of charged amino acid residues with solvent clusters of various sizes, from single molecules to full solvent, are an essential factor in the determination of biophysically important phenomena, such as the changes in the extent of solvation and in the pK values of amino acid residues upon conformational changes in proteins in protonating environments.[10,11] We think that the quantitative determination by mass spectrometric studies of solute–solvent interactions for ions of biologically important compounds will provide information relevant to the energetics of such ions in their biological environments. Similarly the information available from mass spectrometric studies on the energies of interaction between protonated and nonprotonated amino acids may be helpful in the understanding of the role of such interactions on the determination of protein conformation.

Association complexes of the type ValH⁺·Val, etc., were shown by Leclerq and Desiderio[4] to form preferentially in a "head-to-tail" configuration and to decompose in several condensation processes including the loss of H_2O, presumably leading to the production of protonated dipeptides. Association reactions of the types investigated in this study may therefore constitute the first step in reactions leading to the abiotic synthesis of large molecules of potential biogenetic significance, under ionizing conditions that are frequently assumed in environments of interest in biogenetic and exobiological studies.

(10) T. Schleich and P. H. von Hippel, *Biochemistry*, 9, 1059 (1970).
(11) G. C. K. Roberts, D. H. Meadows, and O. Jardetzky, *Biochemistry*, 8, 2053 (1969).

Displacement Reactions of Neopentyl-1-d Tosylate without Rearrangement and Optical Rotatory Dispersion Spectra of Chiral Compounds with Four Different Groups of Either C_{3v} or $C_{\infty v}$ Symmetry Attached to a Central Carbon[1,2]

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Abstract: (S)-Neopentyl-1-d tosylate in hexamethylphosphoramide solvent undergoes substitution with inversion and without detectable rearrangement by a number of nucleophiles (F⁻, Cl⁻, Br⁻, I⁻, CN⁻, N_3^-, SH⁻, and CH_3^- [as $(CH_3)_2CuLi$]) to give good yields of chiral neopentyl-1-d derivatives. Thus in hexamethylphosphoramide solvent neopentyl tosylate undergoes the normal SN2 substitutions without rearrangement and with inversion of configuration. The syntheses of these neopentyl compounds (Me₃CC*HDX, X = F, Cl, Br, I, CN, N₃, SH, and CH₃) and derivatives (X = NH₂, ⁺NMe₃, SO₃H) are described. Compounds of this series display an unusually simple conformational symmetry and are therefore of special interest from an ORD standpoint. (R)-Neopentyl-1-d derivatives with X = F, Cl, Br, I, ⁺NH₃, ⁺NMe₃ and the configurationally related (S)-2,2-dimethylbutane-3-d (X = CH₃), in which the X substituents have either C_{3v} or $C_{\infty v}$ symmetry, gave plain negative ORD curves while (R)-neopentyl-1-d derivatives with X = SH, SO₃, NH₂, and CN gave plain positive curves down to approximately 350 nm. (R)-Neopentyl-1-d azide has a substantial optical rotation: $[\alpha]^{20}$D +3.2° (neat); ORD maximum $[\phi]^{20}_{305}$ +41° (cyclohexane). Its CD maximum $[\theta]^{20}_{288}$ +30 (methylcyclohexane–isopentane) is unshifted at 77°K and has only slightly higher intensity.

In the course of studying the SN2 displacement reactions of chiral neopentyl-1-d tosylates and halides[2,3] we realized that molecules with structure **1a** constitute a group of chiral compounds which are conformationally very simple and potentially interesting for experimental and theoretical ORD studies. Each substituent on the chiral carbon considered separately and viewed along the bond axis to the chiral carbon possesses either C_{3v} symmetry (tert-butyl, ⁺NMe₃, CH₃, ⁺NH₃, SO₃⁻) or $C_{\infty v}$ symmetry (H, D, halogen, CN, S⁻). The major conformational variable for neopentyl compounds with such substituents with $C_{\infty v}$ symmetry is the rotation between the three indistinguishable staggered forms (**1b**) over the three indistinguishable eclipsed barriers (**1c**).[4] There is also
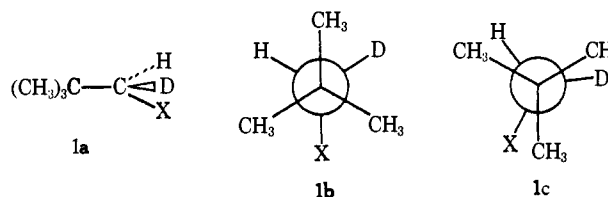
the rotation of each C_{3v} symmetrical methyl group which makes up the tert-butyl group itself. (Dynamic displacements of bond angles and bond distances are
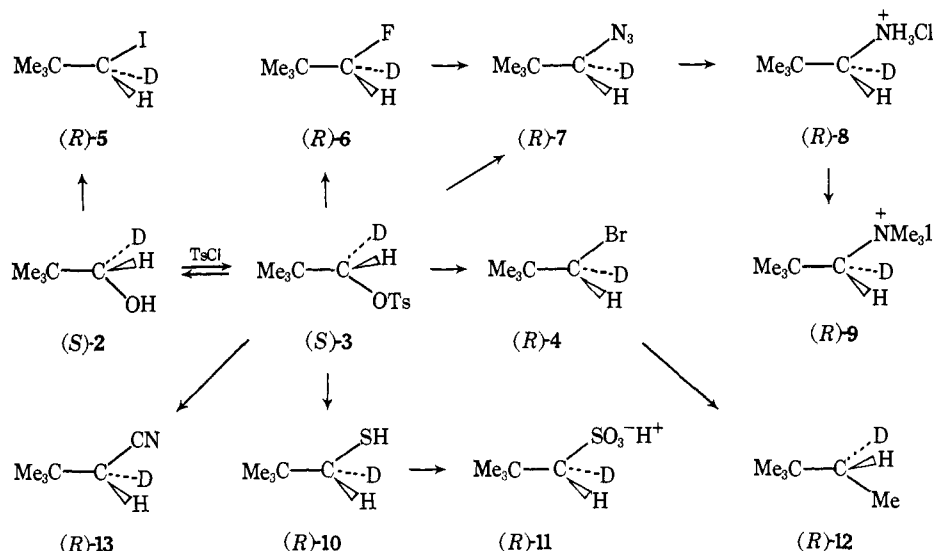
(1) We gratefully acknowledge support of this study by the National Science Foundation (NSF GP 27448) and the USPHS (NIH ROIGM 19554).
(2) Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract ORGN-36.
(3) B. Stephenson, G. Solladié, and H. S. Mosher, *J. Amer. Chem. Soc.*, 94, 4184 (1972).
(4) J. Applequist, P. Rivers, and D. E. Applequist, *J. Amer. Chem. Soc.*, 91, 5705 (1969).

