amino nitrogen atom is in the trans position across the C^{α}-C^{β} bond from the near sulfur atom. The maximum at 672 cm^{-1} is somewhat more intense, implying more of the first conformation in BSA, but this statement has only qualitative significance under the present circumstances.

Spectrum of Lyophilized Powder BSA. Using the same sample as that of the present study Mendelsohn[24] had earlier obtained the Raman spectrum of the lyophilized powder. This spectrum shows more COOH (1732 cm^{-1}) and less CO_2^- (1415 cm^{-1}) than the aqueous solution at pH 6. In addition, the amide I and amide III lines suggest some decrease in the α-helical content: the former is broader and shifted upward (to 1660 cm^{-1}) and the latter shows more intensity in the neighborhood of 1245 cm^{-1} and less at 1280 cm^{-1}. Other differences include a substantial decrease in the band at 941 cm^{-1} and a slight alteration in the intensity ratio of the tyrosine doublet (to 10:9). All of the observed changes are consistent with some denaturation in the process of lyophilization, a result also observed by Yu et al.[25] for ribonuclease and other proteins.

Conclusions

The presence of a large amount (about 60%) of helical structure in native BSA, previously found by several different techniques, is confirmed by its Raman spectrum. The remainder of the polypeptide backbone was determined to have random-coil conformation and no indication of β-pleated-sheet conformation was observed. The tyrosyl residues are weakly hydrogen bonded, regardless of whether they are "buried" or "exposed" as determined by other methods. The disulfide bridges vary in conformation to a limited extent but not enough to alter their adjacent carbon chains from the gauche,gauche,gauche conformation.

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References and Notes

(1) W. H. Stein and S. Moore, *J. Biol. Chem.*, **178**, 88 (1949).
(2) M. O. Dayhoff in "Atlas of Protein Sequence and Structure", Vol. 5, National Biomedical Research Foundation, Silver Spring, Md., 1972, p D315, and the references cited therein.
(3) (a) K. M. Parker, Ph.D. Thesis, The University of Texas, Austin, Texas, 1972; (b) *Diss. Abstr. Int. B*, **34**, 573 (1973).
(4) P. Urnes and P. Doty, *Adv. Protein Chem.*, **16**, 401 (1961).
(5) E. Shechter and E. R. Blout, *Proc. Natl. Acad. Sci. U.S.A.*, **51**, 695 (1964).
(6) S. N. Timasheff, H. Susi, R. Townend, L. Stevens, M. J. Gorbunoff, and T. F. Kumosinski, *Conform. Biopolym., Pap. Int. Symp., 1967*, **1**, 173 (1967).
(7) A. M. Bellocq, R. C. Lord, and R. Mendelsohn, *Biochem. Biophys. Acta*, **257**, 280 (1972).
(8) M. C. Chen and R. C. Lord, *J. Am. Chem. Soc.*, **96**, 4750 (1974).
(9) B. G. Frushour and J. L. Koenig, *Biopolymers*, **13**, 455 (1974).
(10) T. J. Yu, J. L. Lippert, and W. L. Peticolas, *Biopolymers*, **12**, 2161 (1973).
(11) N. T. Yu, B. H. Jo, and D. C. O'Shea, *Arch. Biochem. Biophys.*, **156**, 171 (1973).
(12) M. N. Siamwiza, R. C. Lord, M. C. Chen, T. Takamatsu, I. Harada, H. Matsuura, and T. Shimanouchi, *Biochemistry*, **14**, 4870 (1975).
(13) T. T. Herskovits and M. Laskowski, Jr., *J. Biol. Chem.*, **237**, 2481 (1962).
(14) J. F. Riodan, W. E. C. Wacker, and B. L. Vallee, *Biochemistry*, **4**, 1758 (1965).
(15) M. Sokolovsky, J. F. Riodan, and B. L. Vallee, *Biochemistry*, **5**, 3582 (1966).
(16) M. J. Gorbunoff, *Arch. Biochem. Biophys.*, **138**, 684 (1970).
(17) R. C. Lord and N. T. Yu, *J. Mol. Biol.*, **50**, 509 (1970).
(18) H. E. Van Wart, A. Lewis, H. A. Scheraga, and F. D. Seava, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2619 (1973).
(19) E. J. Bastian, Jr., and R. B. Martin, *J. Phys. Chem.*, **77**, 1129 (1973).
(20) R. B. Martin, *J. Phys. Chem.*, **78**, 855 (1974).
(21) H. Sugeta, A. Go, and T. Miyazawa, *Chem. Lett.*, 83 (1972).
(22) H. Sugeta, A. Go, and T. Miyazawa, *Bull. Chem. Soc. Jpn.*, **46**, 3407 (1973).
(23) T. Miyazawa and H. Sugeta, U.S.-Japan Joint Seminar, "The Raman Spectroscopy of Biological Molecules", Cleveland, Ohio, 1974.
(24) R. Mendelsohn, Ph.D. Thesis, Massachusetts Institute of Technology, 1972.
(25) N. T. Yu, B. H. Jo, and C. S. Liu, *J. Am. Chem. Soc.*, **94**, 7572 (1972).

The Secondary β-Deuterium Isotope Effect in the Formation of Ethyl Radical from Decomposition of Methylethylethyl-*2,2,2-d_3*-carbinyloxy Radical[1a]

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Abstract: The intramolecular secondary β-deuterium isotope effect in the decomposition of methylethylethyl-*2,2,2-d_3*-carbinyloxy radical to methyl ethyl ketone and ethyl radical is $k_{H_3}/k_{D_3} = 1.25$ and is relatively temperature independent between 0 and 80 °C. The comparison of the observed effect with previous theoretical predictions is discussed as well as the predicted temperature dependence.

