flow rate 35 mL/min). IR (neat) cm^{-1}: 3076, 2988, 2960, 2860, 1825, 1775, 1651, 1644, 1464, 1446, 1430, 1418, 1409, 1217, 989, 905, 875. NMR (360 MHz, $CDCl_3$): δ 5.69 (ddd, 1, $^3J_{trans}$ = 17.1, $^3J_{cis}$ = 10.1, ^3J = 8.0 Hz, =C*H*), 5.04-4.99 (complex, 2, decoupling at 2.90 ppm reveals ddd, $^3J_{trans}$ = 17.1, $^3J_{cis}$ = 10.1, ^2J = 2.0 Hz, =CH_2), 4.93 (br s, 1, =CH_2), 4.79 (br s, 1, =CH_2), 2.90 (complex, 1, C*H*), 2.30 (complex, 2, CH_2), 2.00-1.30 (complex 4, CH_2). Mass spectrum (70 eV), *m/z* 108 (24.2%), 107 (7.6%), 105 (3.2%), 93 (100%), 91 (41.1%), 80 (22.4%), 79 (83.3%), 78 (14.6%), 77 (46.6%), 67 (22.8%), 66 (7.2%), 65 (12.9%), 54 (7.5%), 53 (14.0%), 52 (6.6%), 51 (11.6%), 41 (23.8%), 39 (34.0%). We thank K. Facchine for his assistance with the NMR spectroscopy of this compound.

3-Methylenecycloheptene (11). This compound was synthesized by using the method of Wittig and Schoellkopf[32] with 3-cycloheptenone (Aldrich Chemical Co.) and (triphenylmethyl)phosphonium bromide (Aldrich Chemical Co.). The product was purified with gas chromatography (2 m, 5% didecylphthalate, 1.25% triethanolamine on Chromosorb B, column temperature of 100 °C, flow rate of 50 mL/min). IR spectrum (neat) cm^{-1}: 3073, 3010, 2920, 2855, 1770, 1640, 1595, 1450, 880, 844, 760. NMR (90 MHz, $CDCl_3$): δ 6.07 (d, 1, ^3H = 12.0 Hz, =C*H*), 5.64 (dt, 1, ^3J = 12.0, ^3J = 6.0 Hz, =C*H*), 4.75 (br s, 2, =CH_2), 2.52-2.02 (complex, 4, CH_2), 1.83-1.54 (complex, 4, CH_2). Mass spectrum (70 eV), *m/z* 108 (49.7%), 107 (6.7%), 105 (3.0%), 93 (100%), 91 (45.4%), 80 (24.0%), 79 (56.1%), 78 (11.2%), 77 (46.2%), 67 (9.6%), 66 (5.9%), 65 (10.4%), 54 (3.5%), 53 (7.5%), 52 (4.7%), 51 (8.1%), 41 (14.4%), 39 (20.6%).

Bicyclo[4.2.0]oct-7-ene (14). This sample was prepared from 1,3-cyclooctadiene by using the method of Liu.[33] The product was purified by gas chromatography (2 m, 5% SE30, column temperature of 100 °C, flow rate of 50 mL/min). NMR (90 MHz, $CDCl_3$): δ 6.03 (s, 2, =C*H*), 2.95-2.78 (m, 2, C*H*), 1.85-1.30 (complex, 8, CH_2). Mass spectrum (70 eV), *m/z* 108 (1.7%), 107 (3.0%), 105 (1.3%), 93 (52.4%), 91 (19.8%), 80 (51.5%), 79 (100%), 78 (9.8%), 77 (30.2%), 67 (59.8%), 66 (20.1%), 65 (13.3%), 54 (14.9%), 53 (7.0%), 52 (4.7%), 51 (7.8%), 41 (27.6%), 39 (25.0%).