Scheme I

Me₃C—C(I)(---D)(H) (R)-5   →   Me₃C—C(F)(---D)(H) (R)-6   →   Me₃C—C(N₃)(---D)(H) (R)-7   →   Me₃C—C(⁺NH₃Cl)(---D)(H) (R)-8

Me₃C—C(D)(H)(OH) (S)-2   ⇌ (TsCl)   Me₃C—C(D)(H)(OTs) (S)-3   →   Me₃C—C(Br)(---D)(H) (R)-4

Me₃C—C(⁺NMe₃I)(---D)(H) (R)-9

Me₃C—C(CN)(---D)(H) (R)-13   Me₃C—C(SH)(---D)(H) (R)-10   →   Me₃C—C(SO₃⁻H⁺)(---D)(H) (R)-11   Me₃C—C(D)(H)(Me) (R)-12

not considered conformational variables.) Only a few examples which satisfy these conditions have been reported to our knowledge, e.g., CH₃CH(CN)Br,[4,5] CH₃CH(CN)⁺NH₃,[6] ClICHSO₃⁻,[7] the special case of 3-methyl-5-bromo-1-cyanoadamantane,[4] and partially active fluorochlorobromomethane.[8] When the X substituent possesses C_{3v} symmetry the conformational possibilities are only slightly more complex. Thus these neopentyl-1-d compounds approximate the conformationally unique situation in which four groups with $C_{\infty v}$ symmetry are attached to a central carbon atom as in fluorochlorobromomethane,[8] which exists in a single conformation.

Molecules of these types lack the complicating variables of molecular conformations which contribute to ORD behavior. Therefore, theoretical treatment of optical rotation vs. molecular structure should be simplified for such compounds in comparison to conformationally mobile molecules containing groups of more complex symmetry types. Thus an intrarelated set of conformationally simple chiral molecules of this type should be very useful to such studies. In addition, the synthesis of these compounds further explores the stereochemistry of displacements on primary carbons of the neopentyl type.

Results

Scheme I summarizes the method of synthesis of the compounds (4–12) of type 1. The major approach exploited SN2 displacement reactions on (S)-neopentyl-1-d tosylate[9] in hexamethylphosphoramide (HMPA) solvent[10] according to the general procedure developed earlier.

A previous attempt[2,3] to make neopentyl fluoride by

the action of sodium fluoride on neopentyl tosylate (3) at 150° in HMPA was unsuccessful. Normant and Bernardin[11] have reported that tetraethylammonium fluoride in HMPA displaced bromide and tosylate at room temperature to give alkyl fluorides with less side reaction (elimination) than when lithium fluoride was employed. Because tetraethylammonium fluoride has been reported to decompose above 80°,[12] and tetramethylammonium salts are known to be more stable than tetraethylammonium salts,[13] we used tetramethylammonium fluoride. Neopentyl-1-d fluoride (6) was distilled from the reaction mixture (110–115°) under vacuum as formed in a yield of 80%. This is an improvement on yields reported for other such displacement by fluoride ion.[11] Since this neopentyl-1-d fluoride is made by a general process which is clearly an SN2 displacement, and since the possibility of isoracemization resulting from attack on the neopentyl-1-d fluoride by the very poorly nucleophilic fluoride ion is remote, we conclude that product 6 has the same enantiomeric purity, but opposite R configuration, as that of the (S)-neopentyl-1-d tosylate (3)[14] from which it was made.[15]

(R)-Neopentyl-1-d bromide (4) was prepared as previously described,[3] except under anhydrous conditions, by the displacement reaction of lithium bromide on an excess of tosylate 3. Working under vacuum and vigorous stirring so that the bromide was removed from the HMPA solvent as formed resulted in a somewhat better yield (82%) and slightly higher optical rotation ([α]²⁰D −0.148° vs. [α]²³D −0.124°, neat) than previously

(5) (a) K. L. Berry and J. M. Sturtevant, J. Amer. Chem. Soc., 61, 3583 (1939); (b) W. Kauzmann, F. B. Clough, and I. Tobias, Tetrahedron, 13, 57 (1961).

(6) M. Delephine, Bull. Soc. Chem. Fr., 29, 1195 (1903).

(7) J. Read and A. M. McMath, J. Chem. Soc., 2723 (1932).

(8) (a) M. K. Hargreaves and B. Moderai [Chem. Commun., 16 (1969)] have reported making fluorochlorobromomethane in optically active form but it must be of very low enantiomeric purity in view of its method of synthesis. (b) S. H. Wilen, M. J. Wieder, C. M. Kasheres, unpublished results; S. H. Wilen, Top. Stereochem., 6, 122 (1971).

(9) G. Solladié, M. Muskatirović, and H. S. Mosher, Chem. Commun., 809 (1968).

(10) J. F. Normant, Angew. Chem., Int. Ed. Engl., 6, 1046 (1967).

(11) J.-F. Normant and J. Bernardin, C. R. Acad. Sci., Ser. C, 268, 2352 (1969).

(12) J. Hayami, N. Omo, and A. Kaji, Tetrahedron Lett., 1385 (1968).

(13) W. Hanhard and C. K. Ingold, J. Chem. Soc., 997 (1927); A. C. Cope and E. R. Trumbell, Org. React., 11, 317 (1960).

(14) The (S)-neopentyl-1-d tosylate (3) was prepared from (S)-neopentyl-1-d alcohol (2) which was made by reduction of trimethylacetaldehyde-1-d by actively fermenting yeast [V. E. Althouse, K. Ueda, and H. S. Mosher, J. Amer. Chem. Soc., 82, 5938 (1960)]. The alcohol made by this method has been shown to be enantiomerically pure: K. Mislow and M. Raban, Tetrahedron Lett., 4249 (1965).

(15) The nmr spectra of (R)-neopentyl-1-d fluoride and (R)-neopentyl-1-d bromide in (RS)-phenyltrifluoromethylmethanol show only a single signal for the latter's α proton. Thus the method of Pirkle for determining enantiomeric purity was not applicable as an independent check on this conclusion: W. H. Pirkle and S. D. Beare, J. Amer. Chem. Soc., 91, 5150 (1969).

reported.[3] The water intentionally added in the previous run was thus not necessary, although it did not seem to greatly hinder the reaction. Possible isoracemization caused by attack of bromide ion on the initially formed neopentyl-*1-d* bromide leaves doubt concerning the enantiomeric purity[15] of this product. The doubt is reinforced by the intensity of its ORD curve (Figure 1) relative to the other neopentyl-*1-d* halides.