Several years ago we reported the secondary β-deuterium kinetic isotope effect in the formation of α-phenylethyl-β,β,β-d_3 radical from the concerted decomposition of azobis-α-phenylethane-β,β,β-d_3.[2] The isotope effect, 1.017 per deuterium, is in good agreement with that ($k_H/k_D = 1.02$) found in the concerted decomposition of *tert*-butyl perhydratropate which was reported by Koenig and Brewer while our previous work was in progress.[3] These studies were carried out to gain insight into the role of hyperconjugation in the stabilization of radicals. Subsequently, the β effects in the formation of *tert*-butyl radical from the concerted decomposition of *tert*-butyl perpivalate ($k_H/k_D = 1.02$ per D),[4a] the cumyl radical from *tert*-butyl dimethylphenylperacetate ($k_H/k_D = 1.02$ per D),[4b] the isopropyl radical from *tert*-butylperoxy isobutyrate (k_H/k_D = 1.025 per D),[4c] and the 2-methyl-2-propionitrile radical (k_H/k_D = 1.02 per D) from the decomposition of AIBN[5] have also been reported.

The unique feature of these results is that the secondary β-deuterium effects are so small in these radical forming reactions while they are of considerable magnitude in solvolytic reactions of simple substituted alkanes. Three of the four systems cited above can stabilize the free spin by p_z–π interaction and thus have low requirement for hyperconjugative stabilization. While hyperconjugative stabilization might be expected to be important in the stabilization of *tert*-butyl radical, that part of the free-spin density would be delocalized over nine β hydrogens. Consequently, the β effect per D might be expected to be small.

It was of interest to measure the β secondary effect where hyperconjugative stabilization of the free spin would be expected to be large and other stabilizing interactions would be absent. We therefore have measured the β effect in the formation of ethyl-β,β,β-d_3 radical with the expectation that the largest kinetic β effect for a radical would be found in this system. Moreover, quantum-mechanical calculations coupled with exact calculations to predict the magnitude of β effects have been reported,[6,7] and it was of interest to test these calculations.

Experimental Section

3-Methyl-3-pentanol was obtained from Aldrich Chemical Co. and was purified by preparative GLC (Varian 712) on a 50 ft × ⅜ in. column of 20% SE 30 on 30/60 preparative grade Chromosorb, W A/W DMCS. Nitrogen served as the carrier gas at a flow rate of 150 ml/min, and the column was maintained at 110 °C. The material collected from several injections was distilled at 121 °C at atmospheric pressure and analyzed by GLC. It was shown not to contain any of the original peaks. The collected material amounted to 65% of the original carbinol.

Methyldiethylcarbinyl Hypochlorite. Chlorine monoxide was prepared in carbon tetrachloride solution by procedure A as described previously.[8] It was extracted with water, and the resulting hypochlorous acid solution (1.35 M) was washed once with carbon tetrachloride before storing in the refrigerator.

Methyldiethylcarbinyl hypochlorite was prepared by a previously published method.[9] The corresponding purified alcohol (25 mmol) was dissolved in 25 ml of carbon tetrachloride. The solution was cooled in an ice bath, and 50 mmol of hypochlorous acid solution were added. The mixture was stirred at 0 °C in the dark for 30 min and then at ambient temperature for 3 h. The carbon tetrachloride layer was separated and washed with 5% aqueous sodium carbonate and 25 ml of water. The organic layer was dried over anhydrous magnesium sulfate for 12 h and then filtered. Iodometric titration indicated that the solution was 1.01 M in hypochlorite.

3-Methyl-3-pentan-*1,1,1*-d_3-ol was prepared by the addition of ethyl-*2,2,2*-d_3 magnesium bromide to ethyl methyl ketone.

A solution of 100 g of acetic acid-d_4 (99.5% minimum isotopic purity, Merck) dissolved in a 100 ml of diethyleneglycol diethyl ether (DEC) was added dropwise to a stirred mixture of 60 g of lithium aluminum hydride suspended in 700 ml of anhydrous DEC. After the addition was completed, the mixture was stirred and heated to 100 °C for 8 h, cooled, and 560 ml diethyleneglycol monomethyl ether added dropwise. The mixture was then carefully heated to drive off the anhydrous ethanol, boiling at 77.5–78.5 °C (uncor). Yield of ethanol-*2,2,2*-d_3 was 81%.

A three-neck flask fitted with a magnetic stirrer, a dry ice condenser, and a dropping funnel were dried by flushing with nitrogen as they were heated. On cooling, 41 g of ethanol-*2,2,2*-d_3 was added and the flask immersed on a dry ice-isopropyl alcohol bath, keeping the contents under nitrogen. Phosphorus tribromide (35 ml) was added over a period of 4 h with vigorous stirring. The mixture was then warmed slowly and heated for 4 h at a maximum temperature of 60 °C. Distillation afforded an 80% yield of ethyl bromide (bp 38–39 °C) after drying over calcium chloride and redistillation from phosphorus pentoxide. The ethyl-*2,2,2*-d_3 bromide was analyzed by combustion, followed by the falling-drop method of deuterium (Németh, University of Illinois).

Table I

m/e	Multiplier potential	
	1.5 kV	1.75 kV
	3-Methyl-3-pentanol	
87	100.0	100.0
86	0.44	0.18
85	0.45	0.30
84	1.75	1.55
	3-Methyl-3-pentanol-*1,1,1*-d_3	
90	100.0	100.0
89	1.57	0.89
88	4.47	2.57
87	11.6	11.6

Anal. Calcd for $C_2H_2D_3Br$: D, 5.40. Found: D, 5.39.

