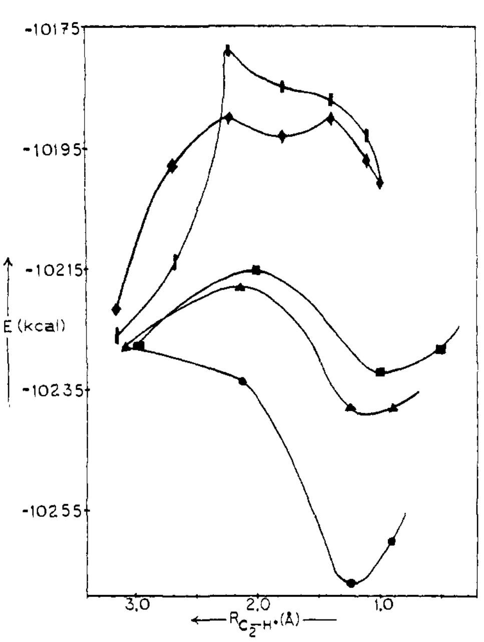
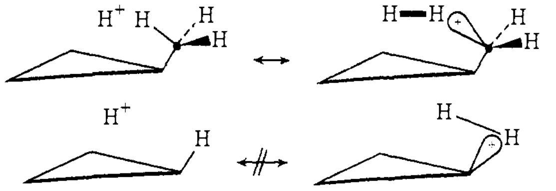


Figure 1. Calculated energies for five H^+ approach channels to cyclopropanol (**1**): (1) 1,2-edge approach (●); (2) 2,3-edge approach (▲); (3) corner approach (■); (4) syn-center face approach (◆); and (5) anti-center face approach (▮).

ring. The exact nature of this interaction is revealed by the resulting overlap populations and atomic charges. At 2.0 Å from the center of the ring the approaching proton withdraws electron density from the proximate C_4–H_{10} bond ($OP_{C_4-H_{10}}$ = 0.3396 *vs.* 0.8216 in unperturbed **2**, while the atomic charge on C_4 increases to +0.3468 from −0.2545) to achieve strong positive overlap with the methyl hydrogen (H_{10}) lying over the cyclopropane ring ($OP_{H_{10}-H^+}$ = 0.6625). The hyperconjugative interaction illustrated below with its resulting cyclopropylcarbinyl resonance hybrid is, therefore, responsible for this unusual stabilization of a face-protonated cyclopropane.[29] A similar interaction in the parent system should be highly unfavorable.



Experimental work[30] on the solvolysis of 4-tricyclyl-trifluoromethanesulfonate has been carried out to gauge the significance of interaction between a cationic center and the face of a cyclopropane ring. While these studies never claimed to bear on the sort of methyl–H^+ interaction uncovered here, the tricyclyl ring system does appear too constrained to permit the hyperconjugation shown above where an alkyl hydrogen is required directly over the face of the cyclopropane ring. Thus, a valid test case has not yet been examined.

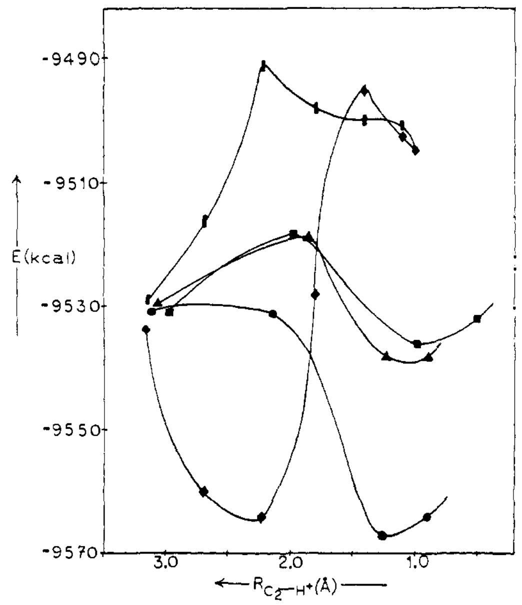


Figure 2. Calculated energies for five approach channels to methylcyclopropane (**2**): (1) 1,2-edge approach (●); (2) 2,3-edge approach (▲); (3) corner approach (■); (4) syn-center face approach (◆); and (5) anti-center face approach (▮).

