and solvent were interchanged (eq 13). Similarly, the above

$$\left(\frac{k_1}{k_3}\right)_{OD}^{CH} = 9\left(\frac{k_1}{k_3}\right)_{OH}^{CD} \qquad (13)$$

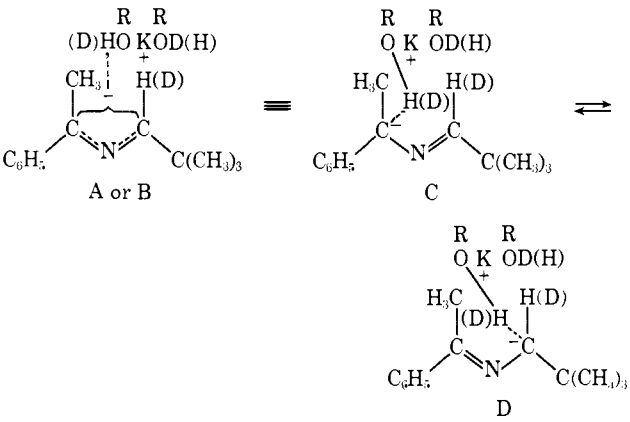
facts eliminate a mechanism with two or more intermediates which equilibrated faster than they collapsed to the covalent state.

The simplest mechanistic model (Chart V) compatible

Chart V



with the data (and the assumption that the collapse ratio has no isotope effect) involves two ion pair intermediates, A and B. In A, azaallylic carbanion **a** is hydrogen bonded to the alcohol molecule just generated in the ionization. The second intermediate, B, is a new ion pair in which an alcohol molecule from the solvent has taken the place of the original alcohol molecule. Interconversion of A and B and their collapse to the covalent states are also included, and each step is assigned a rate constant. Substantial evidence has accumulated that delocalized carbanions in hydroxylic solvents have only one hydrogen bond per anion.[17,21] In ion pair intermediate A, either ROH is hydrogen bonded to both charge-carrying centers at the same time, or what is more likely, ROH is shuffling between centers at a rate much greater than the rates at which A and B interconvert or collapse to the covalent state (C $\rightleftarrows$ D). Similar possibilities apply to ROD in B. Although the four-intermediate scheme is more likely, C and D are not included in Chart V since the two- and four-intermediate schemes reduce to the same kinetic relationships, provided the above condition is met.



In Chart V the two intermediates, A and B, are interconverted by rotation of the potassium ion and its ligands. Thus, exchange of positions of ROH and ROD involves *rotation* of the cation and its ligand in the ion pair. This process must be slower than the *shuffle*, and not a lot faster than *collapse*.

The macroscopic rate constants calculated from the data (k_r, k_1, k_2, and k_3) are related to the microscopic rate constants of Chart V by eq 14–17, which were de-

$$k_r = \frac{k_a k_{-a}(k_c + k_{-e} + k_d)}{(k_{-a} + k_e + k_b)(k_c + k_{-e} + k_d) - k_e k_{-e}} \qquad (14)$$

$$k_1 = \frac{k_a k_b(k_c + k_{-e} + k_d)}{(k_{-a} + k_e + k_b)(k_c + k_{-e} + k_d) - k_e k_{-e}} \qquad (15)$$

$$k_2 = \frac{k_a k_e k_c}{(k_{-a} + k_e + k_b)(k_c + k_{-e} + k_d) - k_e k_{-e}} \qquad (16)$$

$$k_3 = \frac{k_a k_e k_d}{(k_{-a} + k_e + k_b)(k_c + k_{-e} + k_d) - k_e k_{-e}} \qquad (17)$$

rived making use of the steady-state approximation and the reasonable assumption that k_a must be much lower valued than any of the other rate constants.[22]

Division of eq 16 by eq 17 gives $k_2/k_3 = k_c/k_d$, and, thus, the definition of k_2/k_3 as a collapse ratio is justified.

Isotope Effects. The rate constants of Table XII provide a means of calculating a series of approximate substrate, solvent, and combined isotope effects. Table XIII lists the values, some of which involve rate constants calculated with the averaged collapse ratio of 4.4. These isotope effects are assigned limits of

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

(21) (a) D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *ibid.*, **88**, 2759 (1966); (b) W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 4661 (1967); (c) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968).

(22) The authors wish to thank Dr. John Almy, who derived these relationships in connection with another study.

Table XIII. Isotope Effects for Ionization and Component Reactions of Imine I in *tert*-Butyl Alcohol at 75°

Process	Rate constant	k_{OH}^{CH}/k_{OH}^{CD} [a]	k_{OD}^{CH}/k_{OD}^{CD} [a]	k_{OH}^{CH}/k_{OD}^{CH} [a]	k_{OH}^{CD}/k_{OD}^{CD} [a]	k_{OD}^{CH}/k_{OH}^{CD} [a]
Total ionization	k_t	3.0 ± 0.9	3.7 ± 1.3	0.53 ± 0.18	0.60 ± 0.17	6.0 ± 0.8
Return to starting material	k_r	34 ± 19	1.7 ± 0.9	1.6 ± 0.9	0.076 ± 0.044	26 ± 16
Rearr, no exchange	k_1	27	1.4	1.3	0.063	25
Exchange, no rearr	k_2					4.6
Rearr with exchange	k_3					3.9

[a] CH, CD, OH, and OD refer to starting states.

error based on the limiting collapse ratios of 3.0 and 5.7. Some of the errors are very large, and only qualitative comparisons between these isotope effects are possible.

Of these isotope effects, only those associated with k_t, the total ionization rate constant, involve only one stage. Substrate isotope effects in deuterated and nondeuterated solvent are positive as expected (3.0 ± 0.9, 3.7, and 1.3) and are close to that observed for racemization of optically active 4-biphenylylmethoxyphenylmethane (k_H/k_D = 2.7 at 116°) in *tert*-butyl alcohol-*O*-*d*–potassium *tert*-butoxide.[15]

Solvent isotope effects for k_t are negative and almost independent of substrate label (0.53 ± 0.18 and 0.60 ± 0.17). The fact that these values are less than unity probably reflects higher activity for $R\bar{O}\cdots DOR$ than for $R\bar{O}\cdots HOR$. Similar values have been observed in the same medium for isomerization of phenylpropenyl to phenylvinyl systems.[18]

The isotope effects for substrate and solvent for generation of unexchanged starting material and product (rate constants, k_r and k_1, respectively) vary from 34 ± 19 to 0.063, depending on the combinations of positions of isotopic labels. These isotope effects are composite and represent combinations of large numbers of individual rate constants, each with its own substrate and solvent contributions (see eq 14 and 15). However, comparisons of k_{OH}^{CH}/k_{OH}^{CD} with k_{OD}^{CH}/k_{OD}^{CD} and of k_{OH}^{CH}/k_{OD}^{CH} with k_{OH}^{CD}/k_{OD}^{CD} for k_r and k_1 lead to the conclusion that isotopic drowning of *tert*-butyl alcohol-*O*-*d* generated in a pool of *tert*-butyl alcohol occurs faster than that of *tert*-butyl alcohol generated in a pool of *tert*-butyl alcohol-*O*-*d*. Furthermore, this conclusion is valid even when substrate and solvent isotope effects for prior ionization are considered. The same preference for deuterium over protium drowning has been observed in methanol–potassium methoxide,[23] and generally, intramolecularity is greater with protium rather than with deuterium transfer in a great number of solvent–base systems.[24]

Experimental Section

General. All melting and boiling points are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on Varian A-60 and A-60-D instruments with tetramethylsilane (TMS) as internal standard except when deuterium oxide was solvent, in which case TMS in chloroform was external standard. A Varian C-1024 time-averaging computer was used for quantitative determinations by nmr.

