Configuration, Stereochemical Purity, and Stereospecific Rearrangement of Neopentyl-1-*d* Alcohol[1,2]

W. A. Sanderson and Harry S. Mosher

Contribution from the Department of Chemistry, Stanford University, Stanford, California. *Received April 30, 1966*

Abstract: Neopentyl-1-*d* alcohol, prepared by the reduction of trimethylacetaldehyde-1-*d* by actively fermenting yeast, has been shown by chemical transformations to possess the absolute *S* configuration and to be either stereochemically pure or nearly so. By treatment of (*S*)-neopentyl-1-*d* alcohol (IV) with bromoform and potassium hydroxide (dibromocarbene reagent in the "de-oxideation" reaction), a rearrangement to (*S*)-(+)-2-methyl-1-butene-3-*d* (V) was achieved. This optically active olefin was converted to the saturated hydrocarbon (*S*)-(−)-2-methylbutane-3-*d* (VI) by a diimide reduction. The optical rotation of this hydrocarbon, $[\alpha]^{17}\mathrm{D}$ −0.85 ± 0.03° (neat), was about 10% higher than that for the hydrocarbon, $[\alpha]^{20}\mathrm{D}$ +0.76 ± 0.02° (neat), from the lithium aluminum deuteride reduction of the tosylate (VII) of stereochemically pure (*S*)-(+)-3-methyl-2-butanol (VIII). Since the anticipated racemization in this latter reaction is small and the rotation of the (*S*)-(−)-2-methylbutane-3-*d* is high for such a substance, it is reasonable to assume that the neopentyl-1-*d* alcohol obtained by yeast reduction is enantiomorphically pure or nearly so and that this neopentyl rearrangement is highly stereoselective and quite possibly stereospecific. This is interpreted to mean that the rearrangement takes place with inversion at the deuterium-substituted carbon and does not proceed *via* a free neopentyl cation. The implications of these results with respect to the nature of the neopentyl cation and the over-all mechanism of this rearrangement are discussed.

Independent evidence concerning the absolute configuration and the stereochemical purity of the neopentyl-1-*d* alcohol obtained by fermentative reduction of trimethylacetaldehyde-1-*d* was required in order to test previous predictions[3] made in connection with the chemical asymmetric reduction of this aldehyde. Furthermore, this neopentyl system, which was optically active by virtue of deuterium substitution, offered a unique opportunity to study the nature of the neopentyl cation which has served as a classical example for the Wagner–Meerwein rearrangement. In particular, although the rearrangement of neopentyl compounds to tertiary amyl systems has been studied extensively, the extent to which the intermediate cation is "free," bound in a solvent cage, or rearranges *via* synchronous ionization and rearrangement, is not settled. A preliminary communication,[2] reporting that optical activity was retained during this rearrangement, has been given; the present account completes the details on this reaction and configurationally relates the compounds by known reactions to methylisopropylcarbinol of known configuration and stereochemical purity.

Table I. Properties of Deuterium Compounds

Compound	Yield, %[a]	Deuterium content[b]	Specific rotation[g] $[\alpha]\mathrm{D}$, deg (temp, °C)
Trimethylacetaldehyde-1-*d* (1)	58[c]	0.88 ± 0.05[d]	
Trimethylacetaldehyde-1-*d* (2)[2]	58[c]	0.85[d]	
Neopentyl-1-*d* alcohol (1)	43	0.85 ± 0.01[e]	−1.15 ± 0.03 (26)[f]
Neopentyl-1-*d* alcohol (2)[2]	49	1.00 ± 0.05[d]	−1.00 ± 0.05 (26)[f]
2-Methyl-1-butene-3-*d* (1)	39[h]		+1.01 ± 0.02 (20)[j]
2-Methyl-1-butene-3-*d* (2)[2]	40[c,i]	0.97 ± 0.05[d]	+0.96 ± 0.06 (23)
2-Methylbutane-3-*d* (1)	51	0.83 ± 0.01[e]	−0.85 ± 0.03 (17)
2-Methylbutane-3-*d*	68[k]	0.94 ± 0.01[e]	+0.76 ± 0.02 (20)

[a] Yields denote preparative gas chromatographically purified products. [b] Expressed as number of deuterium atoms per molecule. [c] Corrected for recovered starting material. [d] Analysis by integration of nmr spectrum.[35] This difference in deuterium content between trimethylacetaldehyde-1-*d* and neopentyl-1-*d* alcohol made by fermentation appears real and was confirmed in another experiment. [e] Analysis was by mass spectrograph on benzoate ester.[36] [f] Rotation of the purified acid phthalate (*c* 20, acetone). [g] Specific rotation corrected to 1 deuterium atom per molecule. All rotations were taken in center-filled tubes with zero reading taken on empty tube without disturbing the end plates. The density of the deuterium compound was estimated from that of the hydrogen compound at the specified temperature by applying the correction of the McLean–Adams equation: A. McLean and R. Adams, *J. Am. Chem. Soc.*, **58**, 804 (1936). [h] Also recovered 2-methyl-2-butene (17%), olefin ratio 70:30. [i] Also recovered 2-methyl-2-butene (19%), olefin ratio 68:32, neopentyl-1-*d* alcohol, 24%, acid phthalate $[\alpha]^{25}\mathrm{D}$ −1.12 ± 0.03° (*c* 9, acetone),[g] and *t*-amyl alcohol, 3%, $\alpha^{27}\mathrm{D}$ −0.55° (neat, $l = 1$). [j] Based on the deuterium content of its precursor. [k] Also recovered 23.5% 2-methyl-2-butene.

