Mass Spectrometry in Structural and Stereochemical Problems. CLXX.[1] A Study of the Effect of Ring Size in Reciprocal Hydrogen Transfer[2]

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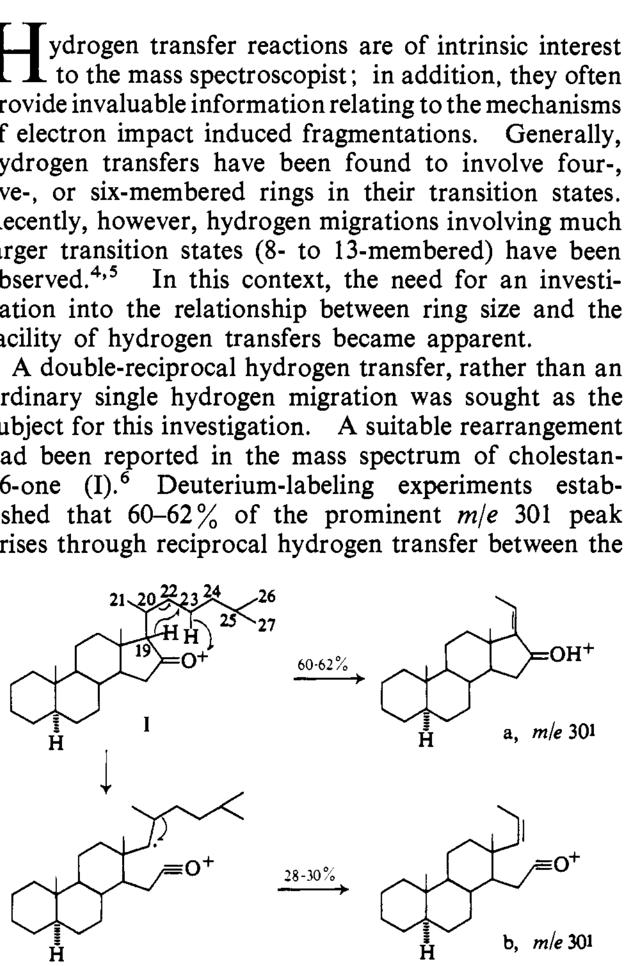
Abstract: Recent reports of nonspecific hydrogen migrations involving large ring transition states prompted an investigation into the relationship between ring size and the facility of hydrogen transfer. Using 2-(1′-octyl)-cyclohexanone as a model compound for reciprocal hydrogen transfer, deuterium labeling confirms that ring size plays a crucial role in determining the ease of hydrogen migration.

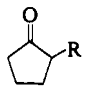
Hydrogen transfer reactions are of intrinsic interest to the mass spectroscopist; in addition, they often provide invaluable information relating to the mechanisms of electron impact induced fragmentations. Generally, hydrogen transfers have been found to involve four-, five-, or six-membered rings in their transition states. Recently, however, hydrogen migrations involving much larger transition states (8- to 13-membered) have been observed.[4,5] In this context, the need for an investigation into the relationship between ring size and the facility of hydrogen transfers became apparent.

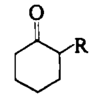
A double-reciprocal hydrogen transfer, rather than an ordinary single hydrogen migration was sought as the subject for this investigation. A suitable rearrangement had been reported in the mass spectrum of cholestan-16-one (I).[6] Deuterium-labeling experiments established that 60–62% of the prominent m/e 301 peak arises through reciprocal hydrogen transfer between the alkyl side chain and the steroid nucleus (see, for instance, I → a). Transfer from the side chain occurs from C-22 (3–3.5%), C-23 (32–38%), C-24 (32–35%), and C-25 (25–27%), but not C-26 and C-27 (0%), while back-transfer originates almost exclusively from C-17.