The ethyl-*2,2,2*-d_3 bromide (20 g) was converted to the Grignard reagent by standard methods in 200 ml of diethyl ether. A solution of 12 g of ethyl methyl ketone in 50 ml of ether was added dropwise, and the reaction mixture was allowed to stir at room temperature overnight. After pouring the mixture into an aqueous ammonium sulfate solution, it was worked up in the usual manner to afford 16 g (85%) of 3-methyl-3-pentanol-*1,1,1*-d_3 boiling at 121–123 °C. Infrared examination of the product showed a carbonyl impurity which was readily removed by treatment with Girard's T reagent in methanol.

Anal. Calcd for $C_6H_{11}D_3O$: C, 68.50; H, 10.54; D, 5.75. Found: C, 68.41; H(D), 16.31.

The alcohol was purified by GLC as described above. It was analyzed directly for deuterium content on a Hitachi Perkin-Elmer RMU-7 mass spectrometer operating with an ionization potential of 7 V and multiplier potentials of 1.5 and 1.7 kV. The low ionization potential was chosen to minimize fragmentation of the parent ion. Nevertheless, the parent ion was too small to reliably use for analysis. Therefore the $M^+ - 15$ to $M^+ - 18$ region was used for analysis. The normalized cracking patterns which were observed are shown in Table I. It was assumed that the ratio of the intensities of the ($M^+ - 16$) to the ($M^+ - 15$) ions in the cracking pattern of the d_3 compound would be the same as in the cracking pattern of the natural compound. Any residual, after correction, in the *m/e* 89 was assumed to be derived from 3-methyl-3-pentanol-*1,1*-d_2. Thus it could be calculated that the relative concentrations of d_3 to d_2 compounds are 1:0.009, and the labeled methyl group contains 99.7 atom % deuterium.

Methylethylethyl-*2,2,2*-d_3-carbinyl hypochlorite was prepared in the same way as described above for the undeuterated compound. Starting with 1.84 g of the carbinol, 23 ml of a 0.76 M (iodometric titration) carbon tetrachloride solution of the hypochlorite was formed (>99% conversion). The solution was stored in a refrigerator protected from exposure to light.

Decomposition studies of methyldiethylcarbinyl hypochlorite were carried out in sealed degassed tubes. In a typical run, 1 ml of the carbon tetrachloride solution containing hypochlorite was added to a tube having a break-seal, greaseless joint, and a standard taper joint. Then 4 ml of a glacial acetic acid–acetonitrile (45:55 v/v) or a 0.37 M cyclohexane in carbon tetrachloride solution was added. The contents were degassed on a high-vacuum line by standard freeze–pump–thaw cycle techniques. The tubes were brought to room temperature, shaken to ensure complete solution, and placed in thermostated baths at 0, 40 (water-ethylene glycol), 80, and 120 °C (clear mineral oil). Chain reactions were initiated by a submerged 100-W air-cooled lamp at a distance of 10 cm, which was turned on automatically during the heat cycle of the bath. Typically, sample tubes were immersed in the bath for 20 h and had a total irradiation time of 16 hr.

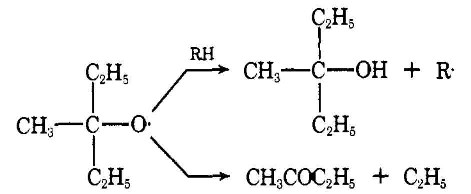
After the reaction period, the tubes were stored in liquid nitrogen until they were opened for GLC purification of ethyl chloride. The contents of the tube were transferred by high-vacuum distillation to a receiver (injector flask), which could be directly connected by swagelock to the injector port of a Varian Aerograph 712 GLC. Viton O-rings were used at all joints and stopcocks were of Teflon, thereby avoiding the use of grease and ensuring complete recovery of the ethyl chloride. After transfer, the injector flask was vented with nitrogen to a pressure of about 1 atm and connected to the automatic injector. Samples (1.5 ml) of the product solution were injected and chromatographed through a 30 ft × ⅜ in. column of 20% Ucon oil LB-550x on Chromosorb W A/W DMCS 30/60 (prep grade). The following conditions were used: column temperature, 50 °C; injector and detector, 145 °C; exit tip, ambient temperature; carrier gas, helium, 50 ml/min; detector, flame ionization with a 1:100 stream splitter. An efficient radiator trap[10] having greaseless stopcocks and joints was connected to the exit of the GLC, and it in turn was connected to a tube containing drierite. The trap was partially immersed in liquid nitrogen at the appropriate time to freeze out the effluent ethyl chloride. After the complete peak passed through the GLC, the trap was removed, and the contents were transferred on a high-vacuum line to another flask used in mass spectrometric analysis. Mass spectrometric analysis of the ethyl chloride-ethyl-*2,2,2-d*$_3$ chloride mixture was performed on a Hitachi Perkin-Elmer RMU-7 instrument. Several determinations of the ratios of *m/e* 64 to 67 for each sample were obtained. These were bracketed by mass spectrometric determinations of a standard CH_3CH_2Cl-CD_3CH_2Cl mixture.

In runs made with nonlabeled reactant to determine product distribution, a known quantity of 1-chloropropane was added to the reactant solution to serve as an internal standard. Prior to GLC analysis, standard solutions containing methyl chloride, ethyl chloride, 3-methyl-2-pentene, 3-methyl-3-pentanol, and the internal standard were injected to obtain the relative response of these compounds to the flame ionization detector. With these correction factors, the relative quantities of products were determined by GLC analysis of mixtures obtained from reaction at 0, 40, 80, and 120 °C. A 3 m × 0.25 in. column of 30% Carbowax 1500 on Chromosorb W A/W DMCS 30/60 (prep grade) connected to a 12 m × 0.25 in. column of 30% diisodecyl phthalate on the same support was used to separate the various components of the mixture. The conditions were: column, 50 °C isothermal (26 min) and then programmed for a 1 °C/min rise to 140 °C; injector and detector 145 °C; carrier gas, nitrogen 175 ml/min. The sample was injected by syringe.