Results

Table I summarizes the present findings. Trimethylpyruvic acid (II) prepared by the oxidation of pinacolone (I) was subjected to deuterium exchange and decarboxylation in the presence of deuterated glycine to give

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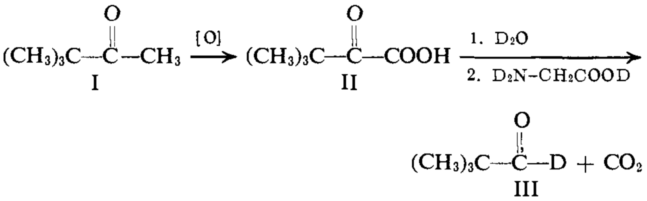
(1) We acknowledge with gratitude the support of these studies by the National Science Foundation (NSF GP 3888) and the U. S. Public Health Service (NIH GM 5248).

(2) Preliminary communication of these results has been made: W. A. Sanderson and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 5033 (1961).

(3) V. A. Althouse, K. Ueda, and H. S. Mosher, *ibid.*, **82**, 5938 (1960).

trimethylacetaldehyde-1-*d* (III) in 58% yield containing 0.88 deuterium atom per molecule.

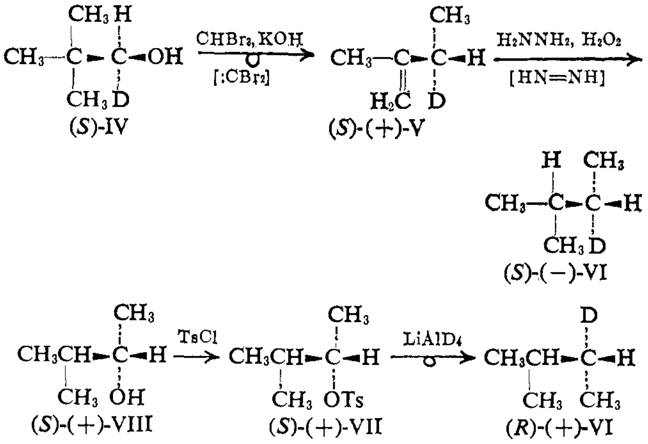


This aldehyde was reduced by actively fermenting yeast[3] to neopentyl-1-*d* alcohol which, as previously reported, had no appreciable optical rotation in the visible region but gave, nevertheless, an acid phthalate with $[\alpha]^{26}\text{D}$ $-1.15°$.[4] Treatment of this alcohol in boiling aqueous potassium hydroxide with bromoform, the method of dehydration of alcohols investigated by Hine and co-workers[5] and applied to neopentyl alcohol by Skell and Starer[6] (who used the term "de-oxideation" to describe the reaction), gave optically active 2-methyl-1-butene-3-*d* (V), 39% yield, along with 2-methyl-2-butene, 17% yield (isomer ratio 70:30), and recovered neopentyl-1-*d* alcohol, which gave an acid phthalate with optical rotation unchanged from that of the starting alcohol. The 2-methyl-1-butene-3-*d* (V) which was purified by preparative vapor phase chromatography (vpc) had a rotation of $\alpha^{20}\text{D}$ $+0.67 \pm 0.005°$ (neat, $l = 1$),[4] $[\alpha]^{20}\text{D}$ $+1.01 \pm 0.01°$ (neat).[4] This olefin was reduced with hydrazine and hydrogen peroxide[7] and the product purified by vpc to give 2-methylbutane-3-*d* (VI), $\alpha^{17}\text{D}$ $-0.54 \pm 0.02°$ (neat, $l = 1$),[4] $[\alpha]^{17}\text{D}$ $-0.85 \pm 0.03°$ (neat).[4]

This same optically active hydrocarbon VI was made by established steps starting with resolved (*S*)-(+)-methylisopropylcarbinol (VIII)[8] by conversion to the tosylate (VII) in quantitative yield and subjecting it to lithium aluminum deuteride reduction in diglyme. The reduction product obtained in 90% crude yield was a 3:1 mixture of 2-methylbutane-3-*d* and 2-methyl-2-butene. This mixture was purified by preparative vpc to give 2-methylbutane-3-*d*, $\alpha^{20}\text{D}$ $+0.48 \pm 0.01°$ (neat, $l = 1$), $[\alpha]^{20}\text{D}$ $+0.76 \pm 0.02°$ (neat).[4] This compares with the value of $[\alpha]^{17}\text{D}$ $-0.85 \pm 0.03°$ (neat) obtained for the hydrocarbon *via* the fermentative reduction and neopentyl rearrangement.

Discussion

Configuration. The absolute *S* configuration has been predicted[3] for the neopentyl-1-*d* alcohol obtained by the reduction of trimethylacetaldehyde-1-*d* by actively fermenting Baker's yeast. The rearrangement of this optically active alcohol IV to 2-methyl-1-butene-3-*d* (V) could be predicted to involve racemization or inversion of configuration at the neopentyl carbon atom but *not* retention of configuration, irrespective of the nature of the intermediates. Since the product was optically active, we must conclude that inversion took place. This olefin was proven to have the absolute (*S*)-(+) configuration by conversion to (*S*)-(−)-2-methylbutane-3-*d*, whose absolute configuration was established by known steps from (*S*)-(+)-methylisopropylcarbinol,[8] as indicated in the sequence VIII → VII → VI. These results, therefore, completely confirm on a chemical basis the previous conclusion concerning the absolute *S* configuration of this neopentyl-1-*d* alcohol which gives a (−)-acid phthalate.