The data obtained by earlier workers[6] are not, however, suitable for use in this study because of the presence of several extraneous factors. The differences in migratory aptitude of tertiary, secondary, and primary hydrogen atoms are well known.[7] Thus, it seemed possible that the contribution in the steroid I from the tertiary carbon (C-25) was inflated, and that of the primary carbons (C-26 and C-27) was reduced. Furthermore, extraneous steric effects introduced by the rigid steroid geometry might be expected to play an important role in determining favored ring sizes for hydrogen transfer. For example, it has been demonstrated that steric interactions between C-18 and the side chain restrict rotation about the C-17–C-20 bond.[8] Thus, a simpler model system was sought, one relatively free of unwanted steric factors, and one containing a normal alkyl side chain of sufficient length to preclude transfer from the penultimate (final secondary) carbon.

Initially, attention was centered on 2-(2′-octyl)cyclopentanone (II) and the corresponding cyclohexanone (III). The mass spectrum of each exhibited a peak attributable to a double hydrogen transfer analogous to that described above (I → a). In order to avoid complications due to the possibility of hindered rotation about the C-2–C-2′ bond, it seemed desirable to choose as a model a compound with an unbranched side chain. Thus, 2-(1′-octyl)cyclopentanone (IV) and 2-(1′-octyl)-cyclohexanone (V) were prepared and their mass spectra examined. Each showed an ion attributable to the double hydrogen transfer. Because the latter compound could be prepared in somewhat better yield, it was chosen as the object of more detailed study by means of appropriate deuterium labeling.





II, R = $CH(CH_3)(CH_2)_5CH_3$
IV, R = $CH_2(CH_2)_6CH_3$

III, R = $CH(CH_3)(CH_2)_5CH_3$
V, R = $CH_2(CH_2)_6CH_3$

Discussion of Mass Spectral Results

1. Reciprocal Hydrogen Transfer. The mass spectrum of 2-(1′-octyl)cyclohexanone as determined with a

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[1] For paper CLXIX, see J. Diekman, J. K. MacLeod, C. Djerassi and J. D. Baldeschwieler, *J. Am. Chem. Soc.*, **91**, 2069 (1969).

[2] Financial support (Grant No. AM-12758) from the National Institutes of Health is gratefully acknowledged.

[3] National Institutes of Health Predoctoral Fellow, 1968–1969.

[4] R. Brandt and C. Djerassi, *Helv. Chim. Acta*, **51**, 1750 (1968).

[5] C. Wolff, R. Wolff, and J. A. McCloskey, *Tetrahedron Letters*, 4335 (1966); W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 160 (1968); R. Wolff, M. Greff, and J. A. McCloskey, *Advan. Mass Spectry.*, **4**, 193 (1968).

[6] C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).

[7] See, for example, H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometric Identification of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., Sections 3–7, 1967.

[8] H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966); H. Fritz, H. Budzikiewicz, and C. Djerassi, *Chem. Ber.*, **99**, 35 (1966).

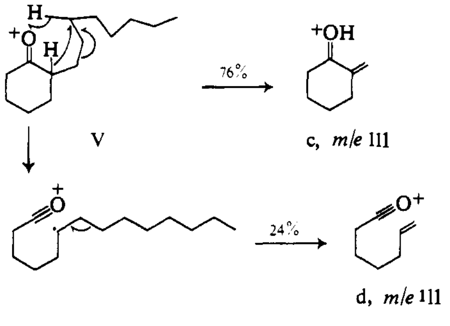
Table I. Shifts[a] of *m/e* 111 Peak in Deuterated Analogs of 2-(1′-Octyl)cyclohexanone (V)

Compound	Isotopic purity, %	70 eV, %	15 eV, %
2-(1′-Octyl)cyclohexanone-2′,2′-d_2[b]	d_2, 98 d_1, 2	2	0
2-(1′-Octyl)cyclohexanone-3′,3′-d_2[b]	d_2, 98 d_1, 2	56	57
2-(1′-Octyl)cyclohexanone-4′,4′-d_2[b]	d_2, 92 d_1, 8	30	31
2-(1′-Octyl)cyclohexanone-5′,5′-d_2[b]	d_2, 98 d_1, 2	10	10
2-(1′-Octyl)cyclohexanone-6′,6′-d_2[c]	d_2, 98 d_1, 2	0	0

[a] Shifts are corrected for the presence of isotopic impurities and for the presence of the α-cleavage ion (*d*) of mass 111. [b] Data determined in CEC Model 21-103C mass spectrometer with heated all-glass inlet system, [c] Data determined in AEI MS-9 mass spectrometer with heated inlet system. Shifts are independent of instrument used.