Ethyl Chloride–Ethyl-β,β,β-d_3 Chloride Standard Mixture. Measurement of the quantities and mixing of the two compounds were carried out in a high-vacuum line having a calibrated gas buret, manometer, and Toepler pump. Ethyl-β,β,β-d_3 chloride[11] (7.55 ml, STP) and 10.33 ml (STP) of ethyl chloride (Matheson Co.) were measured individually and Toepler-pumped through greaseless stopcocks to a gas-sample bulb. The ratio, $[CH_3CH_2Cl]/[CD_3CH_2Cl]$, corrected for isotopic content was calculated to be 1.389.

Results and Discussion

3-Methyl-3-pentanol was converted to the corresponding hypochlorite by standard methods.[9] The decomposition of the compound was studied at 0, 40, 80, and 120 °C in a carbon tetrachloride–glacial acetic acid–acetonitrile (20:36:44 by volume) solvent mixture. Reactant solutions, which were generally about 0.2 M in hypochlorite, were thoroughly degassed under high vacuum. Chain decomposition was initiated by radiation from an incandescent lamp. The products of the reaction mixture were analyzed by GLC. Major products of reaction in this solvent mixture are ethyl chloride + 2-butanone and 3-methyl-3-pentanol, which amount to 70–80 and 0–22%, respectively. β scission, competitive with H abstraction, is expected to result in the predominant loss of ethyl radical from 3-methyl-3-pentoxyl (eq 1).[9]



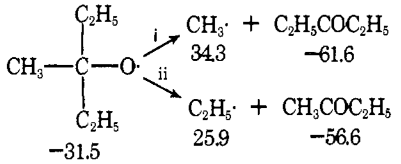
$$CH_3C(C_2H_5)_2O\cdot \xrightarrow{RH} CH_3C(C_2H_5)_2OH + R\cdot \qquad CH_3C(C_2H_5)_2O\cdot \longrightarrow CH_3COC_2H_5 + C_2H_5 \tag{1}$$

Ethyl radical abstracts chlorine from the reactant hypochlorite, thereby propagating the chain.

The particular solvent system used here, chosen in anticipation of future studies with copper ion, is relatively acidic and is responsible for the low yield of 3-methyl-3-pentanol at higher temperatures. In those cases 3-methyl-2-pentene was found to be present. Methyl chloride, also formed in this reaction, is a relatively minor product amounting from 0.7 to 3% and is formed by β scission in competition with ethyl chloride formation. It was of interest to explore the relative rates and activation energies in forming a methyl vs. an ethyl radical from the oxy radical. Since the reactant is the same in both reactions, the rate constants for β scission are in direct proportion to the quantities of methyl and ethyl chlorides formed if it is assumed that chlorine abstraction is rapid compared to β scission. This relation holds for all chain lengths.

Four runs were made at each of four temperatures. Each sample was analyzed two to three times by GLC. The averaged data are shown plotted in Figure 1 as log ($[CH_3Cl]/[C_2H_5Cl]$) vs. $1/T$. The data at 0 °C appear to be considerably out of line, probably because of errors in determining the very low ratio at this temperature, and these data were omitted from the plot. The difference in activation energies derived from the slope is 7.1 kcal/mol.

The difference in activation energies reflects the difference in stabilities of methyl and ethyl radicals and the two different ketone products. Heats of formation of reactant and product species, as calculated from functional group heats of formation in kcal/mol, are summarized in eq 2.[12,13]



$$\underset{-31.5}{CH_3C(C_2H_5)_2O\cdot} \xrightarrow{\text{i}} \underset{34.3}{CH_3\cdot} + \underset{-61.6}{C_2H_5COC_2H_5} \qquad \xrightarrow{\text{ii}} \underset{25.9}{C_2H_5\cdot} + \underset{-56.6}{CH_3COC_2H_5} \tag{2}$$

Heats of formation of methyl and ethyl radical have been measured by various methods. It has been suggested that those obtained from iodination kinetics are presently the most reliable.[12] From these data, path i is estimated to be endothermic by 4.2 kcal/mol, while path ii is endothermic by 0.8 kcal/mol. The 8.4-kcal/mol difference in stabilities between methyl and ethyl radicals is thus partially offset by the difference in ketone stabilities and results in only a 3.4-kcal/mol difference in heats of reaction between the two paths. The observed difference in activation energies for the two paths, 7.1 kcal/mol, is reasonable and suggests that stabilization of the ketone at the transition state is not fully realized. Had the ketone reached full stabilization at the transition state, a $\Delta\Delta H^\ddagger$ closer to 3.5 kcal/mol might have been observed. A previous study of the difference in activation energies for CH_3 vs. ethyl cleavage from an oxy radical has been reported by Walling and Padwa.[9] The activation energy differences for hydrogen abstraction and β scission for *tert*-butyl hypochlorite and dimethylethylcarbinyl hypochlorite were compared. From the assumption that the rate of hydrogen abstraction by the oxy radical is relatively independent of its structure, the activation energy difference for forming methyl from *tert*-butoxy and forming ethyl from 2-methyl-2-butoxy is 6.7 kcal/mol. Here the ketone products are the same but the reactants are different.

Secondary Deuterium Isotope Effect. 3-Methyl-3-pentanol-*1,1,1-d*$_3$ was prepared by the addition of ethyl-*2,2,2-d*$_3$ magnesium bromide to methyl ethyl ketone. The alcohol, after GLC purification, was shown by mass spectrometric analysis to be composed of 99.1 and 0.89% of the d_3 and d_2 compounds, respectively. The alcohol was converted to the hypochlorite by hypochlorous acid.