Stereochemical Purity. It is remarkable that there was about 10% less racemization in the sequence III → IV → V → VI, $[\alpha]^{17}\text{D}$ $-0.85 \pm 0.03°$, than in the sequence VIII → VII → VI, $[\alpha]^{20}\text{D}$ $+0.76 \pm 0.02°$. That the optical rotation of the two samples of 2-methylbutane-3-*d* made by these two different routes are nearly the same is strong evidence that (1) the neopentyl-1-*d* alcohol is stereochemically pure (or nearly so),[9] and (2) that the neopentyl rearrangement is highly stereoselective and perhaps stereospecific. There should be no racemization during the synthesis of the tosylate VIII, but the lithium aluminum deuteride displacement on halides[10] and mesylates[11] has been accompanied by small amounts of racemization in other reported cases: (−)-butane-2-*d* made by the lithium deuteride reductions from (+)-2-butyl methanesulfonate was about 84 ± 5% stereochemically pure, and from (+)-2-bromobutane about 90 ± 5% stereochemically pure. The assumption of about 10% racemization in this step (VII → VI) and no racemization in the sequence IV → V → VI would rationalize these findings and seems to be reasonable. It is, of course, possible to rationalize the results by assuming racemization in both sequences, but about 10% more in the former. The rotation of the (−)-2-methylbutane-3-*d*, $[\alpha]^{17}\text{D}$ $-0.85°$ (neat), is higher than that of (−)-butane-2-*d*,[10] $[\alpha]^{20}\text{D}$ $-0.56°$ (neat), and on this basis it is reasonable to assume that it is relatively pure.

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(4) These numbers have been corrected to correspond to the compounds containing 1.0 deuterium atom per molecule.

(5) (a) J. Hine, E. L. Pollitzer, and H. Wagner, *J. Am. Chem. Soc.*, **75**, 5607 (1953); (b) J. Hine, A. D. Ketley, and K. Tanabe, *ibid.*, **82**, 1398 (1960), and references therein.

(6) P. S. Skell and I. H. Starer, *ibid.*, **81**, 4117 (1959).

(7) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Letters*, **11**, 347 (1961).

(8) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **101**, 620 (1912).

(9) We have just learned from Professor Kurt Mislow that this neopentyl-1-*d* alcohol obtained by fermentative reduction is 99 ± 1% enantiomorphically pure, as revealed by nmr studies of its esters with (*R*)-, (*S*)-, and racemic *O*-methylmandelyl chloride. The chemical shift of the signal for the two α hydrogens of the neopentyl system in these diastereomeric esters is large enough to make possible a quantitative analysis of the isomer composition. We are indebted to Professor Mislow for communicating these results to us prior to publication.

(10) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 19.

(11) G. K. Helmkamp and G. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

Mechanism. Skell and Starer,[6] who studied the reaction of both neopentyl alcohol and *t*-amyl alcohol with bromoform and potassium hydroxide, proposed the following sequence of steps and at the same time pointed out the similarity of the diazonium ion XI

$$\begin{aligned}
&KOH + CHBr_3 \longrightarrow :CBr_2 + KBr + H_2O\\
&RO^- + :CBr_2 \longrightarrow RO\ddot{C}Br + Br^-\\
&RO\ddot{C}Br\ (IX) \longrightarrow ROC:^+ + Br^-\\
&ROC:^+\ (X) \longrightarrow CO + R^+ \longrightarrow \text{products}\\
&RN_2^+\ (XI) \longrightarrow N_2 + R^+ \longrightarrow \text{products}
\end{aligned}$$

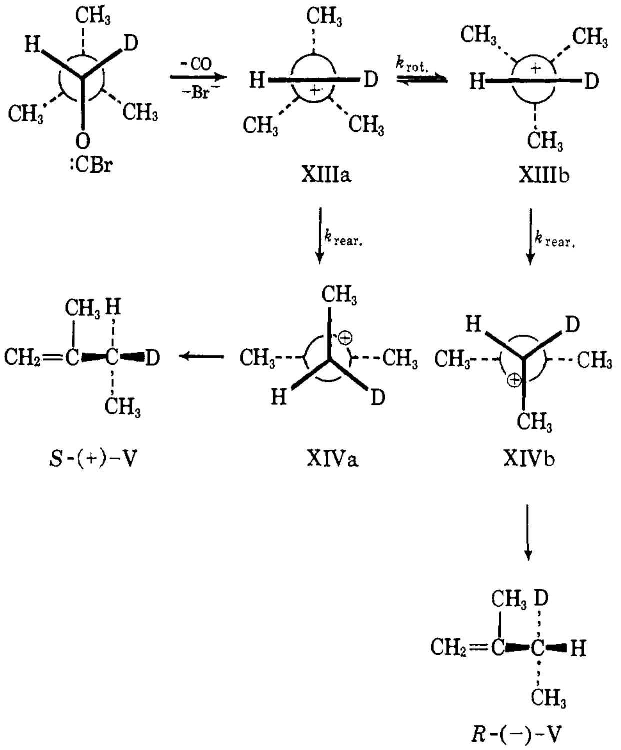
and the proposed intermediate X in the "de-oxideation" reaction.