Solvents and Bases. The purification of *tert*-butyl alcohol has been described,[25] and *tert*-butyl alcohol-*O*-*d*,[26] methanol-*O*-*d*,[27] and dimethyl-d_6 sulfoxide[28] were prepared using established procedures. Tetrahydrofuran (THF) was purified by distillation from lithium aluminum hydride and was used immediately thereafter. Other solvents were reagent grade and were used without further purification.

The preparation of solutions of potassium *tert*-butoxide in *tert*-butyl alcohol and in *tert*-butyl alcohol-*O*-*d*[25] and of solutions of potassium methoxide in methanol-*O*-*d*[27] has been described. Solutions of potassium methoxide in dimethyl-d_6 sulfoxide–methanol-*O*-*d* were prepared by dilution of methanol-*O*-*d*-potassium methoxide solutions with dimethyl-d_6 sulfoxide. Potassium alkoxide solutions were standardized by titration with hydrochloric acid to either a methyl red–brom cresol green or a phenolphthalein end point.

Gas–Liquid Chromatography (Glc). Analytical and Preparative. Analyses and preparative separations were carried out on ten columns: column A, 6 or 10 ft × 1/4 in. column packed with 5% *m*-phenyl ether on >20 mesh Fluoropack; column B, 6 ft × 3/4 in. column packed with 20% SE-30 on 60–80 mesh firebrick; column C, 6 ft × 1/4 in. column packed with 15–20% Carbowax M on 60–80 mesh firebrick; column D, 6 ft × 3/8 in. column packed with 20% SE-30 on 60–80 mesh DCDMS Chromosorb W; column E, 10 ft × 1/4 in. column packed with 24% Apiezon L on 60–80 mesh DCDMS Chromosorb W; column F, 6 or 10 ft × 1/4 in. column packed with 20% SE-30 on 60–80 or 80–100 mesh HMDS Chromosorb W; column G, 10 ft × 1/4 in. column packed with 15 or 20% SE-30 on 60–80 mesh DCDMS Chromosorb W; column H, 10 ft × 1/4 in. column packed with 20% SF-96 on 60–80 mesh Chromosorb W; column I, 20 ft × 3/8 in. column packed with 30% SE-30 on 40–60 mesh firebrick; column J, 6 ft × 1/8 in. column packed with 15% SE-30 on 60–80 mesh Chromosorb W.

(−)-(*S*)-*N*-(Neopentylidene)-α-phenylethylamine [(−)-I-H,H]. During 2 hr, 7.43 g (61.5 mmol) of (−)-α-phenylethylamine,[6a] $\alpha^{25}D$ −37.56° (neat, 1 dm), was added to 5.4 g (63 mmol) of pivalaldehyde (freshly distilled, bp 71–73°) at 0° with stirring. After warming to 25° and standing for 16 hr, the mixture was added to 100 ml of pentane. The pentane solution was washed with three 30-ml portions of aqueous 1% acetic acid and 10 ml of aqueous 5% sodium bicarbonate, and dried by filtration through sodium sulfate. Most of the pentane was removed by distillation through a short Vigreux column, and rotary evaporation gave 10.48 g (90%) of a mobile oil. By glc (column A, 185°) this material contained greater than 99% (−)-I-H,H, and it was purified by preparative glc (column B, 120°) and collected in a spiral collector packed with glass helices and cooled in a Dry Ice–acetone bath. The product was washed out with pentane, and after rotary evaporation, the residue was distilled to give 9.35 g (80%) of (−)-I-H,H, bp 105° (15 mm), α^{25}_{346} −50.46° (neat, 1 dm). *Anal.* Calcd for $C_{13}H_{25}N$: C, 82.48; H, 10.12. Found: C, 82.54; H, 10.12.

The ir spectrum of (−)-I-H,H in carbon tetrachloride (5%) displayed an intense band at 6.00 μ, which was assigned to C=N stretch. The nmr spectrum (neat liquid) exhibited a singlet at δ 1.00 (*tert*-butyl protons, 8.7), a doublet centered at 1.37, J = 7.0 Hz (α-methyl protons, 3.1), a quartet centered at 4.15, J = 7.0 Hz (methine proton, 0.86), a complex multiplet from 6.9 to 7.4 (phenyl protons, 5.2), and a singlet at 7.49 (vinyl proton, 1.1). The uv spectrum in absolute ethanol displayed a shoulder with fine structure from 240 to 270 nm with λ_{max} 275 nm, log ϵ_{max} 2.42.

(23) J. Almy, D. C. Garwood, and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 4321 (1970).

(24) For examples and discussion, see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter V.

(25) D. H. Hunter and D. J. Cram, *J. Amer. Chem. Soc.*, **86**, 5478 (1964).

(26) D. J. Cram and B. Rickborn, *ibid.*, **83**, 2178 (1961).

(27) D. J. Cram and A. S. Wingrove, *ibid.*, 86, 5490 (1964).

(28) (a) E. Buncel, E. A. Symons, and A. W. Zabel, *Chem. Commun.*, **9**, 173 (1965); (b) L. Gosser and D. J. Cram, unpublished results.

In other preparations with essentially the same procedure, (−)-α-phenylethylamine, $\alpha^{25}D$ −38.18° (neat, 1 dm), $\alpha^{25}D$ −38.20° (neat, 1 dm), and $\alpha^{25}D$ −38.16 ± 0.03° (neat, 1 dm), gave (−)-I-H,H $\alpha^{25}D$ −42.24° (neat, 1 dm), $\alpha^{25}D$ −42.43° (neat, 1 dm), $n^{25}D$ 1.4871, and $[\alpha]^{25}_{546}$ −80.2 ± 0.7°, $[\alpha]^{25}_{436}$ −145.1 ± 1.0°, $[\alpha]^{25}_{365}$ −244.9 ± 1.4° (*c* 0.739, chloroform), respectively. Analysis of the latter material by glc (column C, 143°) indicated it to be essentially 100% pure.

(±)-*N*-(Neopentylidene)-α-phenylethylamine [(±)-I-H,H]. The procedure essentially followed that for the preparation of (−)-I-H,H. From 10.2 g (0.08 mol) of α-phenylethylamine and 9.0 g (0.1 mol) of pivalaldehyde was obtained 16.3 g (86%) of (±)-I-H,H, bp 58° (0.6 mm), $n^{25}D$ 1.4872.

(−)-(*S*)-*N*-(Neopentylidene)-α-phenylethylamine-α-*d* [(−)-I-D,H]. The procedure essentially followed that for the preparation of (−)-I-H,H. From 4.78 g (39.3 mmol) of (−)-α-phenylethylamine-α-*d* (0.943 atom of deuterium in the methine position and 0.995 atom of excess deuterium per molecule), $\alpha^{25}D$ −40.36° (neat, 1 dm), and 3.70 g (43.0 mmol) of pivalaldehyde was obtained 6.8 g (91%) of (−)-I-D,H after preparative glc (column D, 116°) followed by distillation. By glc this material contained 0.2% of α-phenylethylamine and 4% of a volatile component as impurities; by nmr (−)-I-D,H contained 0.939 atom of deuterium at the methine position. Fractional distillation of this material gave 5.5 g of (−)-I-D,H, bp 115° (24 mm), $\alpha^{25}D$ −43.84° (neat, 1 dm), which was pure by glc except for 0.2% of α-phenylethylamine.