Earlier attempts at the preparation of optically active neopentyl-*1-d* iodide (5) by displacement on the tosylate[3] (3) were unsuccessful, presumably due to rapid isoracemization of the initially formed product. The Landauer–Rydon reaction[16] on neopentyl-*1-d* alcohol (ROH + Ph₃P + MeI) had once given optically active material[17] but this could not be repeated.[3] The recently described modification of this reaction which involved the preparation of the crystalline methyltriphenoxyphosphonium iodide reagent[18] in HMPA solvent was successful, giving a 66% yield of neopentyl-*1-d* iodide [(5), [α]²⁰D −0.282° (neat)]. There is no independent check on the enantiomeric purity and configuration of this product; again we assume the *R* configuration based on the probable stereochemical course of this reaction[8] for the corresponding bromide and chloride[8,19] and the uniformly negative ORD curves for these neopentyl halides which are made by the same or related processes.

(*R*)-(+)-Neopentyl-*1-d* thiol (10, [α]²⁰D +0.345°, neat) was prepared utilizing hydrosulfide displacement on the tosylate (3) in HMPA solvent in analogy to this reaction performed previously in methyl Cellosolve solvent.[20] Again we assign the *R* configuration for this product and assume it to be enantiomerically pure. This thiol was converted to the (*R*)-(+)-neopentyl-*1-d*-sulfonic acid (11) by hydrogen peroxide oxidation in acetic acid.[21]

(*R*)-(+)-2,2-Dimethylbutane-*3-d* (12) was prepared by treating (*R*)-neopentyl-*1-d* bromide (4) with lithium dimethylcuprate.[22] In the case of the reaction of lithium diphenylcuprate with (*R*)-2-bromobutane, this coupling reaction has been reported to go with inversion in stereoselectivities of 84–92%. It is logical to assume that coupling with the primary neopentyl system also goes with inversion and probably with a stereoselectivity as high as that encountered in the secondary butyl system. We therefore assume that product 12 has the *R* configuration[22] and has an enantiomeric purity which is at least 80% of that of the bromide from which it was prepared.

(*R*)-Neopentyl-*1-d*-amine, whose synthesis has been described[3] and whose enantiomeric purity and absolute configuration have been independently established,[23]
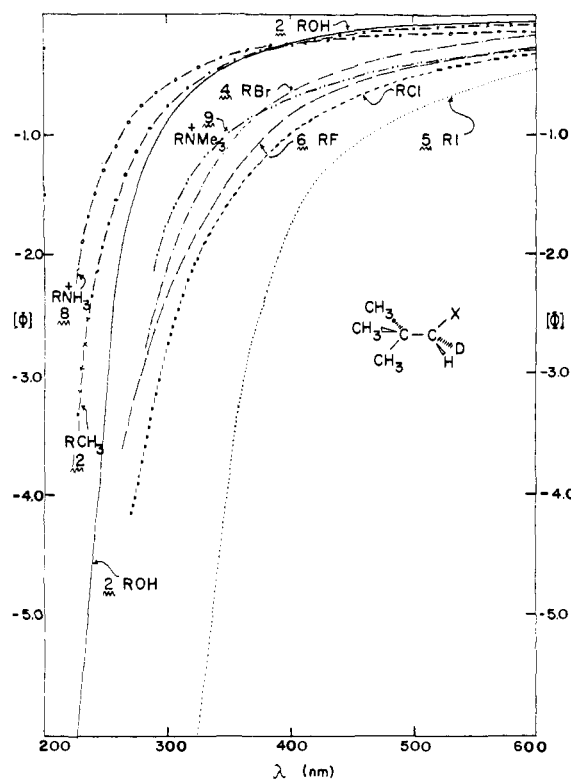
(16) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2225 (1953).

(17) W. A. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, **83**, 5033 (1961).

(18) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319, 2868 (1970).

(19) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971).

(20) F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Amer. Chem. Soc.*, **73**, 5004 (1951).

(21) E. S. Balakirev, G. N. Anisimova, and N. S. Malyshova, *Probl. Poluch. Poluprod. Prom. Org. Sin.*, 5 (1967); *Chem. Abstr.*, **68**, 12626a (1968).

(22) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969). The fact that *R* bromide 4 gives *R* alkane 12 even though the reaction goes with inversion is a consequence of the sequence rules of the *RS* nomenclature system.

Figure 1.

was exhaustively methylated by a procedure described for nondeuterated neopentylamine[24] to give (*R*)-neopentyl-*1-d*-trimethylammonium iodide (9). This process should not affect either configuration or enantiomeric purity. This product has an [α]D −0.06° (*c* 17, H₂O) and gave a plain negative ORD curve (Figure 1).

Optical Rotations. The most useful correlations of configuration, conformation, and optical rotatory power are those based on measurements made in the neighborhood of an absorption band under conditions which give rise to a Cotton effect. Practical applications of semiempirical correlations based on such measurements have been thoroughly reviewed.[25–27] For those chiral molecules which do not have such chromophores and accompanying Cotton effects in the visible and accessible uv regions, the observed optical rotation is the result of residual effect of some (presumably intense) electronically excited state in the vacuum ultraviolet region. Considerable success has been achieved in the interpretation of rotations at the sodium D-line, remote from such absorption maxima, based on empirical correlations,[28] in spite of the fact that our information concerning ORD effects in the vacuum ultraviolet region is meager. Theoretical calculations for the optical rotation of such compounds

(23) R. D. Guthrie, W. Meister, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 5288 (1967). Enantiomerically pure (*R*)-neopentyl-*1-d*-amine [α]²⁵D +0.35° (neat)[3] gives a hydrochloride with opposite rotations [α]²⁵D −0.04° (*c* 30, H₂O).

(24) C. K. Ingold and C. S. Patel, *J. Chem. Soc.*, 67 (1933).

(25) P. Crabbé, "ORD and CD in Chemistry and Biochemistry," Academic Press, New York, N. Y., 1972.

(26) L. Velluz, M. Legraud, and M. Grasjean, "Optical Circular Dichroism," English Translation, Academic Press, New York, N. Y., 1965.

(27) J. A. Shellman, *Accounts Chem. Res.*, 1, 144 (1968).