As in the studies with nonlabeled reactant, deuterated hypochlorite was allowed to decompose in carbon tetrachloride–glacial acetic acid–acetonitrile solution and also in carbon tetrachloride solution containing 0.30 M cyclohexane. Hypochlorite was held between 0.20 and 0.15 M. All solutions were thoroughly degassed before reaction. Product mixtures were transferred on a vacuum line to a vessel specifically designed for direct automatic injection into a Varian 712 GLC. In this way, labeled and unlabeled ethyl chlorides were separated from all other products and their relative concentrations determined by mass spectrometric analysis. The determinations of mass 64 and 67 ion intensities of the product mixtures were bracketed by the same determination for a standard mixture of ethyl chloride-ethyl-β,β,β-d_3 chloride. The ratio was determined with a single collector mass spectrometer since the Consolidated-Nier isotope ratio mass spectrometer can only be used successfully as a dual collector instrument with ions of mass lower than about 50.

For each of the two solvent systems, three to four samples were prepared for decomposition at 0 and 80 °C. Mass spectrometric measurements of each purified ethyl chloride product sample were made at least four times. The data are shown in Tables II and III.

The origin of secondary β-deuterium kinetic isotope effects is well established as reflecting hyperconjugative stabilization differences between reactant and transition states.[14] Evidence for this theory has been gathered from the measurement of isotope effects in numerous solvolysis systems where formation of a carbonium ion or ion pair is expected to be facilitated by hyperconjugation. The demonstration that the magnitude of the β effect also depends on the conformation of the β hydrogen with respect to an incipient vacant p_z orbital of the carbonium ion further strengthens the theory of the β-deuterium isotope effect.[15] The magnitude of the effect in solvolytic reactions ranges from about 10 to 20% per atom of deuterium. Nonbonded interactions and differential "inductive" effects have also been considered as the major factor being responsible for β effects,[16] but this now appears unlikely.[17] In certain systems, however, these factors may be dominant.[18]

ESR hyperfine coupling constants provide independent information about the degree of hyperconjugative interaction in a radical. Hyperconjugation is commonly invoked to account for the development of spin density on the β hydrogens of a radical and hence hyperfine splittings due to β hydrogens.[19] The relationship (eq 3 and 4) between the coupling constant (a^{H}) and the spin density at the α carbon (ρ) has been derived, and their proportionality constants, $Q_{\alpha\text{-H}} = -23$ G and $Q_{\beta\text{-H}} = 28$ G

$$a^{\mathrm{H}_\alpha} = Q_{\alpha\text{-H}}\rho \qquad (3)$$

$$a^{\mathrm{H}_\beta} = Q_{\beta\text{-H}}\rho \qquad (4)$$

have been calculated by McConnell[20] and McLachlan,[21] respectively. Coupling constants treated in this way are for time-averaged conformations which the β hydrogen takes with respect to the half-filled p_z orbital at the α carbon. More recent studies have focused attention on the dependence of a^{H_β} on θ, the H_β-C-C-p_z orbital dihedral angle, which can be represented by

$$a^{\mathrm{H}_\beta} = B_0 + B\cos^2\theta \qquad (5)$$

where $B_0 \cong 3$ G and $B \cong 48$ G.[22] The absence of the temperature dependence of the hyperfine splittings due to β hydrogens indicates that the barrier to rotation about the C_α-C_β bond in the ethyl radical is small.[23]

One might expect some correlation between ρ obtained from experimentally determined a^{H}'s and the secondary β-deuterium effect. These values are shown in Table IV together with secondary β-deuterium isotope effects found in simple radical forming reactions. The correlation is only fair.

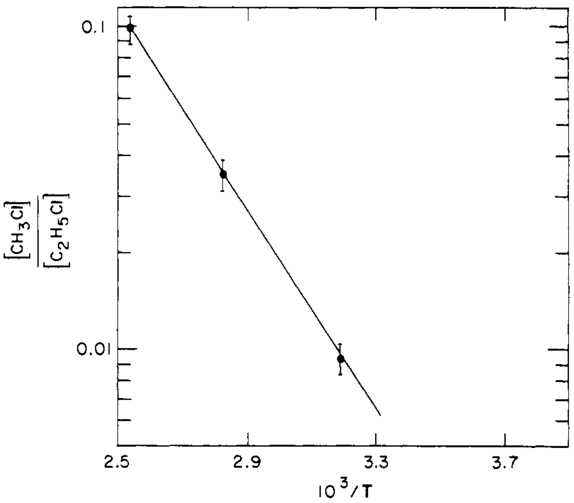


Figure 1. Ratio of the yields of methyl to ethyl chloride vs. $1/T$ in the thermal cleavage of methyldiethylcarbinyloxy radical.

Table II. Ethyl Chloride Parent Ion Intensity Ratios and the Secondary Isotope Effect in the Decomposition of 3-Methyl-3-pentan-*1,1,1*-d_3-ol Hypochlorite in Carbon Tetrachloride–Acetic Acid–Acetonitrile Solution

I_{64}/I_{67}[a]	n[c]	Temp, °C	$k_{\mathrm{H}_3}/k_{\mathrm{D}_3}$	$k_{\mathrm{H}_3}/k_{\mathrm{D}_3}$[d]
(S)[b] 1.055 ± 0.006	6			
0.951 ± 0.005	4	0	1.251 ± 0.010	
0.954 ± 0.003	4	0	1.255 ± 0.008	1.254 ± 0.005
0.955 ± 0.005	4	0	1.256 ± 0.010	
(S)[b] 1.055 ± 0.014	4			
(S)[b] 1.032 ± 0.005	6			
0.921 ± 0.003	6	80	1.239 ± 0.007	
0.918 ± 0.004	6	80	1.234 ± 0.007	1.236 ± 0.003
0.920 ± 0.001	5	80	1.236 ± 0.004	
(S)[b] 1.033 ± 0.003	6			

[a] Ratio of mass 64 to mass 67 ion intensities. [b] Standard mixture. The ratio $[\mathrm{C_2H_5Cl}]/[\mathrm{C_2D_5Cl}]$ was 1.388 ± 0.001. [c] Number of mass spectrometric samples. [d] Grand mean.