(±)-*N*-(Neopentylidene)-α-phenylethylamine-α-*d* [(±)-I-D,H]. The procedure essentially followed that for the preparation of (−)-I-H,H. From 2.03 g (16.6 mmol) of α-phenylethylamine-α-*d* (0.995 ± 0.005 atom of excess deuterium per molecule) and 1.68 g (19.5 mmol) of pivalaldehyde (freshly distilled, bp 72–73°) was obtained 2.85 g (90%) of an oil, which was fractionally distilled to give (±)-I-D,H, bp 32–34° (0.1 mm). This material was homogeneous by glc (column C, 136°), and likewise, glc provided an analytical sample. *Anal.* Calcd for $C_{13}H_{18}DN$: C, 82.05; H + D, 10.59. Found: C, 81.81; H + D, 10.63.

(−)-(*S*)-*N*-(Neopentylidene-*1-d*)-α-phenylethylamine [(−)-I-H,D]. The procedure essentially followed that for the preparation of (−)-I-H,H. From 7.1 g (58 mmol) of (−)-α-phenylethylamine,[6a] $\alpha^{25}D$ −38.18° (neat, 1 dm), and 5.39 g (61.9 mmol) of pivalaldehyde-*1-d* (0.995 atom of excess deuterium per molecule) was obtained 9.92 g (89%) of (−)-I-H,D after preparative glc (column D, 116°). This material was distilled to give (−)-I-H,D, bp 120° (29 mm), $\alpha^{25}D$ −42.30° (neat, 1 dm), and by combustion and falling drop analysis it contained 0.996 atom of excess deuterium per molecule. By glc analysis it contained 0.3% of α-phenylethylamine as its only impurity.

In another preparation, (−)-α-phenylethylamine, $\alpha^{25}D$ −38.20° (neat, 1 dm), and pivalaldehyde-*1-d* gave (−)-I-H,D, $\alpha^{25}D$ −42.46° (neat, 1 dm), $n^{25}D$ 1.4871.

***N*-(α-Methylbenzylidene)neopentylamine (II-H).** To 2 ml of water was added 349 mg (4.0 mmol) of neopentylamine followed by 2 ml of saturated aqueous zinc chloride and an additional 5 ml of water. The resultant finely divided precipitate was collected by filtration and dried under vacuum to give 380 mg of white neopentylamine–zinc chloride complex.

To 75 ml of benzene were added 7.6 g (87 mmol) of neopentylamine, 10.6 g (87 mmol) of acetophenone, and 317 mg of neopentylamine–zinc chloride complex. The reaction mixture was refluxed for 12 hr under a Soxhlet extractor charged with 40 g of sodium sulfate. The benzene solution was extracted with 75- and 25-ml portions of aqueous 1% acetic acid and 20 ml of aqueous 5% sodium bicarbonate, and dried by filtration through sodium sulfate. Benzene was partially removed by distillation through a short Vigreux column, and rotary evaporation left 17.6 g of an oil. By glc (column B, 162°) this material was purified preparatively, and found to contain 12.4% acetophenone. The same collection and isolation procedure used for (−)-I-H,H gave 14 g (85%) of residue which was distilled to give II-H, bp 134° (22 mm). By glc (column A, 185°) this material contained less than 0.2% of acetophenone. *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12. Found: C, 82.50; H, 9.92.

The ir spectrum of II-H in carbon tetrachloride (5%) displayed an intense band at 6.10 μ, which was assigned to C=N stretch. The nmr spectrum (neat liquid) exhibited a singlet at δ 1.06 (*tert*-butyl protons, 8.8), a singlet at 1.87 (α-methyl protons, 3.0), a singlet at 3.02 (methylene protons, 2.0), and two complex multiplets from 7.0 to 7.3 and 7.6 to 7.9 (phenyl protons, 5.1).

Pivalaldehyde-*1-d*. Procedure A. By the method of Hill, *et al.*,[29a] as modified by Streitwieser and Schaeffer,[29b] methyl pivalate was reduced on a 50-g scale to give a 56% yield of neopentyl-*1-d*$_2$ alcohol, bp 102–114°. This material solidified, mp 43–53°, on warming over molecular sieves and was converted to aldehyde without further purification.

In 50 ml of cold pyridine was dissolved 1.0 g of chromium trioxide. To this solution at 10–15° was added a solution of 13.3 g (0.147 mol) of neopentyl-*1-d*$_2$ alcohol in 15 ml of pyridine, followed by 15.0 g of chromium trioxide during 2.5 hr. Pivalaldehyde-*1-d* was distilled directly from the reaction mixture, bp 66–111°. An ether solution of this material was extracted with 5- and 3-ml portions of 10% hydrochloric acid, 1 ml of water, and 2 ml of saturated aqueous sodium chloride. The ether solution was dried and fractionally distilled through a 1-ft column packed with glass helices to give 5.9 g of pivalaldehyde-*1-d*, bp 61–73°. By glc (column E) this material contained 5% ether as the only impurity, and an ir spectrum in carbon tetrachloride (10%) agreed in essential detail with that of authentic pivalaldehyde with the exception of bands consistent with the substitution of deuterium for protium. The band present at 2695 cm^{-1} in the spectrum of pivalaldehyde was completely replaced by bands at 2030 and 2120 cm^{-1} in that of deuterated material. Also, there was a sharp band at 1070 cm^{-1} not exhibited by protio aldehyde. The nmr spectrum of this material showed less than 0.5% of protio aldehyde using benzene as an internal standard.

Procedure B.[8] A mixture of 5.0 g (0.12 mol) of lithium aluminum deuteride (99.5% D) in 180 ml of anhydrous ether was refluxed for 12 hr. Then during 0.5 hr this mixture was added to a solution of 39.5 g (0.48 mol) of pivalonitrile in 100 ml of anhydrous ether at 0°. The reaction mixture was stirred for an additional hour at 0°, and 100 ml of 5 *N* sulfuric acid was added. The layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined organic layers were washed with aqueous saturated sodium chloride, dried, and fractionally distilled on a spinning band column to give 4.0 g of pivalaldehyde-*1-d*, bp 74–75°, 5.1 g of pivalonitrile, and 26.2 g of high boiling residue. The residue was added to 25 ml of 20% sulfuric acid, and with heating, a colorless liquid distilled, which yielded 20.6 g of pivalaldehyde-*1-d* on redistillation; total 24.6 g (60%)

The nmr spectrum of this material displayed only a singlet at δ 1.08 (*tert*-butyl protons).

α-Phenylethylamine-α-*d* by Reduction of Acetophenone Oxime-*O*-*d* with Sodium and Acetic Acid-*O*-*d*. All operations prior to work-up were carried out under dry nitrogen. Reaction flasks were flame-dried under vacuum and filled with nitrogen prior to use. Acetic acid-*O*-*d* was prepared from 580 g (5.0 mol) of pure acetic anhydride and 102 g (5.1 mol) of deuterium oxide (99.8% D). Acetophenone oxime-*O*-*d* was prepared by treating a solution of 108 g (0.80 mol) of protio oxime in 200 ml of anhydrous ether with 10-ml portions of deuterium oxide (99.8% D) until the calculated deuterium content (11 exchanges) was at least 99.5% (neglecting isotope effects). The resultant ether solution of acetophenone oxime-*O*-*d* was transferred to the reaction flask under partial vacuum and the ether removed under vacuum. A sample of the dry residue in carbon tetrachloride showed no hydroxyl absorption by ir analysis. To the dry residue was added 700 ml of anhydrous ether followed by a trace of phenolphthalein as indicator. Then during 10–18 hr, 77 g (3.3 mol) of sodium and 200 ml of acetic acid-*O*-*d* were slowly added to the ether solution stirred at 0° at a rate such that the solution always remained slightly acidic. The product was isolated by conventional methods, wt 59.3 g (59%), bp 80° (16 mm).