Hine, Ketley, and Tanabe[5b] have considered the many alternate mechanistic pathways for the reaction of alkoxide ions with the haloforms. Their results, especially the formation of high yields of triisopropyl orthoformate in the reaction of isopropoxy anion with dichlorofluoromethane, were best interpreted in terms of an alkoxyhalomethylene intermediate (IX), giving an ROC^+: (X) cation. In this case, it was argued that the tendency of the isopropoxyfluoromethylene to lose fluoride to give X would be much less than with the corresponding chloro or bromomethylenes, and thus, further reaction of the more stable $RO\ddot{C}F$ leads to the triisopropoxy orthoformate. This stability of the alkoxyfluoromethylene is confirmed by the isolation of 1,2-di-*t*-butoxy-1,2-difluoroethylene in the reaction of difluorochloromethane with *t*-butoxy anion.[12] Both Hine[13] and Kirmse[14] have reviewed the reaction of haloforms with alkoxides.

Skell and Starer[6,15] showed that neopentyl and *t*-amyl alcohol, when treated with potassium hydroxide and bromoform, gave similar ratios of 2-methyl-2-butene to 2-methyl-1-butene (30:70 and 32:68, respectively), from which they concluded that both reactions went through the same intermediate, namely the classical *t*-amyl cation. It is evident that the analogy between this reaction and the deamination reaction is not complete, since Silver[16] found that the deamination of neopentylamine in acetic acid (either aqueous or initially anhydrous) gave a 60:40 ratio of these olefins, while deamination of *t*-amylamine, under comparable conditions, gave a 37:63 ratio. Furthermore, the classical carbonium ion as produced by solvolysis of either *t*-amyl bromide[16] or neopentyl tosylate[16] in aqueous acetic acid gives a 75:25 olefin ratio. It is difficult to reconcile these results with a truly *common* intermediate. The reaction conditions are, of course, quite different: strongly acidic for the classical dehydrations, weakly acidic for the nitrous acid deaminations in acetic acid and the solvolyses in dilute acetic acid, and strongly basic in the de-oxideation reaction.

We shall assume along with Skell[6] and Hine[5] that the neopentoxybromomethylene is an intermediate in the reaction of bromoform and potassium hydroxide with neopentyl alcohol, but it certainly is not clear that a classical carbonium ion is involved. For the present discussion, we shall consider a free carbonium ion one which becomes planar at the cationic carbon atom.

Whether rearrangement of the Wagner–Meerwein type accompanies or succeeds ionization has been considered frequently.[17,18] Methyl migration in a planar neopentyl cation (XIII) in theory will give racemization if rotation about the C_1–C_2 bond (XIIIa ⇌ XIIIb) can bring more than one of the three methyl groups into a *trans* position suitable for migration.[19]



The possibility that the stereochemistry of the products from a free cation such as XIII might be controlled by the relative rates of rearrangement (k_{rear}) *vs.* rotation about the C_1–C_2 bond (k_{rot}) was considered by Winstein and Grunwald;[20] it has been studied in detail by Collins and Bonner[21] for aromatic systems, and the subject has been reviewed by Pocker.[18] If the rate of rotation is slow compared to the rate of migration, it is possible for the planar cation to be an intermediate and the reaction to proceed without complete racemization. If the barrier to rotation in the cation XII and the stereoselectivity of the methyl migration were known, we could evaluate the importance of this possible mechanism in the present case. The energy barrier to rotation of a methyl group in neopentane is reported to be 4.3 kcal/mole.[22] The barrier to rotation about the C_1–C_2 bond (XIIIa → XIIIb) in the neopentyl cation is unknown but should be appreciably less than this.[23] The bonds on the trigonal carbon are about 120° instead of 109° and

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[12] C. S. Clearer, U. S. Patent 2,853,531; *Chem. Abstr.*, **53**, 5135 (1959).

[13] J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964.

[14] W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 185.

[15] I. H. Starer, Ph.D. Thesis, The Pennsylvania State University, June 1960.

[16] M. Silver, *J. Am. Chem. Soc.*, **83**, 3482 (1961).

[17] (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952); (b) P. S. Skell and C. R. Hauser, *ibid.*, **64**, 2633 (1942); (c) C. G. Swain, *ibid.*, **70**, 1119 (1948).

[18] Y. Pocker, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 11.

[19] D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2866 (1957).

[20] S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

[21] C. J. Collins and W. A. Bonner, *ibid.*, **77**, 92 (1955).

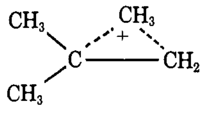
[22] K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951).

[23] L. S. Bartell, *Tetrahedron Letters*, **No. 6**, 13 (1960).

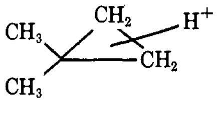
therefore should offer somewhat less interference to rotation. Furthermore, the rotation in the cation does not involve the simultaneous eclipsing of three hydrogens, as in neopentane, but a rotation involving eclipsing of a single hydrogen by methyl will orient a new methyl group for attack at the cationic site. It is estimated that this might lower the rotational barrier by as much as two-thirds; *i.e.*, it is not unreasonable to estimate the energy barrier to rotation in the cation at 1.5 kcal/mole. In support of this, the energy barrier to rotation of the methyl group in toluene is almost zero, in *trans*-2-butene about 1.9 kcal/mole, and in *cis*-2-butene about 0.5 kcal/mole.[22] In each case there is a trigonal carbon attached to a tetrahedral carbon. Data are not available for *t*-butylethylene, which would be a closer analog.