CEC Model 21-103C mass spectrometer using a heated all-glass inlet system is reproduced in Figure 1.

The *m/e* 111 peak, although always considerably smaller than the base peak, becomes the second largest peak at low (12 eV) ionizing voltages. The ion arises partially (76%) from reciprocal hydrogen transfer (V → c) and partially from α cleavage followed by loss of the heptyl radical (V → d). This conclusion was derived from a study of the 2,6,6-d_3 analog of V. Thus,



the *m/e* 111 peak was shifted to the extent of 75–77% to *m/e* 113 and 23–25% to *m/e* 114. The ranges quoted reflect the presence of some (12%) d_2 contaminant whose protium distribution is unknown. The greater importance of the α-cleavage fragment b (38–40% of *m/e* 301) in the steroid I may be a reflection of the strain inherent in the *trans*-fused hydrindane system;[9] this strain would be lessened on α cleavage with attendant ring opening.

The results of the side-chain-labeling experiments are listed in Table I. The bulk of the transfer (56%) originates from C-3′. If a concerted process is assumed (alternatively, the transfer can be envisaged as a two-step process involving larger (seven-, eight-, or nine-membered) rings, but the detailed mechanism of the reaction has little bearing on the conclusions reached here) transition state e involves a five- and a six-membered ring. Transfer from C-4′, corresponding to two six-membered rings in the transition state f, accounts for 30%, while transfer from C-5′, involving six- and seven-membered rings (g) accounts for 10% of the total transfer. The latter figure is considerably lower than the 25–27% transfer reported from the analogous (but tertiary) C-25 of chloestan-6-one (I). No transfer is observed from C-6′, even though inspection of models shows that transfer from C-6′ is sterically feasible.

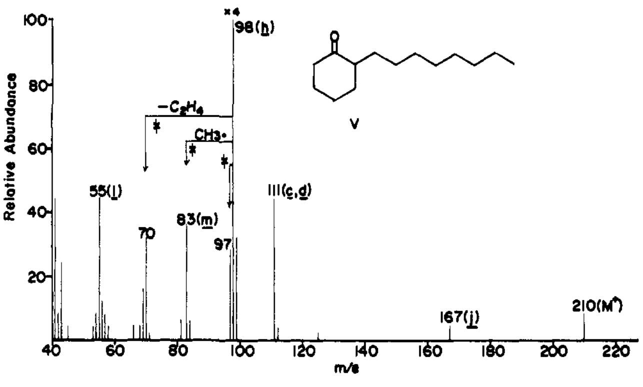
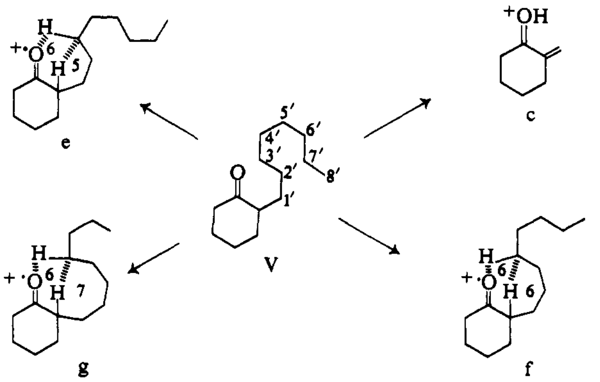


Figure 1.