The α-phenylethylamine-α-*d* was resolved with *d*-tartaric acid[6a] to give 19.0 g (64%) of (−)-α-phenylethylamine-α-*d*, bp 84–84.5° (22 mm), $\alpha^{25}D$ −40.36° (neat, 1 dm). Analysis by nmr showed 0.943 atom of deuterium in the methine position, whereas combustion and falling drop analysis indicated 0.995 atom of excess deuterium per molecule.

α-Phenylethylamine-α-*d* from α-Phenylpropionic-α-*d* Acid. Under very dry conditions in an atmosphere of purified nitrogen a solution of 5.02 g (33.2 mmol) of α-phenylpropionic-α-*d* acid (0.992 ± 0.005 atom of excess deuterium per molecule) in 50 ml of tetrahydrofuran (THF) was cooled in a Dry Ice–acetone bath, and until noted, the temperature of the reaction mixture was maintained between −35 and −25°. A solution of 3.36 g (33.2 mmol)

(29) (a) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor, and C. R. Hauser, *J. Amer. Chem. Soc.*, 74, 5599 (1952); (b) A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, 78, 5598 (1956).

of *N*-methylmorpholine (center cut, bp 111–113°) in 50 ml of THF was added dropwise to the reaction mixture, and the dropping funnel was rinsed with 10 ml of THF, which was added also. The resulting mixture was stirred for 0.5 hr, followed by the dropwise addition of a solution of 4.54 g (33.2 mmol) of *n*-butyl chloroformate (freshly distilled, bp 136–138°) in 50 ml of THF. Again the dropping funnel was rinsed with 10 ml of THF, which was added also. Immediately upon adding the *n*-butyl chloroformate, a white precipitate formed, and the reaction mixture was stirred for 0.5 hr. A solution of 2.19 g (33.7 mmol) of sodium azide in 10.0 ml of water was added dropwise. The funnel was rinsed first with 10 ml of THF and then with 1 ml of water, both washings being added to the reaction mixture. The mixture was stirred for 1 hr, during which time the white precipitate dissolved, and another coarser, white precipitate formed. Finally, the Dry Ice–acetone bath was allowed to warm to 0° and replaced by an ice bath. Stirring was continued for 0.5 hr, and the reaction mixture was added to 500 ml of ice water. The resulting aqueous mixture (pH 8–9) was extracted three times with 250-ml portions of benzene, and the combined extracts were washed with 100 ml of cold 0.1 *N* hydrochloric acid and dried at 0°. The dry benzene solution then was stirred at 25° for 43 hr and at 35–40° for 3 hr. Rotary evaporation of benzene left 5.75 g of a foul smelling, yellow oil. To this oil was added 250 ml of concentrated hydrochloric acid, and the mixture was stirred at 25° for 72 hr and at 40–50° for 3 hr. Then 250 ml of water was added and the acidic solution was extracted three times with ether and basified to pH 10–11 with concentrated aqueous potassium hydroxide. The basic solution was extracted four times with ether, and the combined extracts were dried and rotary evaporated to leave 2.36 g (58%) of α-phenylethylamine-α-*d*. This material was homogeneous by glc (column A, 124°), and likewise, glc provided an analytical sample. *Anal.* Calcd for $C_8H_{10}DN$: C, 78.65; H + D, 9.89. Found: C, 78.81; H + D, 9.89.

A portion of this amine was converted to its *N*-*p*-toluenesulfonamide derivative, mp 81–82°, using the procedure given in run 5; it contained 0.995 ± 0.005 atom of excess deuterium per molecule by mass spectral analysis and gave mmp 81–82°; with protio material, mp 81–82° (lit.[30] mp 81–82°).

The nmr spectrum of α-phenylethylamine-α-*d* in deuteriochloroform corresponded to that of protio material[31] with the following exceptions: a doublet centered at δ 2.38, J = 1.0 Hz, replaced the doublet at 2.38, J = 6.5 Hz, in the spectrum of protio material, and the quartet centered at 4.10, J = 6.5 Hz, was absent.

From the combined ether extracts of the above acidic hydrolysis solution was recovered about 1 g of a yellow oil which was composed of approximately 75% α-phenylpropionic-α-*d* acid by nmr (deuteriochloroform).

α-Phenylpropionic-α-*d* Acid.[17] In a dry system in a pure nitrogen atmosphere to 60.0 ml of deuterium oxide (99.77% D) at 0° was added 17 g (0.74 g-atom) of clean sodium in small pieces. After the sodium dissolved completely, the ice bath was removed, and 23.0 g (0.092 mol) of pure diethyl methylphenylmalonate (see below) was added. The mixture was refluxed for 64 hr, and an additional 30 ml of deuterium oxide (99.77% D) was added. Volatile material was distilled from the reaction mixture, bp 79–100°, and the distillation was stopped as soon as bp 100° was reached. To the mixture held at 0° was added slowly and with great care 36.4 g (23.0 ml, 0.433 mol) of purified thionyl chloride[32] while a well-vented stream of nitrogen passed over the surface. The resulting mixture was heated at 70–80° for 1 hr, after which time carbon dioxide evolution was slow, and at reflux for 24 hr. Then, volatile material up to bp 100° was collected, and after an additional 31 hr of refluxing, the reaction mixture was washed from the flask and into a separatory funnel with water and pentane. The layers were separated, and the aqueous layer was extracted four times with pentane. The combined pentane layers were washed once with water, dried over sodium sulfate and nonindicating Drierite (calcium sulfate), and rotary evaporated to leave 13.83 g of a clear oil. By nmr this material was essentially pure α-phenylpropionic-α-*d* acid, and it was chromatographed on a column of 1200 g of silica gel packed in pentane. Forty fractions of approximately 750 ml each were collected, and eluent was varied as follows: for 1 and 2, 5% ether–pentane; for 3–9, 10% ether–pentane with 0.5% methanol; for 10–16, 15% ether–pentane with 1% methanol; for 17–40, 25% ether–pentane with 1% methanol. Fractions 18–36 were combined and yielded 11.3 g (81%) of α-phenylpropionic-α-*d* acid, which was homogeneous by glc (column A, 170°). Also, glc (column G, 185°) provided an analytical sample. *Anal.* Calcd for $C_9H_9DO_2$: C, 71.51; H + D, 7.32. Found: C, 71.62; H + D, 7.33.

A portion of this acid was converted to methyl α-phenylpropionate-α-*d* in a refluxing 50/50 mixture of absolute methanol and 1,2-dichloroethane containing a few drops of concentrated sulfuric acid. Preparative glc (column C, 142°) yielded an analytical sample and one for mass spectral analysis. It contained 0.992 ± 0.005 atom of excess deuterium per molecule. *Anal.* Calcd for $C_{10}H_{11}DO_2$: C, 72.71; H + D, 7.92. Found: C, 72.81; H + D, 7.84.

Diethyl Methylphenylmalonate. This material was prepared in 85% yield by methylation of diethyl phenylmalonate potassium salt in *tert*-butyl alcohol by standard procedure, bp 110–112° (0.28 mm). Analysis of this material by glc (column C, 185°) indicated 99.5% purity. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.14; H, 7.14.

Isomerization Runs. General Procedure. Isomerization runs were made in round-bottomed flasks or in glass tubes sealed under vacuum after being degassed with nitrogen. Prior to each run, the reaction vessel was treated with hot sodium dichromate–concentrated sulfuric acid and rinsed with distilled water, with dilute ammonium hydroxide, and again with distilled water. Finally, it was thoroughly dried and filled with pure nitrogen.

Runs 1–4. By calibrated syringe, 29.9 ml of the appropriate solvent–base solution was added to a flask and allowed to equilibrate to bath temperature. Then 1.89 g (2.16 ml) of I was added by calibrated syringe through a rubber septum, and immediately the vessel was swirled and time zero recorded.