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Registry No. 1, 929-20-4; **2**, 24612-83-7; **3**, 925-52-0; **4**, 16626-48-5; **5**, 16177-46-1; **6**, 6553-48-6; **7**, 6196-78-7; **9**, 19841-74-8; **10**, 4982-20-1; **11**, 34564-56-2; **12**, 111-78-4; **13**, 1700-10-3; **14**, 616-10-4; 1,3-butadiene, 106-99-0; 1,3-butadiene cation radical, 34488-62-5; 4-vinylcyclohexene cation radical, 91798-27-5; 4-vinylcyclohexene, 100-40-3; 5-methyl-1,3,6-heptatriene, 925-52-0; 5-methyl-1,3,6-heptatriene cation radical, 92142-91-1; bis(triethylphosphine)nickel(II) chloride, 17523-24-9; *n*-butyllithium, 109-72-8; 3-cycloheptenone, 1121-64-8; triphenylmethylphosphonium bromide, 1779-49-3.

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Reaction of the Vinyl Methyl Ether Cation Radical and 1,3-Butadiene: A Two-Step Cycloaddition

G. S. Groenewold and M. L. Gross*

Contribution from the Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588. *Received August 29, 1983*

Abstract: The structure of the intermediate formed in the ion-molecule reaction of 1,3-butadiene and vinyl methyl ether has been determined by stabilizing the intermediate in a high-pressure chemical ionization source, isolating the intermediate by using the first stage of mass analysis of a tandem mass spectrometer, and finally acquiring its mass spectrum by using collision-activated decomposition (CAD) spectroscopy and the second stage of mass analysis. The structure of the intermediate is demonstrated to be acyclic by comparing its CAD spectrum with CAD spectra of several isomeric $C_7H_{12}O$ reference compounds. This conclusion is in contrast to previous low-pressure ion cyclotron resonance (ICR) and present Fourier transform mass spectrometry (FTMS) experiments, which are interpreted in terms of a cycloaddition. These two interprtations are reconciled by invoking a two-step reaction mechanism in which an acyclic intermediate is initially formed. This intermediate ultimately cyclizes, unless it is intercepted by stabilizing collisions.

Organic cation radicals and their reactions have become important subjects for study in analytical and organic chemistry. Recent research in mass spectrometry and in synthetic organic chemistry has been focused on cycloaddition reactions involving a cation radical reactant. Solution-phase cation radical cycloaddition reactions have been reported recently,[1] and gas-phase cation radical cycloadditions involving *o*-xylylene,[2] fulvene,[3] and 1,3-butadiene[4,5] have been demonstrated also. The cation radical Diels-Alder reaction has also been studied by using theoretical methods, and conflicting interpretations have been drawn. The results of one study point to a nonsynchronous, concerted mechanism[6a] whereas those of another are interpreted in terms of a two-step process.[6b]

van Doorn and co-workers[4] in 1978 reported investigations of gas-phase ion-molecule reactions in ionized mixtures of 1,3-butadiene and vinyl methyl ether. The results of ion cyclotron resonance (ICR) and collision-activated decomposition (CAD) experiments were interpreted in terms of a methoxy-substituted, six-membered cyclic adduct (4-methoxycyclohexene). A Diels-Alder mechanism was suggested,[4] but no evidence was presented to distinguish between a concerted and a two-step process. A stable (1,3-butadiene plus vinyl methyl ether) cation radical adduct could not be observed in that work because the low pressures (≤2 ×

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Table I. CAD Spectra of (Butadiene + Methyl Vinyl Ether) Ion–Molecule Adduct and of Reference Compounds

m/z	adduct I	II	III	IV	V
111	20.6	21.0	20.9	8.1	45.1
97	30.6	29.8	19.5	8.1	16.3
84	0.3	0.5	1.2	0.6	5.3
81	6.9	6.5	5.2	2.4	4.6
80	3.3	4.5	9.2	51.2	1.3
79	5.0	4.8	4.8	7.3	4.1
77	2.3	2.3	2.0	4.1	1.5
71	0.8	0.9	5.4	0.4	0.3
69	1.8	1.5	2.2	0.6	1.0
67	3.2	2.8	2.4	1.2	1.6
65	1.6	1.5	0.9	0.8	0.9
58	0.7	1.0	0.5	0.6	0.1
55	1.7	1.5	2.5	0.8	1.9
53	3.5	3.3	2.9	1.4	2.1
51	1.2	1.4	0.9	1.2	0.9
45	1.3	1.3	1.2	0.8	0.7
43	1.9	2.0	1.8	0.6	1.2
41	5.1	5.0	4.7	2.2	2.9
39	3.4	4.1	3.5	2.2	2.4
29	1.1	1.1	0.8	0.3	0.4
27	1.5	1.8	1.5	0.5	1.3

10^{-5} torr) used in the ICR spectrometer did not permit collisional stabilization of the activated ion–molecule reaction product. An investigation of a stabilized (1,3-butadiene plus vinyl methyl ether) ion–molecule reaction adduct is desirable.