Thus, the conclusion must be drawn that, even for nonspecific hydrogen transfers, ring size plays an important role in determining the facility with which a given hydrogen atom will migrate, and that the earlier observed[6] absence of hydrogen migration from positions 26 and 27 of the steroid I was reflective of unfavorable ring size rather than of the primary nature of the hydrogen atoms.

2. Other Important Peaks. The base peak (*m/e* 98) can be attributed to the well-known McLafferty rearrangement (V → h).[7] As anticipated, the peak shifts quantitatively to *m/e* 99 in the 2′, 2′-d_2 analog. Other important peaks believed to arise from the molecular ion are at *m/e* 55 (V → i) and *m/e* 167 (V → j).[10]

The appropriate metastable peaks support the formation of *m/e* 97, 83, and 70 from the McLafferty ion h. Furthermore, each peak is shifted one mass unit higher in the spectrum of the 2′,2′-d_2 analog.

The genesis of the ion of mass 70 can be ascribed to a retro-Diels–Alder reaction.[10] Formation of the *m/e* 97 peak can best be rationalized as the loss of an allylic hydrogen atom (h → l), while the *m/e* 83 peak must arise through a fairly complex rearrangement, such as

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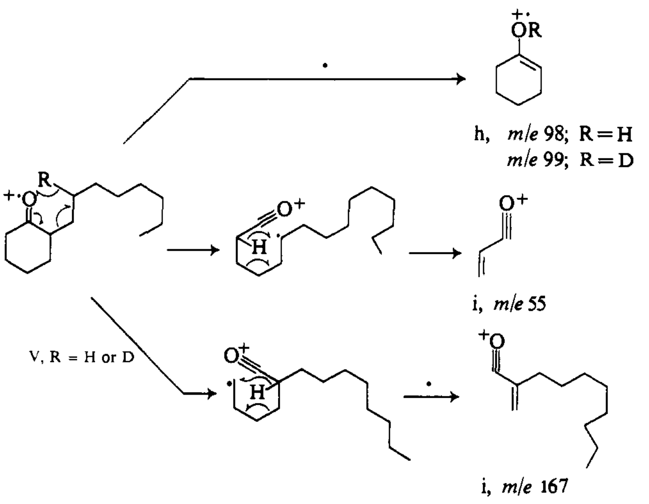
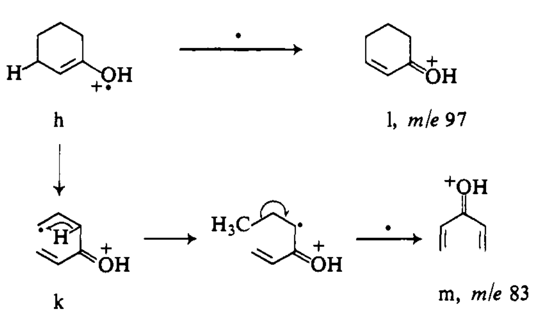
[9] A pronounced effect of the difference in strain energy of five- and six-membered rings has been demonstrated in competitive processes leading to loss of CH_3 from methylcyclopentane and methylcyclohexane. See S. Meyerson, T. D. Nevitt, and P. N. Rylander, *Advan. Mass Spectry.*, **2**, 313 (1963).

[10] D. H. Williams, H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh.*, **95**, 166 (1964).



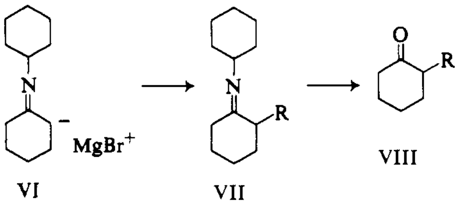
the one depicted below (h → k → m). The latter mechanism is supported by the nearly quantitative shift



of the m/e 83 peak to m/e 85 in the 2,6,6-d_3-labeled compound.