Calculations with other electrophiles as well as appropriate experimentation testing the conclusions reached here are in progress.

Acknowledgment. The author would sincerely like to thank Professor C. H. DePuy for support, valuable discussions, and for initially suggesting this line of research. Professor S. Zumdahl is gratefully acknowledged for his help with the modified EHMO program.

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(29) Note that stabilization is achieved in the perpendicular conformation with the tetrahedral configuration at C_4; compare G. A. Olah, C. L. Jeuell, D. P. Kelly, and R. D. Porter, *J. Amer. Chem. Soc.*, **94**, 146 (1972); Y. E. Rhodes and V. G. DiFate, *ibid.*, **94**, 7582 (1972); W. C. Danen, *ibid.*, **94**, 4835, 8647 (1972); and W. J. Hehre and P. C. Hiberty, *ibid.*, **94**, 5917 (1972).

(30) S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. G. Morris, *ibid.*, **92**, 3469 (1970); and R. C. Bingham, W. F. Sliwinski, and P. v. R. Schleyer, *ibid.*, **92**, 3471 (1970).

Long-Lived Benzyl and Tolyl Cations in the Gas Phase[1]

Sir:

The tropylium ion, **1**, has been proposed as the structure of $C_7H_7^+$ ions formed in a wide variety of unimolecular reactions. Following the classic original work of Meyerson and his coworkers, it has been shown by ^2H and ^{13}C labeling studies that the decomposition of $C_7H_7^+$ ions from many $C_6H_5CH_2Y$ (Y = H, CH_3, OH, Cl, $CH_2C_6H_5$) and $CH_3C_6H_4Y$ (Y = *p*-CH_3, *p*-Cl) derivatives is accompanied by complete isotopic scrambling.[2] Conflicting ionization potential evidence[3] has led to the proposal that ionization even of benzyl radicals yields **1** ions. However, in particular cases sub-

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(1) Metastable Ion Characteristics. XXX. For paper XXIX see K. Levsen and F. W. McLafferty, *Org. Mass Spectrom.*, in press.

(2) (a) P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Amer. Chem. Soc.*, **79**, 842 (1957); (b) J. T. Bursey, M. M. Bursey, and D. G. I. Kingston, *Chem. Rev.*, **73**, 191 (1973); (c) S. Meyerson, H. Hart, and L. C. Leitch, *J. Amer. Chem. Soc.*, **90**, 3419 (1968); (d) A. S. Siegel, *ibid.*, **92**, 5277 (1970); (e) although studies of $C_6H_5CD_2C_6H_5$ indicated the tropylium-*1,2-d₂* ion as the precursor of the $C_5(H,D)_5^+$ product ions,[2c] our measurements on this system are consistent with complete scrambling.

(3) F. P. Lossing, *Can. J. Chem.*, **49**, 357 (1971).

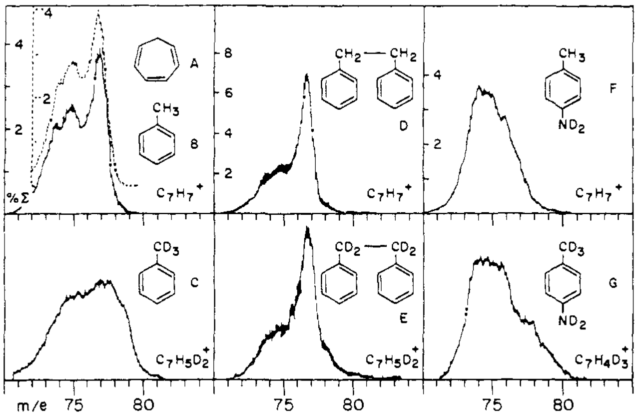
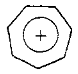


Figure 1. Partial CA spectra of $C_7(H,D)_7^+$ ions from cycloheptatriene (A), toluene (B), toluene-α-d_3 (C), 1,2-diphenylethane (D), 1,2-diphenylethane-*1,1,2,2*-d_4 (E), *p*-nitrotoluene (F), and *p*-nitrotoluene-α-d_3 (G). The *m/e* scale is calculated from the ESA voltage; the peak maxima in the CA spectra appear slightly below the true values due to the activation energy requirement for the decompositions.[16] No total ionization percentages are given for the CA spectra of the deuterated ions because of the many unresolved peak multiplets.