In this study we report that the ion–molecule adduct can be collisionally stabilized in a chemical ionization mass spectrometer source at pressures between 65 and 520 mtorr. The structure of the stabilized $C_7H_{12}O^{+\cdot}$ adduct, analyzed by collision-activated decomposition (CAD) spectroscopy by using a tandem mass spectrometer analyzer (MS/MS),[7] is assigned by comparing the CAD spectrum of the adduct to the spectra of $C_7H_{12}O$ reference compounds.[2] The efficacy of CAD spectroscopy for structural determination is well established.[8]

Results and Discussion

The adduct of principal interest is produced in the reaction (1,3-butadiene plus vinyl methyl ether) cation radical $\rightarrow C_7H_{12}O^{+\cdot}$, m/z 112. No ions of m/z 112 were observed if vinyl methyl ether or if 1,3-butadiene[5] alone were ionized at source pressures of 520 mtorr. However, when vinyl methyl ether and 1,3-butadiene were admitted together to the source at pressures greater than approximately 70 mtorr, a m/z 112 ion was observed of sufficient abundance for analysis by using CAD spectroscopy. Adduct ions of greater abundance were observed at total pressures between 200 and 500 mtorr. Therefore, the CAD analyses of these ions benefit from an enhanced signal/noise ratio, and for this reason, CAD data are reported for ion–molecule adducts formed and stabilized at these higher pressures. The CAD spectra of the adducts did not change as the pressure was varied between 78 and 455 mtorr.

These observations are in contrast to the lower pressure ICR studies in which no ion–molecule adduct was observed. The pressure of the ICR experiments (ca. 10^{-6} torr) is insufficient for collisional stabilization, and, as a result, the energy released in the reaction causes the intermediate to decompose.

The principal collision-activated decompositions of the adduct, stabilized at high pressure, are the losses of hydrogen (to form m/z 111) and methyl (to form m/z 97), which together account

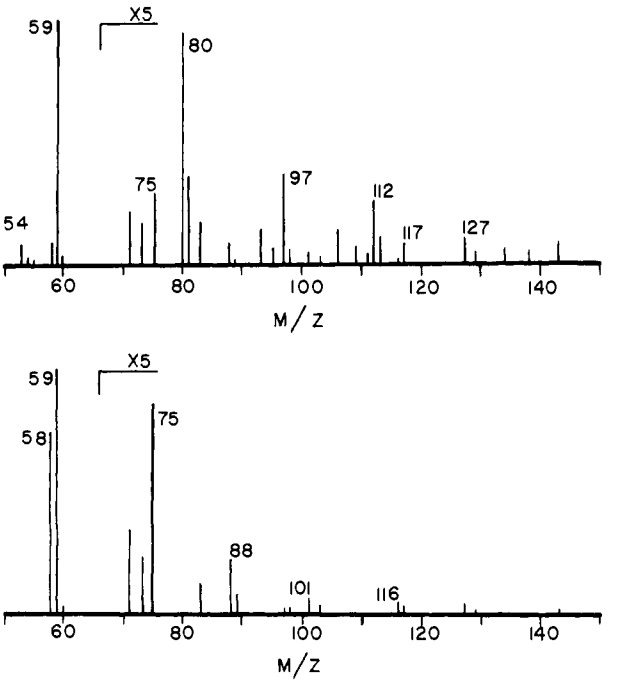

Figure 1. (a) Mass spectrum of a 1:1 mixture of 1,3-butadiene and vinyl methyl ether; total pressure = 520 mtorr. (b) Mass spectrum of vinyl methyl ether alone; pressure = 260 mtorr.