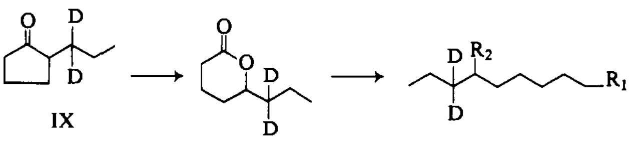
Synthesis of Labeled Compounds

The 2-alkylcycloalkanones utilized in these experiments were prepared by condensing the magnesium salt of the cycloalkanone imine[11] (VI) with the corresponding alkyl iodide; hydrolysis of the resulting imine (VII) liberated the desired ketone.[12]



The preparation of 2,2-d_2-iodooctane was accomplished by the carbonation of the Grignard reagent prepared from 1,1-d_2-bromoheptane, followed by the reduction and iodination[13] of the resulting 2,2-d_2-octanoic acid. The 3,3-d_2-, 4,4-d_2-, and 5,5-d_2-iodooctanes were prepared by diethyl malonate homologation[14] of the corresponding deuterated bromohexanes, and subsequent reduction and iodination in the usual manner.

The preparation of 6,6-d_2-iodooctane was accomplished less directly. Alkylation of cyclopentanone with 1,1-d_2-iodopropane produced 2-(1′-propyl)cyclopentanone-1′,1′-d_2 (IX). Conversion of IX into the corresponding lactone (X) was accomplished by treatment with *m*-chloroperbenzoic acid; reduction with lithium aluminum hydride gave 6,6-d_2-octane-1,5-diol (XI). Reaction of the diol XI with trityl chloride produced the 1-trityl derivative XII.[15] Treatment of XII with *p*-toluene sulfonyl chloride produced the corresponding tosylate (XIII)[16] which, on reduction with lithium aluminum hydride, gave triphenylmethyl-6,6-d_2-octyl ether (XIV). Hydrolysis of XIV[15] yielded 6,6-d_2-octanol (XV) which was converted into the corresponding iodooctane in the usual manner.



XI, $R_1 = R_2 = OH$
XII, $R_1 = OC(C_6H_5)_3$; $R_2 = OH$
XIII, $R_1 = OC(C_6H_5)_3$; $R_2 = OTs$
XIV, $R_1 = OC(C_6H_5)_3$; $R_2 = H$
XV, $R_1 = OH$; $R_2 = H$

The isotopic purity of the 2-(1-octyl)cyclohexanones was confirmed by preparing the N-methylisatoic derivative[17] of the labeled precursor octanol.

Experimental Section[18]

2-(1′-Octyl)cyclohexanone (V) was prepared by the method of Stork and Dowd.[12] To the Grignard reagent prepared from the reaction of 0.60 g of ethyl bromide with 0.14 g of magnesium turnings in dry tetrahydrofuran was added 0.84 g of N-cyclohexylidine cyclohexylamine.[11] The resulting solution was heated under reflux in an atmosphere of nitrogen until the evolution of gas (ethane) was complete, usually 3–5 hr. After the solution cooled to room temperature, 1.20 g of 1-iodooctane was added with stirring. After overnight reflux, hydrolysis was effected with a threefold excess of 10% hydrochloric acid. The product was isolated by extraction with ethyl ether and distillation (bp 134–136° (12 mm)). The material was further purified by vpc (10-ft Carbowax 20M column operated at 215°). The over-all yield varied between 60 and 70%.

Other 2-alkylcycloalkanones were prepared by analogous procedures, although in slightly poorer yields.

2-(1′-Octyl)cyclohexanone-2,6,6-d_3 was prepared by repeated equilibration of the parent ketone (V) with deuteriomethanol containing 10% heavy water and catalytic amount of sodium deuterioxide. The product was recovered by evaporating the solvent at 25° under vacuum. The discolored liquid was further purified by vapor phase chromatography through a Carbowax 20M column (215°) preequilibrated with heavy water.[19]

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[11] K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).

[12] G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

[13] A. I. Vogel, "Practical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1962, p 288.