stituent effect,[4] appearance potential,[5] and metastable ion[6] evidence has indicated that ring position identity is not lost during *formation* of benzyl (**2**) and tolyl (**3**)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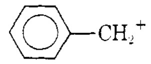
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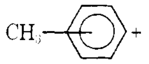
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ions; examples include the formation of **2** ions from $C_6H_5CH_2OC_6H_5$[4a] and $(C_6H_5CH_2)_2$[4b] and **3** ions from $CH_3C_6H_4X$ (X = *o*-, *m*-, and *p*-Br and -I[5] and *p*-NO_2[6]). Low-energy toluene ions can be formed which do not isomerize;[7-9] evidence[9-11] has been presented that toluene ions of energy sufficient to form $C_7H_7^+$ mainly isomerize before decomposition, although recent results suggest that unrearranged **2** ions are formed.[12] Also, chemical ionization and radiolysis of toluene[13,14] and ethylbenzene[14] can *initially* produce ions of structure **2**. Evidence has been presented for substituted **2** ions that are stable in strong acid solution but not for **3** or unsubstituted **2** ions.[15]

We now show that although $C_7H_7^+$ ions formed from many compounds isomerize to a common structure, presumably **1**, in 10^{-5} sec, it is possible to form **2** and **3** ions that are stable for this relatively long lifetime. We have used collisional activation (CA) spectra to identify **1**, **2**, and **3** as ion products; such spectra have been shown to be characteristic of ion structure, independent of internal energy, for ions of lifetimes ~10^{-5} sec or greater.[9,16]

Three types of characteristic patterns (Figure 1) were found for the C_6 region (*m/e* 72–78) of the CA spectra[17] of $C_7H_7^+$ ions from a wide variety of precursors. Data from cycloheptatriene (**4**) and toluene (**5**) illustrate (Figure 1A,B) the first spectral type. The tropylium ion (**1**) should be produced from **4**;[2] the CA data show that most of the $C_7H_7^+$ ions from **5** also have structure **1**, as expected from most,[2,9-11] but not all,[12] previous conclusions. (A more careful comparison of a variety of spectra, to be discussed in the full paper, indicates that **4** as well as **5** also produce some **2** ions.) Consistent with **5** → **1** the CA spectra of $C_7H_5D_2^+$ from $C_6H_5CD_3$ (Figure 1C) and $C_7H_2D_5^+$ from $C_6D_5CH_3$ correspond to the CA spectra expected from ions in which the H/D atoms have lost their positional identity. Spectra similar to Figure 1A,B were also found for $C_7H_7^+$ ions from 2,5-norbornadiene and many $C_6H_5CH_2Y$ (Y = C_6H_5, $CH(OH)C_6H_5$, COC_3H_7, COC_6H_5, COOH, $OCH_2C_6H_5$) and $CH_3C_6H_4Y$ (*p*-C_6H_5, *p*-Cl, *m*-Br, *p*-Br) derivatives.

A second type of CA spectrum (Figure 1D) is found for $C_7H_7^+$ ions from the benzyl derivatives $C_6H_5CH_2Y$, where Y = $CH_2C_6H_5$, OC_6H_5, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2CH{=}CH_2$, and NO_2. Very little of the dominant peak at *m/e* 77 ($C_7H_7^+ - CH_2$:) is shifted to *m/e* 78 in the CA spectrum of $C_7H_5D_2^+$ from $C_6H_5CD_2CD_2C_6H_5$ (Figure 1E), providing strong support for the benzylic structure $C_6H_5CD_2^+$. This confirms not only the conclusion that **2** ions are formed from $C_6H_5CH_2OC_6H_5$[4a] and $C_6H_5CH_2CH_2C_6H_5$[4b] but shows that these $C_7H_7^+$ ions have not isomerized appreciably in 10^{-5} sec after formation. The CA spectra of the $C_7H_7^+$ ions from $C_6H_5CH_2Y$ where Y = CH_3, C_3H_7, C_9H_{19}, and CH_2OH indicate that these compounds give a mixture of **1** and **2**. The lower degree of isomerization of $C_7H_7^+$ formed from $C_6H_5CH_2CH_3$ than from $C_6H_5CH_3$ parallels the behavior of these ions formed by radiolysis,[14] although isomerization was less for the latter experiments due to trapping of the ions in $\ll 10^{-5}$ sec.