Kinetic points were taken by removal of *ca.* 1-ml aliquots which were quenched in a mixture of 30 ml of pentane and 20 ml of ice water. The pentane layer was separated, washed several times with ice water, and dried over sodium sulfate. Then, the solution was filtered through a pad of sodium sulfate, and most of the pentane was distilled through a short Vigreux column. The resultant concentrate was analyzed by glc (column G).

For isolation after the last kinetic point, work-up was carried out in the same manner on approximately 10 times the above scale, and imines I and II were preparatively separated by glc (column D). On standing together, imines I and II yielded two impurities whose glc retention times were the same as *N*-(neopentylidene)neopentylamine and *N*-(α-methylbenzylidene)-α-phenylethylamine. Care was taken to remove the latter compound from the glc column between injections, and collected I and II were again subjected to preparative glc to give material of high purity. In one run, when pentane was almost completely removed and the product mixture allowed to stand at room temperature for 3 days, the above-mentioned impurities developed to the extent of 5–15% each. Another aliquot removed from the reaction mixture at the same time and kept for 3 days as a dilute pentane solution showed only about 2% of the same impurities by glc. Even when a dilute pentane solution was stored in the cold and concentrated in small aliquots immediately prior to preparative glc, imines I and II still had to be resubmitted to glc to obtain high purity.

Run 5. In a glass tube were sealed 0.526 g (0.600 ml, 2.77 mol) of (±)-I-D,H (0.995 ± 0.005 atom of excess deuterium per molecule) and 8.9 ml of *tert*-butyl alcohol, 0.483 *M* in potassium *tert*-butoxide. After 4350 min at 75.00 ± 0.05°, the tube was opened, and its contents were emptied into a separatory funnel containing 75 ml of pentane and 25 ml of cold water. The tube was washed with small amounts of the above solvents, which were added to the separatory funnel also. The layers were separated, and the aqueous layer was extracted twice with pentane. The combined pentane layers were dried over sodium sulfate and rotary evaporated to leave a light yellow oil. By glc (column C, 136°) the residue was composed of I, II, and a few very low retention time impurities. The I–II mixture contained 45.6 ± 0.2% II, and I and II were preparatively separated.

To 0.096 g (0.51 mmol) of recovered II in a 10-ml flask was added 2 ml of 15% hydrochloric acid. The mixture was heated on a steam bath for 0.75 hr under a gentle stream of nitrogen and extracted twice with 4-ml portions of dichloromethane. The acidic solution, 10 ml of aqueous 20% potassium hydroxide, and 0.50 g (2.6 mmol) of *p*-toluenesulfonyl chloride were added to a 50-ml round-bottomed flask equipped with a magnetic stirrer, and

(30) A. Pinner, *Chem. Ber.*, **34**, 4231 (1901).

(31) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Ed., "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962.

(32) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1158. Two distillations from triphenyl phosphite were emloyed in the procedure.

the resulting mixture was stirred vigorously for 10 hr. During this period, it appeared as if excess *p*-toluenesulfonyl chloride hydrolyzed and *N*-(neopentyl)-*p*-toluenesulfonamide began to precipitate. The mixture was filtered, and the material collected was washed with water and dried to give 89 mg of sulfonamide (odorless). Upon acidification of the filtrate, a small amount of white solid precipitated, which was collected by filtration, washed with water, and dried to give an additional 13 mg of sulfonamide. The combined fractions, 102 mg (82%), were recrystallized from aqueous methanol to give 74 mg of *N*-(neopentyl)-*p*-toluenesulfonamide, mp 115–116°. By mass spectral analysis this material contained 0.0394 ± 0.0015 atom of excess deuterium per molecule, and it gave mmp 115–116° with an equal amount of *N*-(neopentyl)-*p*-toluenesulfonamide, mp 115–116° (lit.[33] mp 117°), prepared in a similar manner from II-H.

To 88 mg (0.46 mmol) of recovered I in a 10-ml flask was added 2 ml of 15% hydrochloric acid. The mixture was heated on a steam bath for 0.5 hr under a gentle stream of nitrogen and transferred with 4 ml of water to a 50-ml round-bottomed flask. Rotary evaporation of volatiles left a clear oil to which were added 2 ml each of water, THF, and triethylamine, followed by 0.50 g (2.6 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 25° for 16 hr, and volatile material was removed by rotary evaporation. The residue was extracted with ether, and the combined extracts were dried over sodium sulfate and rotary evaporated to leave a clear, yellow oil. This material was chromatographed on a column of 30 g of silica gel packed in pentane, and 20-ml fractions were taken. Fractions 1–16 were eluted with 15% ether–pentane and 17–41 with 25% ether–pentane. Sulfonamide, 107 mg (84%), was contained in fractions 24–38 and crystallized on standing after complete removal of solvent on a rotary evaporator. This material was recrystallized from 2 ml of cyclohexane to give *N*-(α-phenylethyl)-*p*-toluenesulfonamide, mp 81–82°. By mass spectral analysis this material contained 0.398 ± 0.004 atom of excess deuterium per molecule.

Runs 6–10 and 15–21. In a glass tube were sealed substrate and solvent–base solution. After the reaction period, the tube was opened and its contents added to a mixture of *ca.* 25 ml of ice water and 20–50 ml of pentane. The pentane layer was separated, dried by filtration through sodium sulfate, and concentrated by distillation through a short Vigreux column. The resultant solution was analyzed by glc (column F, 125°), and I and II were preparatively separated by glc (column B, 120°).

Run 11. In a glass tube were sealed 0.352 g (0.946 mmol) of 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane,[9] mp 30–56°, a mixture of diastereomers (crown ether, III), 0.131 g (0.150 ml, 0.693 mmol) of (−)-I-H,H, $[\alpha]^{25}_{546}$ −80.2 ± 0.7° (*c* 0.739, chloroform), and 1.90 ml of *tert*-butyl alcohol, 0.483 *M* in potassium *tert*-butoxide. After 10.0 min at 75.00 ± 0.05°, the tube was opened and its contents were emptied into a separatory funnel containing 4 ml each of pentane and water. The tube was washed with small amounts of these solvents, which were added to the mixture. The layers were separated, and the water layer was extracted three times with 4-ml portions of pentane. The combined pentane layers were dried over sodium sulfate and rotary evaporated to leave a yellow oil. By glc (column C, 136°) this material was composed of I, II, and a few very low retention time impurities; the I–II mixture contained 9.3 ± 0.2% II, and I and II were preparatively separated. Isolated I gave the following rotations in chloroform: $[\alpha]^{25}_{546}$ −49.8 ± 0.4° (*c* 0.613) and $[\alpha]^{25}_{546}$ −49.8 ± 0.4° (*c* 0.813). Reinjection (column A) of a sample of I from which the rotation solutions were made showed no impurities.

Run 12. In a glass tube were sealed 0.344 g (0.925 mmol) of crown ether III, 0.130 g (0.148 ml, 0.688 mmol) of (−)-I-H,H, $[\alpha]^{25}_{546}$ −80.2 ± 0.7° (*c* 0.828, chloroform), and 1.90 ml of *tert*-butyl alcohol, 0.483 *M* in potassium *tert*-butoxide. After 89.0 min at 75.00 ± 0.05°, the tube was opened, and as in run 11, the reaction mixture was analyzed by glc (column C, 136°). The I–II mixture contained 63.9 ± 0.1% II, and recovered I gave rotation $[\alpha]^{25}_{546}$ −0.1 ± 0.1° (*c* 0.596, chloroform), observed α^{25}_{346} −0.008 ± 0.003°. Reinjection (column A) of a sample of I from which the rotation solution was made showed no impurities.