[14] (a) R. Adams and R. M. Kamm, "Organic Synthesis," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p 250; (b) E. Vliet, C. S. Marvel, and C. M. Hseuh, "Organic Synthesis," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 416.

[15] M. Ehrenstein, A. R. Johnson, R. C. Olmstend, V. I. Vivian, and M. A. Wagner, *J. Org. Chem.* **15**,, 264 (1960).

[16] L. F. and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 1180.

[17] R. M. Teeter, *Anal. Chem.*, **38**, 1736 (1966).

[18] The mass spectral data were obtained by Mr. R. Ross on an MS-9 mass spectrometer using a heated glass inlet system with steel manifolding, and by Mr. R. Liedtke on a CEC 21-103C mass spectrometer using a heated all-glass inlet system. Silica gel H_{254} was the adsorbent used for all thin layer chromatography.

[19] M. Sonn, W. J. Richter and A. L. Burlingame, *J. Am. Chem. Soc.*, **87**, 680 (1965); W. J. Richter, M. Sonn, and A. L. Burlingame, *Tetrahedron Letters*, 1235 (1965); D. K. Albert and S. Myerson, *Anal. Chem.*, **39**, 1904 (1967).

2-(1′-Octyl)cyclohexanone-2′,2′,-d_2. Carbonation of the Grignard reagent prepared from 1,1-d_2-heptyl bromide produced the corresponding octanoic acid. After reduction with lithium aluminum hydride and halogenation with phosphorus and iodine,[13] the resulting octyl iodide was utilized in the above-described alkylation reaction.

2-(1′Octyl)cyclohexanone-3′,3′-d_2,-4′,4′-d_2,-5′,5′-d_2. The corresponding labeled hexyl bromides were condensed with diethyl malonate;[14a] hydrolysis and decarboxylation[14b] yielded the corresponding octanoic acids, which were reduced and halogenated in the usual manner. The resulting labeled octyl iodides were used in the above-described alkylation procedure.

2-(1′-Octyl)cyclohexanone-6,6-d_2. Alkylation of cyclopentanone with 1,1-d_2-iodopropane in the usual manner resulted in a good yield of 2-(1′-propyl)cyclopentanone-1′,1′-d_2 (IX).

Anal. Calcd for $C_8H_{12}D_2O$: mol wt, 128. Found: mol wt, 128 (by mass spectroscopy).

To a solution of 1.28 g (10 mm) of IX in dichloroethane was added 2.14 g (10.5 mm) of 85% pure *m*-chloroperbenzoic acid. After the solution had been heated under reflux for 7 hr, it was allowed to cool, extracted with 1.05 equiv of sodium bicarbonate, washed with water, dried over magnesium sulfate, and distilled. The resulting clear liquid (bp 108–110° (12 mm)) was subjected to reduction with lithium aluminum hydride without further purification. The resulting 6,6-d_2-octane-1,5-diol (XI) was purified by preparative tlc using ethyl acetate eluent. The clear oil (bp 150–152° (13 mm), n_2^{20} 1.4550; lit.[20] bp 144–146° (11 mm), n_d^{17} 1.4561) exhibited a single peak when subjected to vpc (10-ft 2% SE-30 column operated at 225°). The over-all yield based on IX was 77%.

The 1-trityl derivative of XI was prepared by allowing a dry pyridine solution containing 2.10 g (7.5 mm) of trityl chloride and 1.11 g (7.5 mm) of the diol to stand for 3 days at room temperature;[15] the progress of the reaction was conveniently followed by tlc. The trityl ether was worked up in the usual manner, and purified by tlc (eluent pentane(2)–ethyl ether (1)). The product, a viscous oil, weighed 2.02 g (69% yield). The monotrityl ether was converted into the trityl ether–tosylate (XIII) using a standard procedure.[16] Purification by preparative tlc resulted in an excellent yield of viscous yellow oil, which was treated with a fourfold excess of lithium aluminum hydride at room temperature; tlc showed the reaction to be complete after 20 min. Work-up in the usual manner followed by preparative tlc (eluent pentane(9)–ethyl ether (1)) gave triphenylmethyl-6,6-d_2 octyl ether (XIV) in over-all yield of 51% based on the diol XI.