The energy of activation for the methyl migration is unknown. However, by assuming that it approaches zero, one can estimate the maximum difference ($\Delta\Delta G^*$) between the barrier to rotation (ΔG_{rot}), and the energy of activation for methyl migration (ΔG_{rear}) required by this assumed mechanism based on the observed stereoselectivity of the reaction, *i.e.*, $\Delta\Delta G^* = G_{\text{rot}} - \Delta G_{\text{rear}}$. For a reaction which is 98% stereoselective at 100°, $\Delta\Delta G^*$ would be about 3 kcal/mole, for a reaction which is 90% stereoselective, about 2 kcal/mole.[24] Our data indicate that the observed stereoselectivity in this rearrangement is high and perhaps approaches 100%. The probability that the stereoselectivity exceeds 90% is very high. If the amount of racemization in the lithium aluminum deuteride displacement (VIII → VII) is 10%, then the rearrangement must be 100% stereoselective; if, however, the racemization is 20%, then the rearrangement must be 90% stereoselective. In the latter case, our results would be compatible with a carbonium ion in which the difference between the energy barrier to rotation and the energy of activation was 2 kcal/mole. However, it seems reasonable to assume that the energy barrier alone is less than this, and the stereoselectivity is greater. Therefore, we are inclined to discount this interpretation although it cannot be positively discarded until the stereochemical purity of 2-methyl-2-butene-3-*d*, $[\alpha]^{17}\text{D}$ −0.85°, can be established.

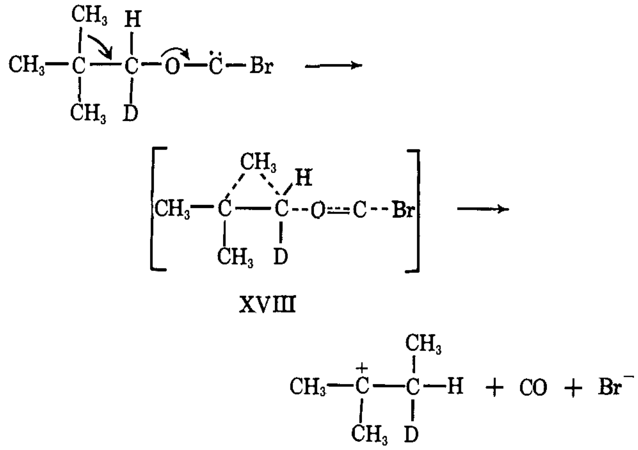
An intermediate bridged cation such as XVI and a protonated cyclopropane intermediate such as XVII have been postulated as intermediates in neopentyl cation rearrangements,[25,26] but they have been ruled out the basis of labeling experiments.



XVI



XVII



Our results are best accounted for by some type of *concerted process*. Formula XVIII can be considered the transition state between the neopentylbromomethylene and a *t*-amyl cation during simultaneous ionization and methyl migration. Such a process would be stereospecific and would lead to inversion. The final products would be those expected from the classical *t*-amyl cation, namely *t*-amyl alcohol and a mixture of 2-methyl-2-butene and 2-methyl-1-butene. The ratio of these two olefins is crucial to a critical evaluation of the mechanism of this reaction. Several reactions which presumably proceed *via* a *t*-amyl cation give 2-methyl-2-butene and 2-methyl-1-butene in approximately a 75:25 ratio; this is also the approximate thermodynamic equilibrium ratio of these two olefins.[27] These reactions have been summarized by Silver[16] and include solvolysis of *t*-amyl and neopentyl halides, solvolysis of neopentyl tosylate and *t*-amyldimethylsulfonium iodide. However, neither the deamination of neopentylamine nor of *t*-amylamine fits this pattern, giving, respectively, 60:40 ratios of 2-methyl-2-butene to 2-methyl-1-butene. Silver[16] found that the composition of the olefin mixtures from these solvolyses and deaminations was relatively insensitive to solvent. The olefin ratios found for the $CHBr_3$–KOH reaction on both neopentyl and *t*-amyl alcohols[28] was about 30:70.

The fact that the $CHBr_3$–KOH reaction on neopentyl alcohol gave approximately the same ratio of products as from *t*-amyl alcohol led Skell and Starer[6] to propose that both reactions went through a common intermediate, namely the *t*-amyl cation. Starer showed[15,28] that when a stronger base than aqueous potassium hydroxide was used ($CHBr_3$–KO-*t*-Bu) the ratio of 2-methyl-2-butene to 2-methyl-1-butene decreased further to 25:75 in the neopentyl case and 21:79 in the *t*-amyl case, producing more of the thermodynamically less stable olefin isomer. It is, therefore, logical to conclude, as did Starer,[17] that base was involved in the removal of a proton in the kinetically controlling step. This neither proves nor disproves the intermediacy of the discrete *t*-amyl cation since it could be formed and then react with base or its formation and reaction with base could be concerted. However, if a free *t*-amyl cation were formed and then treated with hydroxide ion or water, a major fraction should be converted to *t*-amyl alcohol. Under these circumstances the newly

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(24) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 118.

(25) G. T. Karabatsos and J. D. Graham, *J. Am. Chem. Soc.*, **82**, 5250 (1960).

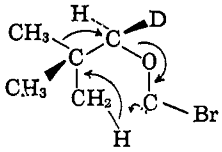
(26) P. S. Skell, I. H. Starer, and A. P. Krapcho, *ibid.*, **82**, 5257 (1960).