(28) (a) J. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1958); (b) see also comments by J. Brewster, *Top. Stereochem.*, 1, 33 (1967).
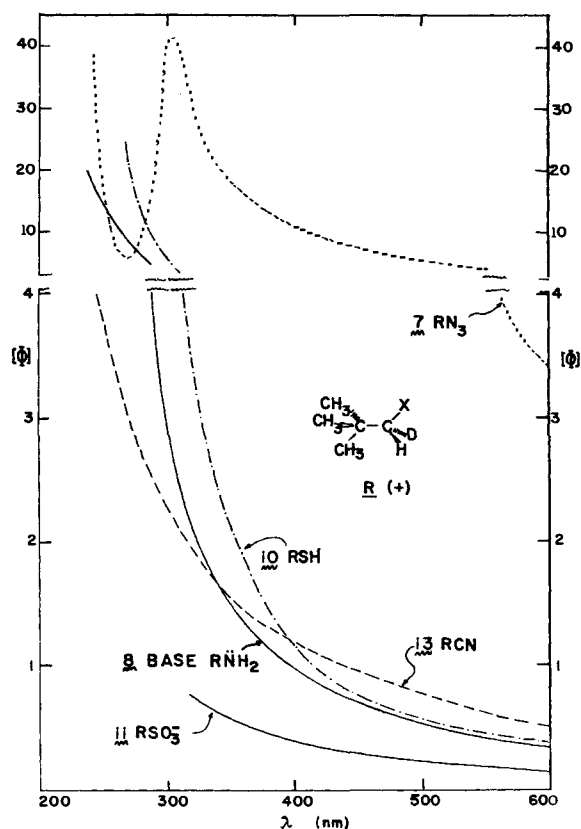
Figure 2.

are in an early stage of development.[4,29] Calculations based on first-order perturbations of perfect tetrahedral structures predict zero rotation for all compounds of the symmetry types considered here.[30,31] Calculations by Applequist, et al.,[4] based on the atom polarizability mechanism of Boys[31] show that third- and fourth-order terms are very important. However, such calculations still do not correctly correlate the sign of rotation and absolute configuration of α-bromopropionitrile.[4] Although the consideration of theoretical approaches to the optical rotation of such chiral compounds of simplified symmetry is beyond our competence, we feel that the data presented here on these neopentyl-1-d compounds may be of considerable value to those persons interested in this problem.

The ORD curves for the configurationally related (R)-neopentyl-1-d compounds[32] are compared in Figures 1 and 2. The following empirical generalizations are evident. (a) All (R)-neopentyl-1-d halogen compounds (1a, X = F, Cl, Br, I) have a plain negative ORD curve. The intensities of the rotations at any specified wavelength above 300 nm are in the order R*I > R*Cl > R*F > R*Br (Figure 1). With the

(29) For a review of the state of such theoretical calculations, see D. J. Caldwell and Henry Eyring, "The Theory of Optical Activity," Wiley-Interscience, New York, N. Y., 1971.

(30) J. G. Kirkwood, J. Chem. Phys., 5, 479 (1937).

(31) S. F. Boys, Proc. Roy. Soc., Ser. A, 144, 655 (1934).

(32) (S)-2,2-Dimethylbutane-3-d (S-12) is considered to be configurationally related to the other (R)-neopentyl-1-d compounds in this study. This is a consequence of the sequence rules of the RS nomenclature scheme; X in 1a takes precedence over tert-butyl in all cases reported here except in the unique hydrocarbon example 12 where X is methyl.

exception of the bromo compound[33] this is the same order as the decreasing atomic polarizabilities of X.[28] (b) Those neopentyl-1-d compounds where X has both C_{3v} symmetry and no free nonbonding electrons (i.e., X = CH₃ ((S)-12), ⁺NH₃ ((R)-8), and ⁺NMe₃ ((R)-9)) show a plain negative ORD curve but at the same time exhibit a generally lower optical rotation than the halogen analogs (Figure 2). Their ORD curves approximate that for (R)-(−)-neopentyl-1-d alcohol.[35,36] (c) Five of the (R)-neopentyl-1-d compounds have positive ORD curves; i.e., (R)-13 (X = CN), (R)-7 (X = N₃), (R)-10 (X = SH), (R)-11, (X = SO₃⁻), and the free amine (X = NH₂). Note that in all of these cases the substituent is known to give rise to Cotton effects in systems where the chirality is due to groups other than hydrogen vs. deuterium.[25] Also observe that the ORD curve for (R)-neopentyl-1-d-amine is plain positive while that for the ammonium salt (X = ⁺NH₃) is negative.

(R)-(−)-2-Iodobutane, -pentane, and -octane[34] show small negative Cotton effects associated with the n–σ* transition of the halogen near 250 nm. However, we were unable to detect any ORD or CD Cotton effect in the 250-nm region for (R)-(−)-neopentyl-1-d iodide. Thus, unlike the corresponding azide, the difference between hydrogen and deuterium does not appear to be sufficient to cause a significant dissymmetric perturbation of the inherently symmetrical iodo chromophore.

The neopentyl-1-d halogen compounds which constitute near perfect examples for application of Brewster's atomic asymmetry rule[28] do indeed conform to the prediction based on the logical assumption that the central carbon atom of the tert-butyl group has a polarizability less than chlorine but greater than hydrogen and that hydrogen is more polarizable than deuterium. The example of (R)-(+)-2,2-dimethylbutane-3-d can be made to conform to Brewster's atomic asymmetry rule[28] by assuming that the central carbon atom of the tert-butyl group is less polarizable than that of the methyl group. This would appear to

(33) This reinforces our reservation concerning the enantiomeric purity of our neopentyl-1-d bromide preparation. Note that a projection of the lower wavelength end of the ORD curve for the bromo compound will cause it to intercept and cross over the curve for the fluoro compound at about 275 nm and very probably that of the chloro compound as well. This is the expected behavior if the neopentyl-1-d bromide is 25–50% enantiomerically pure. The optical rotations of the 2-halobutanes, -pentanes, and -octanes have been compared;[34] although their molecular rotations do not differ widely, they are in the order of R*Cl > R*Br > R*I at 589 nm but in the order of R*I > R*Br > R*Cl at 300 nm.

(34) B. A. Chaudri, D. G. Goodwin, H. R. Hudson, L. Bartlett, and P. M. Scopes, J. Chem. Soc. C, 1329 (1970).

(35) (S)-Neopentyl-1-d alcohol is crystalline (mp 53°) and its rotation therefore has not been taken neat. We previously reported its rotation in 80% acetone solution to be zero within experimental limits down to 300 nm; however, in hexane solution the S enantiomer shows a low-intensity, plain, positive ORD curve and thus should properly be designated (S)-(+)-neopentyl-1-d alcohol. (The mirror image negative curve for the R-(−) enantiomer is shown in Figure 1.) Brewster's atomic asymmetry rules[8] predict that (S)-neopentyl-1-d alcohol should be levorotatory, in accord with (S)-(−)-ethanol-1-d [J. Brewster, Tetrahedron Lett., 23 (1957)]. Since the order of group polarizabilities is not reversed by substituting tert-butyl for methyl, Brewster's rules do not apply here. This analysis is based on atomic refractivities, R_D, for hydrogen and deuterium of 1.028 and 1.004: C. K. Ingold, C. G. Raisin, and C. L. Wilson, J. Chem. Soc., 915 (1936).