for more than 50% of the total ion current of the CAD spectrum (Table I). The structural implications of the adduct CAD spectrum are deduced by comparing it to CAD spectra of several reference compounds. The reference compounds were ionized under conditions of high pressure (approximately 260 mtorr) by using a low-energy charge exchange reaction involving $CS_2^{+\cdot}$ (CS_2 IP $\cong$ 10 eV).[9] The excess, un-ionized CS_2 provided an inert bath gas for collisional stabilization.[9]

The CAD spectrum of the adduct I matches well with the spectrum of 1-methoxy-2,4-hexadiene (II), which in turn is easily distinguished from the CAD spectra of the other reference compounds, III–V. Decompositions of ionized I and II are characterized as abundant losses of hydrogen and methyl radicals (m/z 111 and 97, respectively) which are observed in the CAD spectra in a ratio of 2:3. The only discrepancy revealed by contrasting the CAD spectra of the adduct (I) with that of 1-methoxy-2,4-hexadiene (II) is that the m/z 80 ion is slightly more abundant in the spectrum of II than in the spectrum of the adduct (I). The spectrum of the adduct clearly does not correspond to that of the cycloaddition product, 4-methoxycyclohexene (IV). The elimination of methanol (m/z 80) accounts for greater than 50% of the total ion current in the CAD spectrum of 4-methoxycyclohexene (IV), and this observation is consistent with the reported mass spectral data for this compound.[4]

A mass spectrum was acquired of the 1:1 1,3-butadiene/vinyl methyl ether mixture (520-mtorr total pressure, Figure 1) in order to study the distribution of all product ions which have been formed in the source. The most abundant ion in the spectrum is m/z 59 and corresponds to protonated vinyl methyl ether. This ion results from vinyl methyl ether internal chemistry, as is demonstrated by these and by results published earlier[10] (see Figure 1). The next most abundant product ion is m/z 80, which arises by the loss of methanol from the (1,3-butadiene plus vinyl methyl ether) cation radical adduct.[4] Ion–molecule reactions occurring in ionized 1,3-butadiene also give rise to an ion at m/z 80, but, at the

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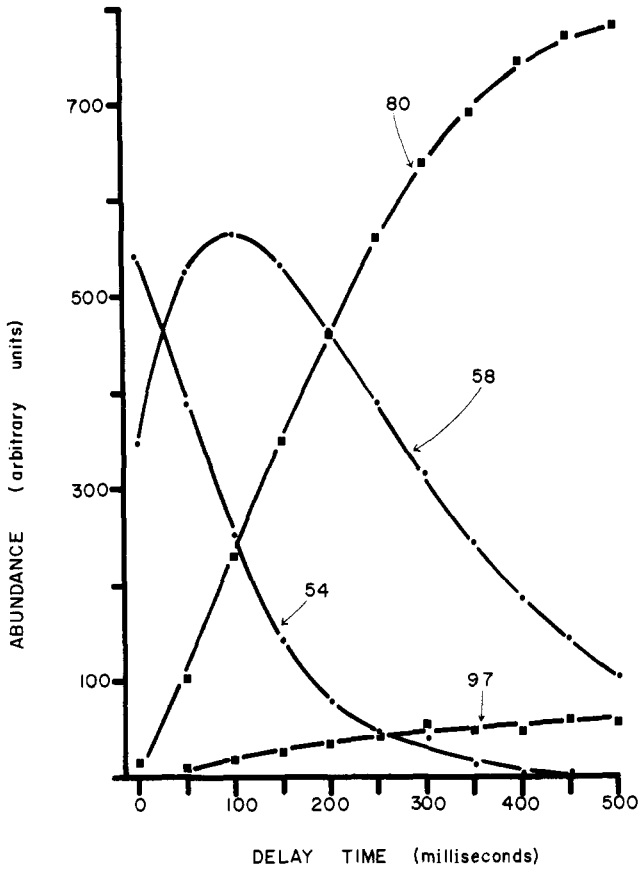


Figure 2. Time-resolved study of the reactions in a 1:1 mixture of 1,3-butadiene and vinyl methyl ether ionized at 15 eV.