A third type of CA spectrum (Figure 1F) is found for $C_7H_7^+$ ions from the tolyl derivatives $CH_3C_6H_4Y$, where Y = *o*-NO_2, *m*-NO_2, *p*-NO_2, *o*-CH_3CO, *p*-CH_3CO, *o*-C_6H_5CO, *p*-C_6H_5CO, *m*-CH_3OCO, *o*-I, and *m*-I. (As will be discussed in the full paper, there appear to be distinguishable differences between the spectra of the ortho and other isomers.) A relatively small proportion of the dominant peaks at *m/e* 74 and 76,

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[4] (a) P. Brown, *J. Amer. Chem. Soc.*, **90**, 2694 (1968); (b) F. W. McLafferty, T. Wachs, C. Lifshitz, G. Innorta, and P. Irving, *ibid.*, **92**, 6867 (1970).

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[14] Y. Yamamoto, S. Takamuku, and H. Sakurai, *ibid.*, **94**, 661 (1972); S. Takamuku, N. Sagi, K. Nagaoka, and H. Sakurai, *ibid.*, **94**, 6217 (1972).

[15] G. Olah, *Angew. Chem., Int. Ed. Engl.*, **12**, 173 (1973).

[16] F. W. McLafferty, P. F. Bente, III, R. Kornfeld, S.-C. Tsai, and I. Howe, *J. Amer. Chem. Soc.*, **95**, 2120 (1973).

[17] Measurements were made on a Hitachi RMU-7 double-focusing mass spectrometer of reversed geometry[18] as described previously.[9,16] An ion accelerating potential of 3.8 kV and ionizing electrons of 100 μA and 70 eV were used. Unimolecular metastable decompositions of the precursor ion selected by the magnetic field occurring in the field-free drift region between the magnetic and electrostatic (ESA) analyzers are measured by scanning the ESA potential. The pressure in the field-free drift region between the magnet and the ESA is then increased with helium until the precursor ion intensity is reduced to 10% of its original value, and the CA ion product abundances are determined in the same manner in a second ESA scan. The contributions from MI products are subtracted from these values to obtain the CA spectrum. The spectra shown are the computer averaged results of at least ten separate scans. Other experimental details will be given in the full paper.

[18] T. Wachs, P. F. Bente, III, and F. W. McLafferty, *Int. J. Mass Spectrom. Ion Phys.*, **9**, 333 (1972).

$(C_7H_7^+ - CH_5)$ and $(C_7H_7^+ - CH_3)$, are shifted to higher masses in the spectrum of $C_7H_4D_3^+$ from p-$CD_3C_6H_4NO_2$ (Figure 1G), strongly supporting the tolyl structure **3** as the major form of these ions.[19] Although appearance potentials indicate that $C_7H_7^+$ ions from *m*- and p-$CH_3C_6H_4Br$ and *o*- and m-CH_3-C_6H_4I have structure **3** on formation,[5] their CA spectra show that only the ions formed from the iodo compounds have retained this structure for 10^{-5} sec. Similarly, in contrast to previous conclusions,[6] our data indicate that ions of structure **3**, not **1**, are formed from p-$CH_3C_6H_4COCH_3$.

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(19) However, we find for p-$CD_3C_6H_4NO_2$ and p-$CH_3C_6D_4NO_2$ that the metastable decompositions used in the previous study[6] involve complete H/D scrambling, indicating that the differences noted by these authors are due to differences in ion internal energy, not to differences in ion structure.[9,16]

(20) Postdoctoral fellow supported by grants from the National Institutes of Health and the Army Research Office, Durham.