(36) Neopentyl-1-d alcohol, thiol, amine, and azide do not belong to the same symmetry type as the neopentyl-1-d halides since in each the X substituent, OH, SH, NH₂, and N₃, is not colinear with the carbon–X bond. Thus the azide group, though linear itself with $C_{∞v}$ symmetry, is attached to carbon in alkyl azides at an angle of approximately 135°.

be illogical[37a] but has been previously proposed to rationalize the rotation and configuration of 1-methyl-3-*tert*-butylallene[37b] by an application of Lowe's rules.[37c,d] Furthermore, the same assumption is also used to reconcile the known (S)-(+) configurations of methyl-*tert*-butylmethanol[38] and the analogous amine[39,40] with Brewster's rules.[28] However, the D-line sign of rotation of the nitrile **13**, the mercaptide **10** and the free amine of **8** cannot be reconciled with Brewster's rule in any simple, consistent fashion. Since thiols are known to have several CD maxima which reverse themselves in the 200–250-nm region,[41] this result for **10** is not unexpected.

The only compound in this series for which we observed a Cotton effect was the (R)-(+)-azide **7**: ORD $[\phi]^{20}_{305}$ +41°, trough $[\phi]_{270}$ +5°; CD $[\theta]^{20}_{288}$ +30. The intensity of this Cotton effect is substantial considering that the chirality is due solely to hydrogen *vs.* deuterium substitution. In methylcyclohexane–isopentane 1:4 glass at 77°K the wavelength of this peak was unchanged and the intensity was slightly increased[42] ($[\theta]^{-196}_{288}$ +38). It is likely that the sharply rising ORD curve observed for (R)-(+)-neopentyl-*1-d* azide below 250 nm is a result of a second more intense Cotton effect due to the azide absorption in the neighborhood of 215 nm (ϵ *ca.* 500, $\sigma \rightarrow \pi^*$ transition).[43]

The Cotton effect associated with the long wavelength uv absorption band of azides in the neighborhood of 280 nm (ϵ *ca.* 25, $n_{N_1} \rightarrow \pi_{N_1N_2}$ transition where N_1 represents the nitrogen attached to carbon) has been made the basis for an azide octant rule[44] analogous to the ketone octant rule.[45] Application of this azide octant rule to (R)-(+)-neopentyl-*1-d* azide, assuming the most stable conformation shown in **14**, reveals that deuterium falls in the positive and hydrogen in the negative quadrant (**15**) while the methyl groups cancel each other. Since the configuration is known to be R and the Cotton effect positive, we must conclude that the deuterium, not hydrogen, acts as the Cotton effect determining group (assuming the conformation shown in **14** and the applicability of this rule to such conformationally mobile compounds).

(37) (a) Whether to consider the polarizability of the atom attached to the chiral center or to consider the polarizability of the group as a whole has been considered by Brewster.[28] In essence this was resolved empirically by considering the rotation of compounds of known configuration. It was concluded that, with the exception of unsaturated groups, the polarizability of the attached atom was a useful and satisfactory criterion for the assignment of substituent rank (see ref 28, notes 11–15). A first-order atomic polarizability model of a compound leaving two alkyl groups with C_{3v} symmetry attached to a chiral center will predict zero optical rotation. The fact that methyl-*tert*-butylmethanol, methyl-*tert*-butylcarbinylamine, and methyl-*tert*-butyl-deuteriomethane clearly show optical activity emphasizes the limitations of the concept which predicts optical rotation based only on the polarizability of the atoms attached to the chiral center. (b) E. L. Eliel, *Tetrahedron Lett.*, No. 8, 16 (1960). (c) J. H. Brewster, *Top. Stereochem.* 2, 1 (1967); *cf.* especially p 36. (d) G. Lowe, *Chem. Commun.*, 411 (1965).

(38) J. Jacobus, Z. Majerski, K. Mislow, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 1998 (1969).

(39) H. Pracejus and S. Winter, *Chem. Ber.*, **97**, 3173 (1964).

(40) W. Meister, R. D. Guthrie, J. L. Maxwell, D. A. Jaeger, and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 4455 (1969).
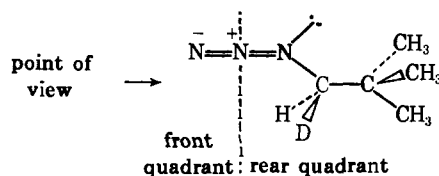
(41) P. Salvadori, *Chem. Commun.*, 1203 (1968).

(42) We are greatly indebted to Dr. Günther Barth for this low temperature determination.
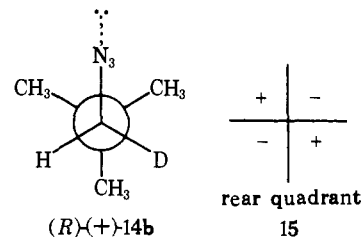
(43) W. D. Clossen and H. B. Gray, *J. Amer. Chem. Soc.*, **85**, 290 (1963).

(44) C. Djerassi, A. Moscowitz, K. Ponsold, and G. Steiner, *J. Amer. Chem. Soc.*, **89**, 347 (1967).

(45) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(R)-(+)-14a

(R)-(+)-14b   rear quadrant
                              15

Since the atomic polarizability of hydrogen is greater than deuterium we would have predicted the reverse.[46]

It seems likely that the ORD data on these compounds will not be satisfactorily resolved until far-ultraviolet CD data become available.

Experimental Section

General. The hexamethylphosphoramide (HMPA) was distilled under vacuum from calcium hydride; other solvents were commercial reagent grade. The routine nmr spectra were determined on either a Varian A-60 or T-60 instrument and the quantitative nmr on a Varian HR-100 instrument, the mass spectra on an Atlas AEI MS-9 spectrometer, the ir spectra on either a Perkin-Elmer 237B or 457 spectrometer and the uv spectra on a Cary 14 spectrometer. Optical rotations were determined on a Perkin-Elmer 141 electronic polarimeter, which reads to 0.001°, using a fixed window, 1-dm, 1-ml capacity, water-jacketed cell; ORD–CD measurements were made on a JASCO ORD/UV-5 spectrometer For the purpose of specific rotations,[47] the densities of the deuterium-containing compounds were calculated from the known densities of the isotopically normal neopentyl compounds[48] using the method of McLean and Adams.[49] Microanalyses were performed in the Stanford microanalytical laboratories. Exploratory runs on nondeuterated neopentyl tosylate were conducted in each case but these experiments are not described. The purity of all volatile neopentyl-*1-d* compounds was checked by gas chromatography.

(S)-Neopentyl-*1-d* Tosylate (3). The chiral (S)-neopentyl-*1-d* tosylate[3,9] was made from (S)-neopentyl-*1-d* alcohol obtained by fermentative reduction.[14] All of the tosylate in the present work was purified in one batch and had 0.910 deuterium atom per molecule as determined by combustion[50] and confirmed by nmr integration of the tosylate and the alcohol from which the tosylate was prepared.