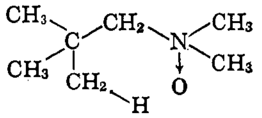
(27) J. F. Kilpatrick, E. J. Prosen, K. S. Pitzer, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **36**, 559 (1946). The calculated thermodynamic gas phase equilibrium at 100° for 2-methyl-2-butene:2-methyl-1-butene is 72:28.

(28) The relative ratios of 2-methyl-2-butene and 2-methyl-1-butene reported by Starer[15] from neopentyl and *t*-amyl alcohols, respectively, were as follows: $CHBr_3$–KOH, 30:70 and 32:68; $CHBr_3$–*t*-C_4H_9OK and $CHBr_3$–*t*-$C_5H_{11}OK$, 25:75 and 21:79; $CHBr_3$–*neo*-$C_5H_{11}OK$ and $CHBr_3$–*t*-$C_5H_{11}OK$, 30:70 and 26:74. Each run was the average of two closely corresponding determinations.

formed *t*-amyl alcohol would further react with the excess KOH–$CHBr_3$ reagent, resulting in considerably more than 1 mole of carbon monoxide per mole of original alcohol. This was not observed.

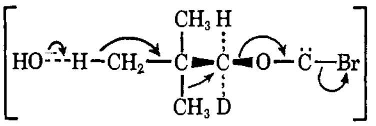
The alkoxybromocarbene could undergo rearrangement by a *cyclic concerted mechanism*, one form of which is represented in XIX. This pathway would


XIX

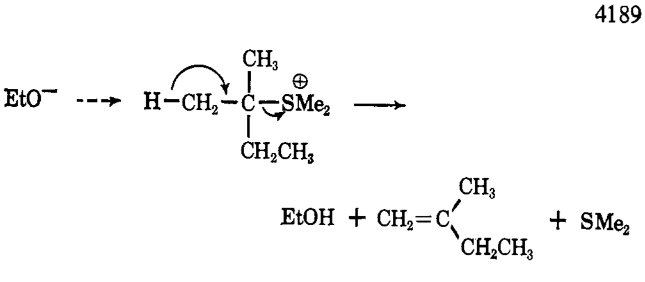

XX

lead to 2-methyl-1-butene and formyl bromide which would decompose into carbon monoxide and hydrogen bromide or react with the base to give formate ion. Other cyclic concerted mechanisms can be visualized which would give carbon monoxide and hydrogen bromide directly (seven-membered ring) or an internal insertion of the carbene into the C–H bond (five-membered ring). Such mechanisms can account for the 2-methyl-1-butene and not for the 2-methyl-2-butene, unless, of course, it is formed subsequent to the rearrangement by way of a base-catalyzed rearrangement[29] or is the product of a competing reaction. An excellent model for such a cyclic elimination reaction would be the decomposition of dimethylneopentylamine oxide (XX). This has been studied,[30] and no 2-methyl-1-butene was detected, the major product instead being neopentoxydimethylamine. Thus, a close model of XIX does not appear to offer a low energy pathway to the olefin. Since the base strength of the reaction medium should have little effect on the cyclic mechanism, this need not be considered further.

A *linear concerted pathway* represented by XXI must be considered in spite of the attack of base on hydrogen of a saturated system. Such a process would explain the stereospecificity of the major reaction, the dependence of olefin ratio upon base strength, and the formation of the thermodynamically less stable isomer.


XXI

There are nine equivalent hydrogens on the γ carbon (*vs.* two on the α) and these are situated so that approach of base from this side would offer minimum interference with the leaving group. This reaction is formally very similar to the E2 elimination of *t*-amyldimethylsulfonium ethoxide (XXII) studied by Hughes, Ingold, and Woolf,[31,32] who found that the less stable olefin, 2-methyl-1-butene, predominated in the ratio of 14:86. Silver[33] discounted the contribution of the E2 mechanism ("Hofmann control") in the deamination of *t*-butylamine based on the small observed deuterium


XXII

isotope effect. The strong basic conditions of the deoxideation reaction should favor the E2 process but certainly the effect is not large enough to give elimination with the neopentyl halides on treatment with strong base.

Although XXI may theoretically represent the pathway for the formation of 2-methyl-1-butene, a similar linear concerted scheme cannot operate for the formation of 2-methyl-2-butene from neopentyl alcohol and thus argues against this mechanism. A study of the β deuterium isotope effect in this and related systems might clarify this point and is planned.

The present study is definite in showing that the rearrangement of (*S*)-neopentyl-1-*d* alcohol in the $CHBr_3$–KOH de-oxideation reaction to 2-methyl-1-butene-3-*d* is highly stereoselective and quite probably stereospecific. This finding almost certainly eliminates any mechanism involving a free neopentyl cation, including that which involves rearrangement within such a cation faster than rotation about the C_1–C_2 bond. It does not, however, settle the nature of the subsequent steps.

Experimental Section

Trimethylacetaldehyde-1-*d*. Trimethylpyruvic acid (128 g, 0.985 mole), prepared by Richard's method,[34] and glycine (25 g, 0.33 mole) were allowed to equilibrate six times with deuterium oxide (99.5%). After the final removal of water by low-temperature, high-vacuum distillation, the reactants were slowly heated to 160° in a slow stream of dry nitrogen and finally heated at 180° for 15 min. The product, 59 g, was collected in two cold traps (−78°) in series, dried, and distilled through a 12-in. spinning-band column to give the purified aldehyde (45 g, 58%), bp 73–74° (763 mm). The residue (13 g, 9%) was shown to be deuterated pivalic acid. Characteristic peaks at 12.5 and 13.7 μ for the nondeuterated aldehyde were absent in this product, and a moderately strong C–D stretching band at 4.95 μ with a shoulder at 4.75 μ was present. The deuterium content was shown by nmr to be 0.88 ± 0.05 atom of deuterium in the 1 position by comparison of the average integrated area of the aldehydic proton with one-ninth the area of the methyl proton signal.[35] Because of its ease of autoxidation, the aldehyde was used immediately in the next step.