Run 13. In a glass tube were sealed 0.129 g (0.346 mmol) of crown ether III, 42 mg (0.048 ml, 0.222 mmol) of I, and 0.68 ml of *tert*-butyl alcohol, 0.48 *M* in potassium *tert*-butoxide. After 1391 min at 75.00 ± 0.05°, the tube was opened, and its contents were worked up using the procedure for run 11 scaled down proportionately. By glc (column C, 136°) the I–II mixture contained 97 ± 2% II.

Run 14. In a glass tube were sealed 0.857 g (2.30 mmol) of crown ether III, 0.175 g (0.200 ml, 0.925 mmol) of (−)-I-H,H, $[\alpha]^{25}_{546}$ −80.2 ± 0.7° (*c* 0.828, chloroform), and 4.5 ml of *tert*-butyl alcohol-*O*-*d*, 0.481 *M* in potassium *tert*-butoxide. After 10.0 min at 75.00 ± 0.05°, the tube was opened, and its contents were treated as in run 11. By glc (column C, 136°) the I–II mixture contained 12.7 ± 0.1% II, and I and II were preparatively separated. By nmr I contained 0.48 ± 0.02 atom of deuterium at the benzyl position, and after it was again submitted to preparative glc it gave rotation $[\alpha]^{25}_{546}$ −35.0 ± 0.3° (*c* 0.718, chloroform).

Runs 22–25. Detailed Procedure for Run 25. To 74.0 ml of *tert*-butyl alcohol, 0.472 *M* in potassium *tert*-butoxide at 75.0°, was added 4.46 g (5.09 ml, 23.6 mmol) of (−)-*N*-(neopentylidene-*1-d*)-α-phenylethylamine (0.996 atom of excess deuterium per molecule), $\alpha^{25}D$ −42.30° (neat, 1 dm). After 166.37 hr at 75.0°, the product was isolated as described for runs 1–4. By glc (column H) the resulting I–II mixture contained 13.1% I, and preparative glc yielded 3.03 g of (+)-*N*-(α-methylbenzylidene)neopentylamine-*1-d*. A small amount of this material was again submitted to preparative glc and flash distilled (*ca.* 0.1 mm) to give (+)-II-D, $\alpha^{25}D$ 5.36° (neat, 1 dm), which by glc contained 0.2% α-phenylethylamine as the only impurity. Recovered I-H,D also was again submitted to preparative glc and flash distilled to give (−)-I-H,D, $\alpha^{25}D$ −36.30° (neat, 1 dm).

***N*-(Neopentyl)-α-phenylethylamine (IV-H).** To a slurry of 8.0 g (0.21 mol) of lithium aluminum hydride in 200 ml of anhydrous ether was added a solution of 40.0 g (0.21 mol) of *N*-(neopentylidene)-α-phenylethylamine during 0.5 hr. The mixture was refluxed for 6 hr and treated successively with 8 ml of water, 8 ml of aqueous 15% sodium hydroxide, and 24 ml of water. The ether layer was separated from the white precipitate, dried over magnesium sulfate, and rotary evaporated. The residue was fractionally distilled to give 38.4 g (95%) of IV-H, bp 38–40° (0.04 mm), $n^{25}D$ 1.4874. *Anal.* Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06. Found: C, 81.43; H, 10.97.

The nmr spectrum of IV-H in deuteriochloroform displayed a singlet at δ 0.85 (*tert*-butyl protons, 9.0), a doublet at 1.28, J = 6.5 Hz (α-methyl protons, 3.0), an AB pattern with doublets at 2.11 and 2.23, J = 11 Hz (methylene protons, 2.1), a quartet centered at 3.64, J = 6.5 Hz (methine proton, 0.99), and a broad singlet at 7.24 (phenyl protons, 5.0). In nmr spectra of IV-H in other solvents also, the methylene protons appeared as an AB quartet with the following chemical shifts and J = 11 Hz: carbon tetrachloride, δ 2.12 and 2.24; cyclohexane, 2.14 and 2.23; benzene, 2.14 and 2.20; dimethyl-d_6 sulfoxide, 2.05 and 2.17. No separate integration of the two methylene protons could be obtained in any of the above nmr spectra.

Treatment of an ether solution of IV-H with hydrogen chloride yielded a precipitate, which was recrystallized from methanol–water to give *N*-(neopentyl)-α-phenylethylamine hydrochloride, mp 268–269° (sealed tube, total immersion). The nmr spectrum of this material in deuterium oxide displayed a singlet at δ 1.37 (*tert*-butyl protons, 9.1), a doublet centered at 2.14, J = 7 Hz (α-methyl protons, 3.1), an AB pattern with doublets at 2.99 and 3.20, J = 12 Hz (methylene protons, 2.0), a quartet centered at 4.87, J = 7 Hz, overlapping with a singlet at 5.14 (methine and amino protons, respectively), and a singlet at 7.98 (phenyl protons, 4.7).

(−)-(*S*)-*N*-(Neopentyl)-α-phenylethylamine (IV-H). By the above procedure, 8.0 g (0.04 mol) of (−)-I-H,H, $\alpha^{25}D$ −42.43° (neat, 1 dm), and 1.9 g (0.04 mol) of lithium aluminum hydride gave 5.8 g (72°) of (−)-IV-H, $\alpha^{25}D$ −67.25° (neat, 1 dm) (lit.[34] $\alpha^{24}D$ 66.9° (neat, 1 dm)).

The above procedure was used to prepare (−)-*N*-(neopentyl)-α-phenylethylamine hydrochloride, $[\alpha]^{25}D$ −22.8° (*c* 2.9, water), mp 284–285° (sealed tube, total immersion) (lit.[34] mp 292–293° dec). *Anal.* Calcd for $C_{13}H_{22}NCl$: C, 68.53; H, 9.74. Found: C, 68.35; H, 9.82.

***N*-(Neopentyl-*1-d*)-α-phenylethylamine (IV-D).** The procedure employed was that given above for the reduction of (±)-*N*-(neopentylidene)-α-phenylethylamine. From 7.4 g (36 mmol) of (+)-*N*-(α-methylbenzylidene)neopentylamine-*1-d* from run 23, $\alpha^{25}D$ 5.24° (neat, 1 dm), and 2.0 g (40 mmol) of lithium aluminum hydride was obtained 5.7 g (77%) of IV-D, a mixture of diastereomers, $\alpha^{25}D$ 1.51° (neat, 1 dm), $n^{25}D$ 1.4875. By mass spectrometry

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(34) D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.*, 74, 5851 (1952).

this material contained >0.99 atom of excess deuterium per molecule, solely in the methylene group.

The above procedure was used to prepare *N*-(neopentyl-*1-d*)-α-phenylethylamine hydrochloride, mp 269–270°, undepressed by admixture with racemic protio material. The nmr spectrum of this material in deuterium oxide displayed a singlet at δ 1.37 (*tert*-butyl protons, 9.1), a doublet centered at 2.15, J = 7 Hz (α-methyl protons, 3.1), singlets at 2.96 and 3.20 (methylene proton, 0.48 each), a quartet centered at 4.88, J = 7 Hz, overlapping with a singlet at 5.10 (methine and amino protons, respectively), and a singlet at 8.00 (phenyl protons, 4.8).