(R)-(−)-Neopentyl-*1-d* Bromide (4). (S)-Neopentyl-*1-d* tosylate (9.75 g, 40 mmol) and anhydrous lithium bromide (3.47 g, 40 mmol) in HMPA (50 ml) were *vigorously* stirred at 110–115° under vacuum (25 mm) for 17 hr and the volatile products were collected as formed in a trap cooled by liquid nitrogen. The product was transferred under high vacuum to a second trap which could be stoppered and centrifuged. The lower layer contained 4.92 g of a colorless liquid (82%): nmr (CDCl₃) δ 1.05 (s, 9 H) and 3.27 ppm (unsym t, *ca.* 1 H); α^{20}D −0.163 ± 0.004° (*l* 1, neat), $[\alpha]^{20}$D

(46) We are indebted to Dr. A. Moscowitz for discussions on this question. He has pointed out that this is a naive viewpoint but that this observation should be extended to other examples and studied further here and in related chiral and deuterio azides.

(47) The specific rotations were corrected to a deuterium content of one atom of deuterium per molecule based on the known 0.91 deuterium atom per molecule of the neopentyl-*1-d* tosylate used as starting material in all syntheses reported in this paper.

(48) F. Whitmore, E. Wittle, and B. Harrison, *J. Amer. Chem. Soc.*, **61**, 1585 (1939).

(49) A. McLean and R. Adams, *J. Amer. Chem. Soc.*, **58**, 804 (1936).

(50) Deuterium analysis according to water density method by Josef Nemeth, Urbana, Ill.

−0.148 ± 0.004° (neat, corrected, and based on a value of d^{20} = 1.199 for the nondeuterated compound[49]). The previously reported[2,3] value was $[\alpha]^{23}$D −0.124 ± 0.006° (neat, corrected[47]).

(R)-(−)-Neopentyl-1-d Fluoride (6). (S)-Neopentyl-1-d tosylate[3] (3, 4.88 g, 20 mmol) and anhydrous tetramethylammonium fluoride (2.1 g, 22 mmol) in HMPA (50 ml) were heated with stirring under vacuum (95–105° (25 mm), 66 hr). The product was collected as formed in a liquid nitrogen cooled trap to give a colorless liquid, 1.29 g (80% yield corrected for unreacted tosylate): α^{20}D −0.213 ± 0.003° (l 1, neat), $[\alpha]^{20}$D −0.297 ± 0.004°, $[\alpha]^{20}_{546}$ −0.361 ± 0.005°, $[\alpha]^{20}_{436}$ −0.635 ± 0.008°, $[\alpha]^{20}_{365}$ −0.975 ± 0.008° (neat, corrected and based on a value of d^{20} = 0.78 for the nondeuterated compound[51]); ir (neat) 1020 cm⁻¹ (C–F); nmr (CDCl₃) δ 0.97 (s, 9 H, t-Bu), 4.07 ppm (d of t; ca. 1 H, $J_{H–F}$ = 48.5 Hz, CHDF); mass spectrum (H compound from identical experiment using nondeuterated tosylate, 70 eV) m/e (rel intensity) 90 (0.2), 75 (42), 57 (100), 55 (47), 47 (39), 41 (46), 39 (20), 29 (45), 27 (18). This compound was too volatile (bp 760 ca. 40°) for accurate conventional analysis but the following approximate result was obtained.

Anal. Calcd for C₅H₁₁F: C, 66.6; H, 12.3. Found: C, 65.6; H, 12.1.

(R)-(+)-2,2-Dimethylbutane-3-d (12). Cuprous iodide[52] (9.44 g, 49.5 mmol) was added to methyllithium (70 ml, 1.4 N in ether, 98 mmol) at 0°. Dry diglyme (40 ml) was added and the ether was removed under vacuum into a liquid nitrogen cooled trap. HMPA (50 ml) was added to the mixture and the removal of ether was continued for 1 hr. The system was returned to 1 atm with nitrogen and cooled to 0°, and a solution of the above (R)-(−)-neopentyl-1-d bromide (4.56 g, 30 mmol) in HMPA (15 ml) was added. After the mixture was stirred (0° for 1.5 hr, then room temperature overnight), volatile material was collected under vacuum in a liquid nitrogen cooled trap. The product was transferred under vacuum to a second trap and then purified by glc (β,β-oxydipropionitrile column, 0.25 in. × 6 ft, 30°, He flow 40 ml/min) to give 1.60 g (64% based on unreacted bromide) of a colorless liquid: $[\alpha]^{20}$D +0.087 ± 0.007°, $[\alpha]^{20}_{546}$ +0.094 ± 0.007°, $[\alpha]^{20}_{436}$ +0.190 ± 0.007, $[\alpha]^{20}_{365}$ +0.35 ± 0.01° (neat, corrected,[47,49] based on d^{20} = 0.6485 for the nondeuterated neohexane); nmr (CDCl₃) δ 1.02 (s, 12 H, t-Bu and CH₃) and 1.17 ppm (complex m, ca. 1 H, –CHD–); mass spectrum (70 eV) m/e (rel intensity) 87 (0.001), 86 (0.02), 85 (0.001), 73 (6), 72 (77), 71 (15), 57 (100), 56 (42), 44 (57), 43 (56), 42 (14), 41 (54), 39 (18), 30 (9), 29 (32), 27 (18).

(R)-Neopentyl-1-d Azide (7) and -amine (8). The azide was prepared as previously described[3] (from 10.0 g of (R)-neopentyl-1-d tosylate, 91.0% deuteration, 5 g of NaN₃, and 50 ml of HMPA) except that the reaction mixture was heated at 105° for 2 hr at 30 mm pressure so that the product was distilled as formed and collected in a trap at −78°. The product containing some HMPA was washed (saturated NaCl, three times without solvent) and distilled, 3.60 g (77% yield), bp 105–107° (760 mm). Additional azide, 0.58 g, was recovered by ether extraction of the aqueous washes. The distilled material gave the following rotations corrected for the 91.0% deuterium content and using a density of d^{20}_4 = 0.860, $[\alpha]^{20}_\lambda$ (neat): 589, +3.12°; 578, +3.26°; 546, +3.76°; 436, +5.86°. These values are slightly lower than those found in cyclohexane solution reported in Figure 2.