Neopentyl-1-*d* Alcohol. This fermentation has already been described.[1] The neopentyl-1-*d* alcohol was purified using the Beckman "Megachrom" with four parallel 12 ft × 5/8 in. Apiezon L columns at 88° and 8 psi (helium). The yield of the purified product was 43%. The deuterium content was shown to be 0.85 ± 0.01 atom per molecule of deuterium in the 1 position by mass spectrographic analysis of the benzoate ester.[36]

Acid Phthalate of Neopentyl-1-*d* Alcohol. This was prepared as previously described[1] to give a product with mp 69.5–70.5°, $[\alpha]^{26}D$ −0.98 ± 0.03° (*c* 20, acetone, 2 dm center-filled tube), $[\alpha]^{26}D$ −1.15 ± 0.03° calculated for one deuterium atom per molecule.

2-Methyl-1-butene-3-*d*. A 500-ml, three-necked, round-bottomed flask was fitted with a dropping funnel with pressure-equalizing by-pass, reflux condenser, an inlet tube for nitrogen, and a 2.5-cm, egg-shaped, Teflon-coated magnetic stirring bar. Volatile

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(29) D. J. Cram, "Fundamentals of Carbonium Chemistry," Academic Press Inc., New York, N. Y., 1965, p 196.

(30) W. A. Sanderson and J. Brauman, private communication.

(31) E. D. Hughes, C. K. Ingold, and L. I. Woolf, *J. Chem. Soc.*, 2084 (1948).

(32) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter VIII.

(33) M. Silver, *J. Am. Chem. Soc.*, **83**, 3487 (1961).

(34) A. Richard, *Ann. Chim. Phys.*, [8] **21**, 323 (1910).

(35) We wish to thank Dr. Lois Durham for these determinations.

(36) We wish to thank Drs. Carl Djerassi and Alan Duffield for these determinations.

products were led from the top of the condenser and collected in two series cold traps at −180°. The exit was attached *via* a three-way stopcock to a rubber balloon so that the gases could be collected and the progress of the reaction monitored. Neopentyl-1-*d* alcohol (10.0 g, 0.11 mole), water (120 ml), and potassium hydroxide (112 g, 2 moles) were placed in the flask and brought to the boiling point under a slow stream of nitrogen with vigorous stirring. Bromoform (86 g, 0.34 mole) was then added dropwise over 1.5 hr. Potassium hydroxide (112 g, 2 moles) in water (60 ml) was then added, followed by a further quantity of bromoform (60 g, 0.24 mole) over 2 hr. The volatile material, which was collected in the traps, was transferred by vacuum distillation in a closed system to give a mixture of 2-methyl-1-butene-3-*d* and 2-methyl-2-butene, 4.4 g, 56%.

Gas chromatographic analysis of this mixture (Aerograph A-90-P3, 5 ft × 0.25 in. Apiezon L, 29°, 30 ml/min of helium) showed that the product consisted of 2-methyl-1-butene-3-*d* (70%) and 2-methyl-2-butene (30%). The retention times were 5.5 and 7.3 min, respectively. These were separated on the Megachrom using four parallel 12 ft × $^5/_8$ in. Apiezon L columns at 25° and 7 psi (helium), the olefins being eluted after 32.6 and 45.6 min, respectively. This procedure yielded 2-methyl-1-butene-3-*d* (2.1 g), $\alpha^{20}\mathrm{D}$ +1.11 ± 0.01° (l = 2, neat, center-filled tube), $[\alpha]^{20}\mathrm{D}$ +1.01 ± 0.02° based on 0.83 ± 0.01 deuterium atom per mole and $d^{20}{}_4$ 0.6635. This product showed a single peak on analytical vpc analysis (Aerograph A-90, 5 ft × 0.25 in. Ucon Polar, 16°).

In a similar experiment,[2] neopentyl-1-*d* alcohol (9.0 g, 0.10 mole) containing 1.00 ± 0.05 atom of deuterium per molecule (nmr)[35] gave an olefin mixture (3.2 g, 45%) of composition 2-methyl-1-butene-3-*d* (69%) and 2-methyl-2-butene (31%). The 2-methyl-1-butene-3-*d* was isolated as described and had the rotation $\alpha^{23}\mathrm{D}$ +1.22 ± 0.02° (neat, l = 2, center-filled tube), and deuterium content of 0.97 ± 0.05 deuterium atom per molecule (nmr).[35] Neopentyl-1-*d* alcohol (2.2 g, 24%) was also recovered; the acid phthalate had the rotation $[\alpha]^{26}\mathrm{D}$ −1.12 ± 0.03° (l = 2, c 9, acetone). A trace of impure deuterated *t*-amyl alcohol (0.3 g, 3%) was also isolated, identified by its infrared spectrum and vpc analysis, which had the rotation $\alpha^{27}\mathrm{D}$ −0.55° (neat, l = 1, center-filled tube).