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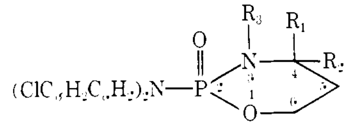
Received June 22, 1973

4-Hydroperoxidation in the Fenton Oxidation of the Antitumor Agent Cyclophosphamide

Sir:

It is becoming increasingly clear that monooxidation at C-4 of cyclophosphamide (I) is essentially responsible for the activation of this antitumor agent by the drug-metabolizing enzymes of the liver.[1-3] The occurrence of aldophosphamide (VI) after activation of I by microsomal preparations[1,2] and the production of acrolein under such conditions[4] are understandable on the basis of prior C-4 hydroxylation. 4-Ketocyclophosphamide (V) and a ring-opened carboxylic acid (VII), which have been identified as end products of metabolism, are ineffective as cytostatic agents.[5-10]



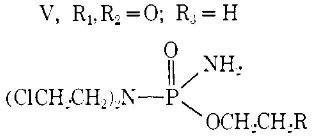
I, $R_1 = R_2 = R_3 = H$

II, $R_1 = OOH;\ R_2 = R_3 = H$

III, $R_1 = R_2 = H;\ R_3 = OH$

IV, $R_1 = OH;\ R_2 = R_3 = H$

V, $R_1, R_2 = O;\ R_3 = H$



$$(ClCH_2CH_2)_2N{-}\overset{O}{\overset{\|}{P}}\begin{smallmatrix}\nearrow NH_2\\ \searrow OCH_2CH_2R\end{smallmatrix}$$

VI, R = CHO

VII, R = COOH

As mentioned earlier,[11] studies of the Fenton oxidation of I led to the isolation of a crystalline compound, to which the structure N_3-hydroxycyclophosphamide (III) was tentatively assigned. The compound was obtained *via* a precursor that has now also been isolated. We wish to discuss here the identification of 4-hydroperoxycyclophosphamide (II) among the Fenton oxidation products of I and to report on the spontaneous conversion of II to 4-hydroxycyclophosphamide (IV) instead of III. The *in vivo* occurrence of IV in mice treated with I is also reported.

After room temperature exposure for some hours, or on reflux, a CH_2Cl_2 extract of a mixture of Fenton oxidation products of I, obtained by the addition of 1 mol of $FeSO_4$ to 1 mol of H_2O_2 and 0.5 mol of I in an unbuffered solution, was shown by tlc on silica gel in CH_2Cl_2–n-BuOH (9:1) to contain a product that appeared at first hand difficult to explain on the basis of C-4 hydroxylation. It was present in a higher amount when a modified Fenton system with a H_2O_2–$FeSO_4$ ratio of 1.5 was used, which would be expected to favor the generation of OOH· radicals (*cf.* ref 12). The compound was shown to oxidize triphenyltetrazolium chloride to the red formazan. Its isolation with the aid of preparative tlc on silica gel in CH_2Cl_2–EtOH (95:5) yielded a crystalline compound: mp 106° dec; yield, 4% relative to the amount of I submitted to oxidation; $\text{ir}_{\text{max}}^{\text{KBr}}$ (cm^{-1}) 3220, 2970, 2905, 1460, 1370, 1325, 1250, 1230, 1210, 1135, 1055, 980, 960, 890, 820, and 730, the broad peak at 3220 cm^{-1} being displaced to 2335 cm^{-1} on deuterium exchange; nmr (TMS, $CDCl_3$) (HA-100 spectrometer) δ 1.70–2.40 (2 H, m), 3.05–3.70 (9 H, m), 3.90–4.80 (2 H, m), 5.23 (1 H, d of q, $J_{P,H}$ = 30 Hz), 6.58 (1 H, br s). On deuterium exchange the signal at δ 6.58 disappeared and the quartets at δ 5.23 degenerated to triplets. Quantitatively, the observed spectra suggested exchange of only one proton; assuming this, an unforced interpretation of the nmr spectral data was possible. Treatment of the compound with H_2O_2 did not give rise to the formation of II (*cf.* ref 3). This was in clear contrast to the behavior (under identical conditions) of an as yet unidentified product of reduction of II by triphenylphosphine that was obtained in a nearly pure state after column chromatography and that probably is one of the two diastereomeres of 4-hydroxycyclophosphamide (IV).

Because of the elemental analytic, ir, and nmr data, and the findings on treatment with H_2O_2, the compound was initially identified as N_3-hydroxycyclophosphamide (III). Exact similarity of the ^{13}C nmr data for the compound with those obtained by Struck, *et al.*,[13]

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