Resolution of *N*-(Neopentyl-*1-d*)-α-phenylethylamine. To a solution of 6.38 g (25.0 mmol) of *d*-10-camphorsulfonic acid in 10 ml of water was added a solution of 4.77 g (25.0 mmol) of *N*-(neopentyl-*1-d*)-α-phenylethylamine prepared above, $\alpha^{25}D$ 1.51° (neat, 1 dm), in 5 ml of acetone. The mixture was refluxed, cooled to 25°, and after crystallization began, cooled to 0°. The crystals were collected and recrystallized six times from water to give a salt whose rotation and melting point did not change on further recrystallization, $[\alpha]^{25}D$ 23.1° (*c* 2.0, water), mp 148.5–149.2°. The mother liquors from the first crystallization yielded a second crop which was systematically recrystallized from other available mother liquors to give salt, $[\alpha]^{25}D$ 23.1° (*c* 2.0 water), mp 148.4–149.2°; total yield, 0.90 g (16%).

A solution of 0.90 g of salt, $[\alpha]^{25}D$ 23.1° (*c* 2.0, water), in 25 ml of water was basified with aqueous 15% sodium hydroxide. The alkaline solution was extracted with three 25-ml portions of ether, which were combined and dried over magnesium sulfate. Rotary evaporation of ether left crude amine, and purification by preparative glc (column I, 165°) gave 208 mg (9%) of (+)-(*R*,*R*)-IV-D, $\alpha^{25}D$ 62.54° (neat, 1 dm), $n^{25}D$ 1.4874.

The above procedure yielded (+)-(*R*,*R*)-*N*-(neopentyl-*1-d*)-α-phenylethylamine hydrochloride, $[\alpha]^{25}D$ 23.0° (*c* 2.7, water), mp 284° and mmp 268–269°, admixed with an equal amount of (−)-(*S*)-*N*-(neopentyl)-α-phenylethylamine hydrochloride.

The nmr spectra of (+)-(*R*,*R*)-*N*-(neopentyl-*1-d*)-α-phenylethylamine hydrochloride, $[\alpha]^{25}D$ 23.0° (*c* 2.7, water), were taken as saturated deuterium oxide solutions (*ca.* 10%). Typical instrument settings for the Varian A-60 spectrometer when used with the time-averaging computer were as follows: sweep width, 50 Hz; sweep time, 10 sec; radio frequency field, 0.01 mG; filter bandwidth, 4 Hz. Generally, 120 scans were made, and integration was made by the cut-and-weight method.

(−)-(*S*,*R*)-*N*-(Neopentyl-*1-d*)-α-phenylethylamine. The original mother liquors from the above resolution were concentrated, basified with aqueous 15% sodium hydroxide, and extracted with three 50-ml portions of ether. The combined ether extracts were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and rotary evaporated to leave an oil which was flash distilled to give 1.45 g of (−)-(*S*,*R*)-IV-D, $\alpha^{25}D$ −7.33° (neat, 1 dm). The above procedure applied to racemic protio material yielded (−)-(*S*,*R*)-*N*-(neopentyl-*1-d*)-α-phenylethylamine hydrochloride, $[\alpha]^{25}D$ −5.36° (*c* 2.7, water), which was recrystallized from 95% ethanol. Concentration of the mother liquors yielded further crops. The first four crops, 810 mg total, showed rotations $[\alpha]^{25}D$ <0.5° (*c* 2.5, water), and subsequent crops, 380 mg total, showed rotations $[\alpha]^{25}D$ −13.0° to −13.6° (*c* 2.5, water). The latter crops were combined and recrystallized from 2:1 chloroform–acetone to give 40 mg of (−)-(*S*,*R*)-IV-D hydrochloride, $[\alpha]^{25}D$ −20.6° (*c* 2.1, water), mp 279–283°, mmp 281–284° with the hydrochloride of (−)-(*S*)-IV-H.

(+)-(*R*)-Neopentylamine-*1-d*. To a solution of 6.0 g (32 mmol) of (+)-(*R*)-*N*-(α-methylbenzylidine)neopentylamine-*1-d*, $\alpha^{25}D$ 5.36° (neat, 1 dm), in 100 ml of acetone was added 5 ml of concentrated hydrochloric acid. The solution was refluxed for 0.5 hr and acetone removed by distillation through a Vigreux column. The residue was dried at 25° under vacuum (0.05 mm) and 10 ml of acetone was added. The solution was refluxed for 10 min and cooled to 0° to yield crystals. After concentration, the mother liquors yielded a second crop at 0°, and the combined crops were sublimed at 160° (0.05 mm) to give 3.47 g (89%) of (*R*)-neopentylamine-*1-d* hydrochloride, mp 298–299° (evacuated tube).

To a solution of 3.47 g of hydrochloride in 20 ml of water was added 25 ml of ether. The mixture was basified with aqueous 15% sodium hydroxide, and the aqueous layer was extracted with two 25-ml portions of ether. All ether layers were combined, washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The ether solution was fractionally distilled through a Vigreux column to yield 1.48 g (54%) of (+)-(*R*)-neopentylamine-*1-d*, bp 80–81°, $\alpha^{25}D$ 0.25 ± 0.05° (neat, 1 dm). By glc (column I, 115°) this material contained 2% ether as the only impurity.

Reconversion of (+)-Neopentylamine-*1-d* to (+)-*N*-(α-Methylbenzylidene)neopentylamine-*1-d* [(+)-(*R*)-II-D]. With use of the above procedure, 2.92 g (15.5 mmol) of (+)-*N*-(α-methylbenzylidene)neopentylamine-*1-d*, $\alpha^{25}D$ 5.36° (neat, 1 dm), from run 25 was hydrolyzed to give 1.56 g of (+)-neopentylamine hydrochloride, mp 300.3–301.1°. To 1.45 g (11.7 mmol) of this hydrochloride was added 1.4 ml of aqueous 40% sodium hydroxide, and the alkaline solution was extracted with 5 ml of ether. The extract was fractionally distilled to give 0.91 g of (+)-neopentylamine-*1-d*, bp 73–76°, $\alpha^{25}D$ 0.25 ± 0.05° (neat, 1 dm), which by glc (column J, 70°) contained ether as the only impurity. To 13 ml of benzene were added 0.84 g of this (+)-neopentylamine-*1-d*, 1.14 g of acetophenone, and 1.5 mg of zinc hydroxide. The mixture was refluxed for 36 hr under a Soxhlet extractor charged with 5 g of sodium sulfate and then concentrated by distillation. Preparative glc (column D, 120°) yielded 0.71 g of (+)-(*R*)-*N*-(α-methylbenzylidene)-neopentylamine-*1-d*, $\alpha^{25}D$ 5.40 ± 0.04° (neat, 1 dm), which was homogeneous by glc (column J, 140°). Combustion and falling drop analysis indicated 0.992 atom of excess deuterium per molecule.

Deuterium Analyses. Analyses by the combustion and falling drop method were performed by J. Nemeth, Urbana, Ill.

All deuterium analyses by mass spectrometry were made on an Associated Electronics Industries, Ltd., Model MS-9 mass spectrometer. For deuterium analysis of methyl α-phenylpropionate-α-*d* (mol wt 165), a 12-eV ionization potential was employed with a heated inlet temperature of *ca.* 130° and a source temperature of *ca.* 140°. Multiple scans of the parent region of protio material[35] (mol wt 164) were recorded on a Leeds and Northrup Model G recorder. The peaks at *m/e* 163 (P − 1) and 164 (P) were measured, and the ratio of the former to the latter, (P − 1)/P, was calculated and designated as F (0.002). Then multiple scans of the parent region of deuterio material were recorded. The peaks at *m/e* 164 and 165 (P) were measured, and the *m/e* 164 peak height was corrected for (P − 1) contribution by subtraction of the quantity $(F) \times (m/e\ 165)$. The ratio of *m/e* 165 to the sum of *m/e* 165 and the corrected value for *m/e* 164 gave the fraction of one atom of excess deuterium per molecule, 0.992 ± 0.005. This calculation method was valid because deuterio ester was highly deuterated and because the ratio F was very low.