2-Methylbutane-3-*d*. After many control experiments, the following procedure was found to give the best results. A 1-l., three-necked flask was equipped with a thermometer dipping into the reaction mixture, a dropping funnel with pressure-equalization side arm, and an efficient cold finger Dry Ice–2-propanol condenser. The reactants were stirred by a 1-in., egg-shaped, Teflon-covered stirring bar, and the flask was surrounded by an ice–water bath. To the flask was added 2-methyl-1-butene-3-*d* (1.9 g, 0.027 mole), $\alpha^{20}\mathrm{D}$ +1.11° (l = 2, neat), *n*-propyl alcohol (500 ml), 95% hydrazine (25 ml, 0.74 mole), and a small crystal of $CuCl_2 \cdot 2H_2O$ (about 5 mg). The contents of the flask were stirred vigorously while 30% hydrogen peroxide (160 ml, 1.5 moles) was added over 6 hr, keeping the temperature of the reactants between 20 and 25°. After the addition, the mixture was distilled and 20 ml of distillate collected in a receiver cooled to −78°. The distillate contained water, isopropyl alcohol, and an 88:12 mixture of alkane to alkene. Preparative vapor phase chromatography of the mixture (Beckman Megachrom, four parallel 12 ft × $^5/_8$ in. Dow 710 silicone oil columns, 31°, 7 psi helium) gave 2-methylbutane-3-*d* (1.0 g, 51%), $\alpha^{17}\mathrm{D}$ −0.45 ± 0.02° (neat, l = 1, center-filled tube), which showed a single peak on analytical vpc (Aerograph A-90, 5 ft × 0.25 in. Dow 710, 24°). The deuterium content obtained from the mass spectrum was 0.83 ± 0.01 atom of deuterium per molecule.

(+)-Methylisopropylcarbinol. The carbinol was resolved by the method of Pickard and Kenyon[8] and gave (+)-methylisopropylcarbinol (19%), gas chromatographically pure, $\alpha^{27}\mathrm{D}$ +8.12 ± 0.02° (l = 2, neat); the literature value[8] of the pure isomer is $\alpha^{28.3}\mathrm{D}$ +3.89° (l = 1, neat). Since this is slightly above the best literature value, we assume it is stereochemically pure.

(5)-Methylisopropylcarbinyl Tosylate.[37] To a magnetically stirred solution of stereochemically pure methylisopropylcarbinol (above) (4.4 g, 0.05 mole) in pyridine (20 ml, Mallinckrodt AR, stored over KOH pellets) maintained at −5 to −10° was added *p*-toluenesulfonyl chloride (11.4 g, 0.06 mole; recrystallized from ether, mp 68–69°). The solution was stirred at −5 to −10° for 3 hr and then poured into a mixture of concentrated hydrochloric acid (40 ml) and ice (100 ml). This mixture was extracted with ether, the combined ether extracts were washed with water, saturated aqueous sodium bicarbonate, and water (three 10-ml portions), and dried ($MgSO_4$). The ether was removed under vacuum and the residue recrystallized at −15° from petroleum ether (12 ml, bp 30–60°, redistilled) to give the tosylate (12.3 g), mp 34–36°, as white needles, $[\alpha]^{20}\mathrm{D}$ +6.56 ± 0.02° (c 45, chloroform). These were recrystallized from petroleum ether as above to give tosylate (12 g), mp 36–37°, after air drying for 16 hr, $[\alpha]^{20}\mathrm{D}$ +6.60 ± 0.02° (c 26, chloroform).

Anal. Calcd for $C_{12}H_8O_3S$: C, 59.49; H, 7.49. Found: C, 59:26; H, 7.25.

This tosylate was unstable and was used immediately in the next step.

(+)-2-Methylbutane-3-*d*. The following conditions were found optimum after several exploratory experiments. A solution of the (+)-tosylate (10.0 g, 0.041 mole) in diglyme (10 ml, distilled from $LiAlH_4$ immediately before use) was added dropwise to a solution of lithium aluminum deuteride (2.0 g, 0.045 mole; Metal Hydrides, Inc., 95.5%) at 30° while a slow stream of dry nitrogen was passed over the reaction mixture and through a liquid nitrogen cold trap which in turn was protected from the atmosphere by a paraffin oil trap. The temperature of the reaction mixture was raised to 50° over 45 min and maintained at 100° for 1 hr. Mild frothing occurred only at 100°. The colorless product (2.75 g, 91% calculated as 2-methylbutane-3-*d*) in the cold trap was vacuum distilled in a closed system. Analysis by vpc (Aerograph A-90-P3, 20 ft × $^3/_8$ in. FFAP, 24°, 60 ml/min, helium) showed this to consist of 2-methylbutane and 2-methyl-2-butene in the ratio 75:25. The retention times were 6.7 and 12.0 min, respectively. The 2-methylbutane-3-*d* (1.05 g, 32% purified yield) was recovered on the Megachrom (four 12 ft × $^5/_8$ in. parallel Ucon Polar columns, 23°, 5 psi helium). The retention times of the 2-methylbutane-3-*d* and 2-methyl-2-butene were 5.1 and 13.8 min, respectively. The 2-methylbutane gave a single peak on the FFAP column under the conditions noted above and had rotation $\alpha^{20}\mathrm{D}$ +0.90 ± 0.02° (neat, l = 2, center-filled tube). The deuterium content, analyzed by the mass spectrum,[36] was 0.94 ± 0.1 atom per molecule.

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(37) A. J. Finlayson and C. C. Lee, *Can. J. Chem.*, 37, 940 (1959).