Table III. Ethyl Chloride Parent Ion Intensity Ratios and the Secondary Isotope Effect in the Decomposition of 3-Methyl-3-pentan-*1,1,1*-d_3-ol Hypochlorite in Carbon Tetrachloride–Cyclohexane Solution

I_{64}/I_{67}[a]	n[c]	Temp, °C	$k_{\mathrm{H}_3}/k_{\mathrm{D}_3}$	$k_{\mathrm{H}_3}/k_{\mathrm{D}_3}$[d]
(S)[b] 1.043 ± 0.011	8			
0.958 ± 0.001	4	0	1.275 ± 0.014	
0.953 ± 0.004	5	0	1.268 ± 0.011	1.271 ± 0.005
0.955 ± 0.002	5	0	1.271 ± 0.007	
(S)[b] 1.043 ± 0.005	5			
(S)[b] 1.036 ± 0.006	8			
0.937 ± 0.002	5	80	1.255 ± 0.008	
0.929 ± 0.003	5	80	1.243 ± 0.008	1.247 ± 0.006
0.933 ± 0.002	5	80	1.246 ± 0.008	
0.933 ± 0.004	6	80	1.245 ± 0.009	
(S)[b] 1.041 ± 0.007	6			

[a] Ratio of mass 64 to mass 67 ion intensities. [b] Standard mixture. The ratio of $[\mathrm{C_2H_5Cl}]/[\mathrm{CD_3CH_2Cl}]$ was 1.388 ± 0.001. [c] Number of mass spectrometric samples. [d] Grand mean.

Hyperfine coupling constants are obtained for radicals which have already attained a degree of stability; they are generally in their most stable geometry. Kinetic isotope effects, however, provide information about the nature of the transition state and how it differs from the reactant. The isotope effect reflects force constant changes which occur in going from reactant to transition state. Depending on the nature of the reaction and the radical produced, the radical

Table IV. Comparison of Secondary β-Deuterium Isotope Effects and Spin Densities[a]

R·	ρ^a	$k_H/k_D{}^f$
$CD_3CH_2\cdot$	0.96^b	1.08^g
$(CD_3)_2CH\cdot$	0.92^b	1.025^l
$(CD_3)_3C\cdot$	0.81^c	$1.02^{h,i}$
$(CD_3)_2\underset{\cdot}{C}CN$	0.73^d	1.02^j
$C_6H_5\underset{\cdot}{C}HCD_3$	$(0.71)^e$	1.017^k–1.02^i
$C_6H_5\underset{\cdot}{C}(CD_3)_2$	$(0.71)^e$	1.02^i

[a] Calculated spin density in $2p_z$ orbital at radical center by eq 3 and 4. [b] R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, 39, 2147 (1963). [c] D. E. Wood, L. F. Williams, R. F. Sprecher, and W. A. Lathan, *J. Am. Chem. Soc.*, 94, 6241 (1972). [d] S. Weiner and G. S. Hammond, *J. Am Chem. Soc.*, 90, 1659 (1968); A. A. Bichutinskii, A. I. Prokof'ev, and V. A. Shabalkin, *Russ. J. Phys. Chem. (Engl. Transl.)*, 38, 534 (1964). [e] This value is for the benzyl radical reported in A. Carington and I. C. P. Smith, *Mol. Phys.*, 9, 137 (1965). [f] Per D atom. [g] This work. [h] T. Koenig and R. Wolf, *J. Am. Chem. Soc.*, 89, 2948 (1967). [i] Reference 4b. [j] Reference 5. [k] Reference 2. [l] Reference 4c.

at the transition state may or may not resemble the fully formed radical. The transition state structure of a relatively stable radical (e.g., α-phenylethyl) is expected to bear less resemblance to the corresponding product radical than the transition state structure of an unstable radical (e.g., ethyl) when it is compared to its corresponding product radical. Thus the correlation of spin density obtained from ESR spectra and the secondary β-deuterium isotope effect might be expected to be poorer at the low-spin density end of the scale. In addition, examples in Table IV are for different reactions at different temperatures, and this also reduces any correlations.

Exact calculations of isotope effects, provided by the combination of the Bigeleisen–Mayer formulation with Schactschneider's program for calculating vibrational frequencies from force constants and atomic positions and masses, have contributed immensely to the understanding of secondary isotope effects.[24] These studies have demonstrated that isotope effects, where there are no force constant changes at the site of isotopic substitution, are generally less than 1% per deuterium and most often insignificant. Thus a substantial (i.e., >1%) β effect due to a hyperconjugative stabilization process would be expected to result from a change of β-C–H force constants in going from reactant to transition state. It should be emphasized, however, that both inductive and nonbonded interaction mechanisms would also be envisaged as resulting in changes in C–H force constants.