The trityl ether XIV was hydrolyzed by 30 hr reflux in 85% acetic acid.[15] The resulting 6,6-d_2-octanol was purified by vpc (10-ft 2% SE-30 column operated at 200°). The oily N-methyl isatoic ester[17] of the labeled octanol was prepared for analysis.

Anal. Calcd for $C_{16}H_{23}D_2NO$: mol wt, 265. Found: mol wt, 265 (by mass spectroscopy).

The 6,6-d_2-octanol was converted into the corresponding octyl iodide and used to effect alkylation in the usual manner.

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(20) R. Paul, *Bull. Soc. Chim. France*, 317 (1935).

Substituent Effects in Mass Spectrometry. Mass Spectra of Substituted Phenyl Benzyl Ethers

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Abstract: From a consideration of smoothed energy distributions, ionization potentials, and appearance potentials, the effect of substituents on the ratio of molecular ion to total daughter ion abundance in the mass spectra of substituted phenyl benzyl ethers ($XC_6H_4OCH_2C_6H_5$) has been calculated. The results show a qualitative agreement with experiment in 20-eV spectra, but for some substituents (*e.g.*, *m*-CH_3O, *m*-OH, and *m*-NH_2), the observed molecular ion abundance is much greater than the calculated value. In these cases it may be that the assumed energy distributions are a poor approximation to those actually occurring and/or isolated electronic states of the molecular ions may be generated upon electron impact.

When an organic molecule is ionized by an energetic electron (*e.g.*, 20 eV) to give a positive parent ion, varying amounts of energy are transmitted from the electron beam to the molecules and hence a distribution of energies in the parent ions is obtained. This energy distribution is fixed in the absence of collisions, and will in general extend from the ionization potential (IP, the minimum energy transferred to give a parent ion) to the electron beam energy, E_{el}. In earlier papers,[1] we have utilized a parabolic energy distribution extending from IP to E_{el}, and in the present paper we utilize (on purely empirical grounds) an energy distribution which weights lower internal energies (less than $(E_{el} - \text{IP})/2$) more than higher internal energies (greater than $(E_{el} - \text{IP})/2$) (Figure 6A).[2] In the figure the ordinate indicates the weighting of a particular internal energy, *i.e.*, $f(E)dE$ is the fraction of ions having energies between E and $E + dE$. This energy distribution will be used as a plausible working model for 20-eV spectra. It is probably unsuitable for much higher (*e.g.*, 70 eV) or much lower (*e.g.*, 14 eV) beam energies.

In this paper, the smoothed energy distribution is used in an approach to substituent effects in mass spectrometry. It will be seen that the approach relies to a large extent on consequences of the quasi-equilibrium theory,[3] and is somewhat different to the approach of McLafferty and Bursey,[4] which first stimulated interest in this field.

Before substituent effects can be reliably evaluated,

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(1) (a) I. Howe and D. H. Williams, *J. Am. Chem. Soc.*, **90**, 5461 (1968); (b) R. G. Cooks, R. S. Ward, I. Howe, and D. H. Williams, *Chem. Commun.*, 837 (1968).

(2) The curve given in Figure 6 is actually a plot of $y = (1 - x^{1/3})\cdot(x-x^2)$.

(3) H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig, and H. Eyring, *Proc. Natl. Acad. Sci. U. S.*, **38**, 667 (1952).

(4) M. M. Bursey and F. W. McLafferty, *J. Am. Chem. Soc.*, **88**, 529 (1966). For a review, see M. M. Bursey, *Org. Mass Spectry.*, **1**, 31 (1968), and for the current status of the approach see F. W. McLafferty, *Chem. Commun.*, 956 (1968).