This procedure was duplicated except that all of the azide was isolated by ether extraction and reduced directly, without distillation, with LiAlH₄ (1.9 g) to give the hydrochloride, 4.5 g, as previously described.[9] The free amine (liberated from 2.43 g of the hydrochloride with saturated KOH solution without benefit of solvent) was dried (KOH pellets) and distilled: bp 74–80° (760 mm), 0.96 g (66% yield). The rotation of the neat amine (which had no detectable impurities by glc) after correcting for 91% deuteriation and using a density of d^{20}_4 = 0.745 was $[\alpha]^{20}_\lambda$ (neat): 589, +0.277°; 578, +0.289°; 546, +0.332°; 436, +0.635°; 365, +1.215°. The solution rotation after correction for 91% deuteriation was $[\alpha]^{20}_\lambda$ (c 16, cyclohexane): 589, +0.36°; 578, +0.41°; 546, +0.47°; 436, +0.85°; 365, +1.29°. The ORD curve is given in Figure 2. The rotation of the ammonium salt made from this same amine by dissolving 0.2060 g in 1.0 ml of 5 N HCl was $[\alpha]^{20}_\lambda$ (c 29.7 calculated as the hydrochloride): 589, −0.04°; 578, −0.03°;

546, −0.07°; 436, −0.22°; 365, −0.25°. The ORD curve is given in Figure 2.

(R)-(+)-Neopentyl-1-d Thiol (10). (S)-Neopentyl-1-d tosylate (4.88 g, 20 mmol) and sodium hydrogen sulfide (1.12 g, 20 mmol) in HMPA (30 ml) were stirred with heating under vacuum (100–110° (25 mm), 15 hr). The product was collected as formed in a liquid nitrogen cooled trap. High vacuum transfer to a second liquid nitrogen cooled trap. High vacuum transfer to a second trap gave 1.59 g (77%) of a colorless liquid, bp 103° (determined by the inverted capillary method) [lit.[20] bp 103°]; α^{20}D +0.276 ± 0.004° (l 1, neat), $[\alpha]^{20}$D +0.345 ± 0.005° (neat, corrected[36] and based on a density for the nondeuterated compound of d^{20} = 0.8298[29]); ir (CCl₄) 2580 cm⁻¹ (SH); nmr (CDCl₃) δ 0.97 (s, 9 H, t-Bu), 1.17 (d of t, 1 H, J = 9 Hz, SH), and 2.40 ppm (d of t, ca. 1 H, J = 9 Hz, –CHD–).

Anal. Calcd for C₅H₂S: C, 57.66; H, 11.61. Found: C, 57.71; H, 11.70.

(R)-(+)-Neopentyl-1-d Sulfonic Acid (11). A solution of (R)-(+)-neopentyl-1-d thiol (0.105 g, 10 mmol) and hydrogen peroxide (1 ml, 30%) in acetic acid (2 ml) was heated (60–65°, 20 hr). The solvent was removed under vacuum and the residue taken up in water, and the process was repeated to remove all acetic acid. The residue was finally stored at 0.1 mm pressure overnight to give 0.145 g (95%) of a colorless oil: ir (CHCl₃) 1167 and 1037 cm⁻¹ (SO₃H); nmr (CDCl₃) 1.17 (s, 9 H, t-Bu), 3.16 (broad, 1 H), and 10.9 ppm (v broad, SO₃H).[21] The ORD curve is recorded in Figure 2. The S-benzylthiouronium salt of the hydrogen compound was prepared, mp 184–186° (lit.[21] 177–178°).

Anal. Calcd for C₁₃H₂₂O₃S₂: C, 49.05; H, 6.97; N, 8.80. Found: C, 49.00; H, 7.05; N, 8.53.

(S)-Neopentyl-1-d Alcohol (2) by Reduction of (S)-Neopentyl-1-d Tosylate (3). A solution of (S)-neopentyl-1-d tosylate (4.88 g, 20 mmol, 0.91 deuterium atom per molecule) in anhydrous ether (15 ml) was added slowly (0.5 hr) to a solution of sodium (2.8 g, 120 mmol) in liquid ammonia (50 ml). This mixture was stirred for an additional 0.5 hr at which time solid ammonium chloride was added until the mixture turned light yellow. Ether and water were then added and the ammonia was allowed to evaporate. The ether extracts of the aqueous layer and the original ether layer were combined, dried (MgSO₄), and concentrated at room temperature under vacuum (ca. 20 mm) to about 10 ml. This was vacuum distilled to leave a residue and give a distillate which was purified by preparative glc (SF-96, 0.25 in. × 6 ft, TMOS treated Chromosorb W column, 30°; He flow 40 ml/min) to give 0.94 g (53%) of (S)-neopentyl-1-d alcohol, acid phthalate $[\alpha]^{20}$D −1.05° (c 12, acetone, uncorrected for deuterium content). This establishes that there has been no racemization during the formation of the tosylate, 3. Preparative glc also yielded 0.18 g (10%) of toluene. In addition, extraction of the basic aqueous solution with ether gave p-tolyl disulfide in undetermined yield: mp 43–45° (sublimed, 0.1 mm, 70°) (lit.[53] mp 45–46°); nmr (CDCl₃) δ 2.32 (s, 6 H, ArCH), 7.12 (B of A₂B₂ system, J_{AB} = 8.5 Hz, 4 H, ArH).

(R)-(−)-N,N,N-Trimethylneopentyl-1-d-ammonium Iodide (9). (R)-(−)-Neopentyl-1-d-amine hydrochloride[9] (8, 0.45 g, 3.6 mmol), paraformaldehyde (2.0 g), and water (0.5 ml) were refluxed together (18 hr). The resulting mixture was cooled, neutralized (50% KOH), and extracted with ether. The ether solution was dried (Na₂SO₄), filtered, and allowed to stand with a large excess of methyl iodide (3 hr, 20°; 48 hr, 5°). The precipitate which formed was collected by filtration and additional solid was obtained by refluxing the filtrate in the dark for 5 days with more methyl iodide followed by filtration in the cold. Tetramethylammonium iodide, a minor by-product, was not soluble when the desired product 9 was dissolved in 95% ethanol. The ethanol solution was evaporated and the residue (0.50 g) crystallized from isopropyl alcohol: mp 288° dec (lit.[24] 240° dec); nmr (D₂O, sodium 3-(trimethylsilyl)perdeuteriopropionate as internal reference) δ 1.22 (s, 9 H, t-Bu), 3.25 (s, 9 H, NMe₃), and 3.35 ppm (broad, ca. 1 H); $[\alpha]^{20}$D −0.06° (c 17, H₂O). The ORD curve is given in Figure 1.

Anal. Calcd (for H compound) C₈H₂₀NI: C, 37.35; H, 7.84; N, 5.45. Found: C, 37.10; H, 7.63; N, 5.42.

(R)-(−)-Neopentyl-1-d Iodide (5). (S)-Neopentyl-1-d alcohol (0.88 g, 9.9 mmol) and methyltriphenoxyphosphonium iodide[18] (4.52 g, 10 mmol) were vigorously stirred in HMPA (25 ml) at room temperature and pressure for 45 min and then at 100–115° under vacuum (25 mm) for 17 hr. The product, which was collected as it formed in a liquid nitrogen cooled trap, was washed with water, separated by centrifugation, and dried (Na₂SO₄) to give 1.30 g (66%) of a colorless liquid: bp 132–133° (lit.[16] bp (for nondeu-

(51) API 44-TRC, Selected Values of Properties of Chemical Compounds, Thermodynamic Research Center Project, Thermodynamic Research Center, Department of Chemistry, Texas A and M University, College Station, Texas: (a) TRC [A] 23-9-2-(1.013)a; (b) TRC [A] 23-14-2-(1.1020)a; (c) TRC [A]23-12-21-(1.013)a.