The quantum-mechanical treatment of hyperconjugation affords an opportunity to describe bonding and configurational changes that occur on forming radicals and ions and can be used to predict secondary β-deuterium isotope effects. Treating the β-methyl group as a pseudo π system in a perturbation vibration theory calculation, Ehrenson[6] has predicted a k_H/k_D per β-D of 1.09 for ethyl radical; isotope effects for other radicals were also calculated. From the model, the equilibrium configurations for the natural and deuterated species are calculated, and from this the $\Delta\Delta G$ is determined, which in turn yields the isotope effect. Koenig and Wolf[4,7] have used the ω-SCF method to calculate π-bond orders and self polarizabilities and, from these, force constant changes. The latter calculations which are for several radicals and ions predict $k_H/k_D = 1.08$ per β-D for fully formed ethyl radical. The latter method requires the evaluation of a parameter which is accomplished by assuming that the β effect is caused solely by a change in the β-C–H stretching frequency. Neglect of differential solvation effects between reactant and transition states and the assumption that the isotope effect is essentially a zero-point energy effect are common to both calculations. Nevertheless, experimental and theoretical values appear to be in very good agreement. Closer examination, however, points up sound differences between experimental and theoretical values.

As shown above (path ii, eq 2), β scission is an almost thermally neutral reaction which would suggest that the transition state is neither product- nor reactantlike. The force constant changes that take place in reaching the transition state, consequently, are expected to be not as large as would be if a free ethyl radical were formed. Thus an experimental kinetic β effect, smaller than the calculated equilibrium β effect, should have been observed, or alternatively, the calculated value is too low.

Since it has generally been assumed that a hyperconjugative isotope effect results primarily from a weakening of the β-C–H stretching force constant, the isotope effect is modeled mainly as a zero-point energy effect. As such, one expects the isotope effect to approximate the relation

$$k_H/k_D = Ae^{B/T} \tag{6}$$

in the moderate-temperature region, where A and B are constants. For most secondary deuterium effects, *A* is expected to be close to unity.

The isotope effect has been measured at 0 and 80 °C in two solvent systems. If temperature dependence of the type shown in eq 6 is assumed, one finds, surprisingly, that the isotope effect is relatively temperature independent. In carbon tetrachloride–glacial acetic acid–acetonitrile, the overall effect can be expressed as

$$k_{H_3}/k_{D_3} = 1.176 \exp{(\Delta H_D{}^\ddagger - \Delta H_H{}^\ddagger)}/RT \tag{7}$$

where $\Delta H_D{}^\ddagger - \Delta H_H{}^\ddagger = 34.5$ cal/mol and is not very different for reaction in carbon tetrachloride–cyclohexane. Only about one-third of the overall effect appears as an apparent zero-point energy effect which is in keeping with the notion that the transition state is neither product- nor reactantlike.

It is of interest to compare previous and present results with theory. The solvolysis of isopropyl-d_6 methanesulfonate in water ($k_{H_6}/k_{D_6} = 1.55$) is essentially temperature independent ($\Delta H_D{}^\ddagger - \Delta H_H{}^\ddagger = 7 \pm 27$ cal/mol).[25] The α-deuterium effect observed in this system suggests a rate-controlling formation of an ion pair in the solvolysis.[26] Other isopropyl analogues show similar behavior.[27] A very careful study of the secondary deuterium isotope effect in the hydrolysis of *tert*-butyl chloride as a function of temperature, however, shows the opposite behavior: $\Delta\Delta G^\ddagger \simeq \Delta\Delta H^\ddagger$.[28] Other investigations of the temperature dependence in β effects were carried out in the early investigations on the solvolyses of 2,3-dimethyl-2-chlorobutane[29] and 2-pentyl chlorosulfite;[30] these studies indicated a strong temperature dependence in the isotope effect. The behavior of the isopropyl compounds has been rationalized by suggesting that a reduction in β-C–H stretching force constant in going from reactant to transition state is offset by an increase of a force constant which in the reactant is very low and gives rise to a very low frequency.[24a] This type of combination leads to a zero-point energy contribution to the isotope effect, which decreases with increasing temperature, and a contribution to the excitation terms (i.e., $1 - e^{-u}$ terms), which increase with increasing temperature. The net effect is apparent temperature independence. The low frequency which increases along the reaction coordinate has been suggested to be due to a β-H–C–C–S torsion associated with substrate–solvent interactions which become stronger because of the greater solvation on forming an ion pair. While the role of solvent is expected to be less important in radical systems, a process of similar design may be responsible for the temperature dependence seen here.

In the reactant oxy radical, all bond angles are probably close to tetrahedral. As the reactant proceeds toward the transition state, the quaternary carbon of the reactant is being converted to an sp^2 carbonyl carbon. In the process, while carbon-carbon bond stretching occurs, the three bond angles that the α carbon of the departing group makes with each of the three groups bonded to the incipient carbonyl carbon approaches 90° and may result in hindering rotation of the methyl group of the departing ethyl. The frequencies of the torsions in the departing ethyl group associated with H_β–C_β–C_α–carbonyl C could thus be increased and result in counterbalancing the zero-point energy decrease associated with the decrease of the H_β–C_β stretching force constant.

References and Notes

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(2) S. Seltzer and E. J. Hamilton, Jr., *J. Am. Chem. Soc.*, **88**, 3775 (1966).

(3) T. Koenig and W. Brewer, *Tetrahedron Lett.*, 2773 (1965).

(4) (a) T. Koenig and R. Wolf, *J. Am. Chem. Soc.*, **89**, 2948 (1967); (b) *ibid.*, **91**, 2574 (1969); (c) T. Koenig and J. G. Huntington, *ibid.*, **96**, 593 (1974).

(5) S. Rummel, H. Hübner, and P. Krumbiegel, *Z. Chem.*, **7**, 351 (1967).

(6) S. Ehrenson, Gordon Research Conference on Chemistry and Physics of Isotopes, July 10–14, 1967, Crystal Mountain, Wash.

(7) T. Koenig and R. Wolf, *J. Am. Chem. Soc.*, **91**, 2569 (1969).

(8) G. H. Cady, *Inorg. Synth.*, **5**, 156 (1957).