For deuterium analysis of *N*-(α-phenylethyl-α-*d*)-*p*-toluenesulfonamide, a 12-eV ionization potential was employed with direct sample insertion and a source temperature of 100–120°.

The above procedure was used for analysis of highly deuterated material resulting from the synthesis of α-phenylethylamine-α-*d*. The analogous ratio F for protiosulfonamide (mol wt 275) was zero, so for deuterio material (mol wt 276), the fraction of one atom of excess deuterium per molecule was equal to the ratio of *m/e* 276 to the sum of *m/e* 276 plus *m/e* 275, 0.995 ± 0.005.

For deuterium analysis of *N*-(α-phenylethyl-α-*d*)-*p*-toluenesulfonamide from run 5, a different calculation method was employed. For this material, the peak heights at *m/e* 275 and 276 were measured, and the ratio of the latter to the former was calculated and designated as R (0.819 ± 0.004). The same ratio for protio material ((P + 1)/P) was calculated to be 0.157 ± 0.001. Then, the fraction of one atom of excess deuterium per molecule was calculated to be 0.398 ± 0.004 by the expression, $(R - 0.157)/[1 + (R - 0.157)]$.

Since the ratio F ((P − 1)/P) for protio material was zero, the (P − 1) contribution of deuterio material (mol wt 276) to *m/e* 275 probably was zero also.

For deuterium analysis of *N*-(neopentyl-*1-d*)-*p*-toluenesulfonamide (mol wt 242) from run 5, a 12-eV ionization potential was employed with direct sample insertion and a source temperature of 100–120°. The parent region was scanned, and since the deuterium content was low, the *m/e* 242 peak was adjusted to about half-scale on the Leeds and Northrup Model G recorder. The larger *m/e* 241 signal was attenuated by a known factor to give a peak on scale. The peak height comparison and the attenuation factor gave the ratio of *m/e* 242:241, designated as R (0.189 ± 0.001). The same ratio for protio material (mol wt 241) ((P + 1)/P) was calculated to be 0.148 ± 0.001. Then, the fraction of one atom of excess deuterium per molecule was calculated to be 0.0394 ± 0.0015, by the expression $(R - 0.148)/[1 + (R - 0.148)]$.

(35) K. Neure, *Justus Liebigs Ann. Chem.*, 250, 152 (1889).

Table XIV. Relative Intensities in the Parent Ion Region in the Mass Spectra of IV-D and IV-H at 12 eV

	P − 2	P − 1	P	P + 1	P + 2
IV-D	15.7	5.3	100	17.7	1.9
IV-H	10.3	4.8	100	16.5	1.8

The ratio F ((P − 1)/P) for protio material was zero. Therefore, the (P − 1) contribution of deuterio material (mol wt 242) to *m/e* 241 probably was zero also.

The solid samples analyzed above had been purified by recrystallization, and it was assumed that no isotopic fractionation occurred. The mixture melting point data above support this assumption. Also, Cram and Whitney[36] demonstrated that isotopic fractionation did not occur in the recrystallization of partially deuterated material in another system.

For deuterium analysis of *N*-(neopentyl-*1-d*)-α-phenylethylamine (IV-D) from the reduction of II-D of run 23, 12- and 70-eV ionization potentials were employed with a heated inlet of *ca.* 125°. None of the above calculated methods could be used because the (P − 1)/P ratio for IV-H was high even at low ionization potential. Therefore, the region about the parent ion in the mass spectrum of IV-D (mol wt 192) at 12 eV was compared with that of IV-H (mol wt 191) at 12 eV. These data are summarized below in Table XIV and led to the conclusion that IV-D contained >0.99 atom of excess deuterium per molecule. Also, comparisons of the relative intensities of other fragments in the mass spectra of IV-D and IV-H at 70 eV showed that excess deuterium was located only at the methylene position.

Yield Controls. To 0.40 ml of a mixture of I and bicyclohexyl, 56.2% I by glc (column F, 160°), was added 3.0 ml of *tert*-butyl alcohol, 0.431 *M* in potassium *tert*-butoxide. The resulting solution was *ca.* 0.3 *M* in I. After 9.67×10^4 sec at 80°, the reaction mixture was worked up in the usual manner. By glc analysis as above, the isolated imine–bicyclohexyl mixture contained 55.6% I + II, and this corresponds to an imine yield of 98 ± 1%. Isomerization of I to II was 39.2%. To an aliquot of the above glc-analyzed I–bicyclohexyl mixture was added a dimethyl sulfoxide solution 2.9 *M* in methanol and 0.30 *M* in potassium methoxide; the resulting solution was *ca.* 0.2 *M* in I. After 33.0 min at 80°, the reaction mixture was worked up in the usual manner. By glc analysis as above, the isolated imine–bicyclohexyl mixture contained 54.5% I + II, and this corresponds to an imine yield of 93 ± 1%. Isomerization of I to II was 66.7%.

Thermal Conductivity of I *vs.* II. Mixtures of I and II were prepared by weight and analyzed by glc (column G, 140°). The results below indicated that glc analyses of I–II mixtures represented the actual compositions of those mixtures.

% II by weight	% II by glc
1.95	1.95 ± 0.04
3.57	3.61 ± 0.05
13.5	13.7 ± 0.2

(36) D. J. Cram and T. A. Whitney, *J. Amer. Chem. Soc.*, **89**, 4651 (1967).

Electrophilic Substitution at Saturated Carbon. XLIX. A Stereospecific Transamination[1,2]

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Abstract: Imines (−)-(*S*)-*N*-(α-methylneopentylidene)-α-phenylethylamine (I) and (+)-(*S*)-*N*-(α-methylbenzylidene)pinacolylamine (II) were prepared in optically pure forms. Potassium *tert*-butoxide catalyzed equilibration of I and II in *tert*-butyl alcohol at 175° gave K = II/I = 4.1 ± 0.3. Under the same reaction conditions, racemization of (−)-I and isomerization of (−)-I to II proceeded at comparable rates. For example, after 11.0% isomerization, (−)-I had undergone 26 ± 1% racemization, and the (−)-II produced was 86 ± 1% optically pure. Since some racemic II was produced from (−)-I that had become racemic prior to rearrangement the optical purity of (−)-II represented a minimal and time-dependent value for the per cent stereospecificity of the isomerization. Use of a kinetic model gave the corrected value, 100 ± 6%. The model treated (+)-II (inverted product) as the stereospecific isomerization product of (+)-I (inverted starting material). The high stereospecificity was interpreted in terms of the intermediacy of a single inherently symmetrical azaallylic carbanion A asymmetrically ion paired with potassium. Azaallylic carbanion A has the two bulky substituents, *tert*-butyl and phenyl, in the two least-hindered positions. The isomerization occurred in a cis or suprafacial manner across the face of delocalized carbanion A. Collapse of A favored I over II by a factor of *ca.* 200 in *tert*-butyl alcohol–potassium *tert*-butoxide at 175°. In *tert*-butyl alcohol-*O-d*–potassium *tert*-butoxide, (−)-I underwent isotopic exchange 41 times as fast as it racemized. In dimethyl sulfoxide–*tert*-butyl alcohol the isomerization of (−)-I to II proceeded with a complete lack of stereospecificity.

Biological transamination[3] involves the base-catalyzed isomerization of intermediate imines derived from pyridoxal and α-amino acids and from pyridoxamine and α-keto acids.[4] The intermediacy of aza-

(1) This investigation was supported by the U. S. Public Health Service, Research Grant No. GM 12640-05 from the Department of Health, Education, and Welfare.

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