(52) G. B. Kaufmann and L. A. Teter, Inorg. Syn., 7, 9 (1963).

(53) W. E. Truce and B. Groten, J. Org. Chem., 27, 128 (1962).

terated compound) 134°) α^{20}D $-0.385 \pm 0.004°$ (*l* 1, neat), $[\alpha]^{20}$D $-0.282 \pm 0.003°$ (neat, corrected,[47] based on $d^{20} = 1.494$ for the nondeuterated compound[49]); uv max (cyclohexane) 254 nm (ϵ 600); nmr (CDCl$_3$) δ 1.08 (s, 9 H, *t*-Bu) and 3.16 ppm (m, *ca.* 1 H, –C*H*D–), corresponding to previous reported values for the racemic compound.[16,17]

Solvolytic Studies of Unsaturated 11-Hydroxymethylbicyclo[4.4.1]undecane 3,5-Dinitrobenzoates. Valence Isomerization Leading to Conformationally Distinguishable Annulated Norcaradienylcarbinyl Cations and the Question of Remote pπ Stabilization of Such σ-Delocalized Systems

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Abstract: Evidence is presented that *syn-* and *anti-*11-hydroxymethylbicyclo[4.4.1]undeca-1,3,5-triene 3,5-dinitrobenzoates undergo solvolysis *via* initial valence isomerization to the epimeric tricyclic norcaradienyl forms. The rates of solvolysis have been compared with those of 11-hydroxymethyl[4.4.1]propella-3,8-diene and 11-hydroxymethyl[4.4.1]propellane 3,5-dinitrobenzoates which contain preformed cyclopropylcarbinyl systems. The "aromatic" 1,6-methanocyclodecapentaene analog was also examined. The products of ionization have been isolated and compared throughout the series. In all cases but the cyclodecapentaene derivative, the formation of bicyclic vinyl alcohols and hydrocarbons is most prevalent signifying that these intermediate cyclopropylcarbinyl cations suffer largely ring opening. The spread of solvolytic rate constants throughout the series is quite small and attempts to dissect these rate constants into their preequilibrium and ionization components are described. Deuterium labeling studies have established that no isotopic scrambling accompanies departure of the 3,5-dinitrobenzoate group.

Sargent's study of the solvolytic behavior of 7-cyclohepta-1,3,5-trienylcarbinyl 3,5-dinitrobenzoate (1) was the first which demonstrated that in certain judiciously chosen molecules ionization can be preceded and perhaps even initiated by valence isomerization.[2] Discovery of its clean, unimolecular hydrolysis to unrearranged alcohol (73%, stable to the reaction conditions) and styrene led to the postulate that 1 solvolyzes with extensive cyclopropyl participation from its norcaradiene valence tautomer.[3–5] Evidence for the intervention of such an intermediate was further deduced from the rate constant which, when appropriately corrected for the preequilibrium, was found to be 100-fold greater than any other reported value for a similarly substituted cyclopropylcarbinyl system. This

highly enhanced reactivity was accounted for in terms of a σ-delocalized ion in which partial double bond character had developed between the carbon atoms β to the site of C–O bond heterolysis resulting in an aromatic-like transition state.

Conformational analysis studies of cycloheptatriene have provided evidence that rapid interconversion between a pair of boat conformations separated by an inversion barrier of *ca.* 6 kcal/mol does operate.[6,7] For 7-substituted cycloheptatrienes, this conformational ring flipping comprises a nondegenerate process, *e.g.*, **1a** ⇌ **1b**, which for most,[8] but not all,[9] derivatives lies in favor of equatorial positioning of the attached group as in **1a**.[10] Since each of these conformers is in turn

(1) Phillips Petroleum Fellow, 1970–1971; University Dissertation Fellow, 1971–1972.

(2) G. D. Sargent, N. Lowry, and S. D. Reich, *J. Amer. Chem. Soc.,* **89,** 5985 (1967).

(3) The intermediacy of cycloheptatrienylcarbinyl cations had been invoked in a number of earlier reactions.[4] The first suggestion of possible valence isomerization to a norcaradienylcarbinyl cation seems to have been advanced by Bonner.[4d]

(4) (a) A. C. Cope, N. A. Nelson, and D. S. Smith, *J. Amer. Chem. Soc.,* **76,** 1100 (1954); (b) C. R. Ganellin and R. Pettit, *J. Chem. Soc.,* 576 (1958), and relevant references cited therein; (c) W. von E. Doering, private communication reported in ref 4b; (d) W. A. Bonner, E. K. Raunio, and D. M. Bowen, *J. Org. Chem.,* **31,** 912 (1966).

(5) More recent studies of 7-cyclohepta-1,3,5-trienylcarbinyl cations include: (a) J. Daub and W. Betz, *Tetrahedron Lett.,* 3451 (1972); (b) S. Kohen and S. J. Weininger, *ibid.,* 4403 (1972).

(6) (a) F. A. L. Anet, *J. Amer. Chem. Soc.,* **86,** 458 (1964); (b) F. R. Jensen and L. A. Smith, *ibid.,* **86,** 956 (1964).

(7) This subject and the cycloheptatriene–norcaradiene equilibrium problem have recently been reviewed: G. Maier, *Angew. Chem., Int. Ed. Engl.,* **6,** 402 (1966); W. Tochtermann, *Fortschr. Chem. Forsch.,* **15,** 378 (1970).

(8) (a) H. Günther, M. Gorlitz, and H. H. Hinrichs, *Tetrahedron,* **24,** 5665 (1968); (b) H. Kessler and E. Muller, *Z. Naturforsch. B,* **22,** 283 (1967); (c) R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.,* **88,** 3527 (1966); (d) A. P. ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas,* **82,** 741 (1963).

(9) W. E. Heyd and C. A. Cupas, *J. Amer. Chem. Soc.,* **91,** 1559 (1969); **93,** 6086 (1971).

(10) A number of 7,7-disubstituted cycloheptatrienes have also been examined. See, for example (a) H. J. Reich, E. Ciganek, and J. D. Roberts, *J. Amer. Chem. Soc.,* **92,** 5166 (1970); (b) J. B. Lambert, L. J. Durham, P. Lepoutere, and J. D. Roberts, *ibid.,* **87,** 3896 (1965); (c) K. Conrow, M. E. Howden, and D. Davis, *ibid.,* **85,** 1929 (1963).