(9) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593 (1963).

(10) S. Seltzer, A. Tsolis, and D. B. Denney, *J. Am. Chem. Soc.*, **91**, 4236 (1969).

(11) Ethyl-β,β,β-d_3 chloride was kindly donated to us by Dr. D. Christman. The compound analyzed for 99.5 atom % deuterium.

(12) H. E. O'Neal and S. W. Benson in "Free Radicals", Vol. II, J. K. Kochi, Ed., Wiley-Interscience, New York, N.Y., 1973, p 275.

(13) S. W. Benson, "Thermochemical Kinetics. Methods for the Estimation of Thermochemical Data and Rate Parameters", Wiley, New York, N.Y., 1968.

(14) V. J. Shiner, Jr., and J. S. Humphrey, *J. Am. Chem. Soc.*, **85**, 2416 (1963).

(15) V. J. Shiner, Jr., and J. G. Jewett, *J. Am. Chem. Soc.*, **86**, 945 (1964); V. J. Shiner, Jr., *ibid.*, **82**, 2655 (1960); V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *ibid.*, **85**, 2413 (1963).

(16) (a) L. S. Bartell, *J. Am. Chem. Soc.*, **83**, 3567 (1961); (b) H. C. Brown, M. E. Azzaro, J. G. Koelling, and G. J. McDonald, *ibid.*, **88**, 2520 (1966).

(17) J. G. Jewett and R. L. Dunlap, *J. Am. Chem. Soc.*, **90**, 809 (1968); V. J. Shiner, Jr., and G. S. Kriz, Jr., *ibid.*, **86**, 2643 (1964).

(18) (a) L. Melander and R. E. Carter, *J. Am. Chem. Soc.*, **86**, 295 (1964); *Acta Chem. Scand.*, **18**, 1138 (1964); (b) G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Scheppele, and R. L. Schone, *J. Am. Chem. Soc.*, **89**, 463 (1967); G. J. Karabatsos and C. G. Papaioannou, *Tetrahedron Lett.*, 2629 (1968).

(19) J. E. Wertz and J. R. Bolton, "Electron Spin Resonance", McGraw-Hill, New York, N.Y., 1972, p 124.

(20) H. M. McConnell, *J. Chem. Phys.*, **24**, 764 (1956).

(21) A. D. McLachlan, *Mol. Phys.*, **1**, 233 (1959).

(22) H. Fisher in "Free Radicals", Vol. II, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, Chapter 19.

(23) Cf. K. S. Chen, D. J. Edge, and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 7036 (1973); P. J. Krusic, P. Meakin, and J. P. Jesson, *J. Phys. Chem.*, **75**, 3438 (1971).

(24) (a) M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, **8**, 225, 325 (1964); (b) M. J. Stern and M. Wolfsberg, *J. Chem. Phys.*, **45**, 4105 (1966).

(25) K. T. Leffek, R. E. Robertson, and S. E. Sugamori, *Chem. Ind.* (*London*), 259 (1961).

(26) K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *Can. J. Chem.*, **38**, 1505 (1960).

(27) K. T. Leffek, R. E. Robertson, and S. Sugamori, *Can. J. Chem.*, **39**, 1989 (1961).

(28) L. Hakka, A. Queen, and R. E. Robertson, *J. Am. Chem. Soc.*, **87**, 161 (1965).

(29) V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **76**, 1603 (1954).

(30) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 6306 (1952).

Kinetics and Mechanisms of the Reactions of Organic Cation Radicals and Dications. IV.[1] First- and Second-Order Reactions of Thianthrene Cation Radical with Phenol

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Abstract: The kinetics of the reaction between the thianthrene cation radical and phenol were studied in dichloromethane in the presence and absence of trifluoroacetic acid (TFA). In the presence of TFA, the reaction was found to be second order in $TH\cdot^+$, inhibited by unoxidized TH, first order in phenol, and the rate decreased markedly with increasing TFA concentration. The mechanism proposed for the reaction on the basis of the kinetics and comparison with other reactions of $TH\cdot^+$, which have previously been studied, involves initial complex formation between $TH\cdot^+$ and phenol followed by oxidation of the complex by $TH\cdot^+$. An altogether different picture emerged when the reaction was carried out in the absence of TFA. In the latter case, the reaction was found to be first order in both $TH\cdot^+$ and phenol, and the rate was independent of the concentration of unoxidized TH. The effect of TFA that brings about the abrupt mechanistic change is to suppress the deprotonation of the initial complex, which is accompanied by formation of a sulfur-carbon bond. In the presence of TFA, the deprotonation does not occur, and oxidation of the complex is necessary before bond formation takes place. The mechanistic conclusions are supported by comparing the reactions of $TH\cdot^+$ with phenol and anisole. In the latter case, the same mechanism holds both in the presence and absence of TFA since the acidic proton of phenol has been replaced by methyl.

The mechanism of the reaction of the thianthrene cation radical ($TH\cdot^+$) with anisole (AN) has recently been studied in detail[1b] and found to follow the following mechanism:

$$TH\cdot^+ + AN \rightleftarrows (TH/AN)\cdot^+ \tag{1}$$

$$(TH/AN)\cdot^+ \rightleftarrows TH + AN\cdot^+ \tag{2}$$

$$(TH/AN)\cdot^+ + TH\cdot^+ \rightleftarrows (TH/AN)^{2+} + TH \tag{3}$$

$$(TH/AN)^{2+} \rightarrow (TH\text{-}AN)^+ + H^+ \tag{4}$$

In both acetonitrile and dichloromethane, at low $TH\cdot^+$ concentration ($\sim 10^{-5}$ M), the only reaction observed was oxidation of AN via dissociation of the initial complex (step 2).