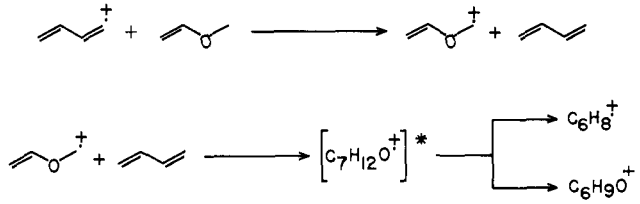
pressures used in this study, the abundance of m/z 80 originating from 1,3-butadiene alone was approximately the same as the abundance of m/z 93.[5] Thus, the majority of the ions of m/z 80 arise via methanol loss from cross chemistry involving the 1,3-butadiene and vinyl methyl ether ions and neutrals.

Other abundant secondary ions were produced in the high-pressure source, and they correspond to the intermediate (m/z 112, vide supra) and to the loss of $\cdot CH_3$ from the intermediate forming m/z 97. The latter ion was reported in the ICR spectrometry study of van Doorn et al.[4] and was also observed by using Fourier transform mass spectrometry (vide infra). The intensity ratio i_{97}/i_{80} from ICR spectrometry was approximately 1:11, whereas the ratio is 1:2 in the high-pressure experiments reported here. It is noted that the i_{80} value was reduced to approximately 85% of its observed value to correct for contributions from 1,3-butadiene internal chemistry. This correction was based on the abundance of the m/z 80 ion relative to that of m/z 93 observed in the ICR spectrum and in the high-pressure experiments with 1,3-butadiene alone.[5]

The time dependence of the (1,3-butadiene plus vinyl methyl ether) cation radical reaction was probed by using Fourier transform mass spectrometry.[11] Both the 1,3-butadiene and the vinyl methyl ether cation radicals disappeared; hence, both are reactive ions (Figure 2). The 1,3-butadiene cation radical is clearly the more reactive ion . Furthermore, the abundance of the m/z 58 ion increases for approximately 100 ms and then decreases. This occurs because the 1,3-butadiene cation radical initially charge exchanges with neutral vinyl methyl ether to produce m/z 58, which subsequently reacts to form m/z 80 and 97.

The rate constant for the reaction of the 1,3-butadiene cation radical and neutral vinyl methyl ether was determined in order

Scheme I



to assess the efficiency of the charge-exchange reaction. This charge exchange appears to be the principal reaction of the 1,3-butadiene cation radical because the extent of disappearance of m/z 54 at short reaction times is nearly compensated for by the increase in the abundance of m/z 58. The rate constant was determined in a relative manner by using the rate constant for the reaction of ionized 1,3-butadiene with its corresponding neutral as a bench mark ($k = 7.4 \times 10^{10}$ cm^3 molecule^{-1} s^{-1}).[5] The rate constant for reaction with vinyl methyl ether is approximately 3.8 times larger than that for reaction with neutral 1,3-butadiene, or $k = 2.8 \times 10^{-9}$ cm^3 molecule^{-1} s^{-1}.

The efficiency of the reaction may be estimated by comparing the experimental rate constant and the theoretical collision constants. These are the Langevin collision constant[12a] (calculated to be 1.2×10^{-9} cm^3 molelcule^{-1} s^{-1}), the average dipole orientation (ADO) collision constant[12b] (calculated to be 1.4×10^{-9} cm^3 molecule^{-1} s^{-1}), and the locked dipole orientation (LDO) collision constant[12b] (calculated to be 3.1×10^{-9} cm^3 molecule^{-1} s^{-1}). The Langevin value is probably too low because the theory does not include any dipole moment in the reacting neutral. The agreement with the ADO constant is poor, which would be expected for a near-resonant charge-exchange reaction (ionizing energy (IE) for 1,3-butadiene is 9.03 eV, IE for vinyl methyl ether is 8.95 eV).[13] This reaction would be expected to be highly efficient because transfer of an electron can occur over long distances.

Double resonance or ion ejection experiments, done by using the FTMS technique, produce results consistent with the above interpretation. Separate experiments in which first m/z 54 and then m/z 58 were ejected resulted in significant and nearly equal decreases in the abundances of m/z 80 and 97. It follows that both the 1,3-butadiene and the vinyl methyl ether cation radicals contribute nearly equally to the product ions that are observed; however, the 1,3-butadiene reacts principally in an *indirect* manner by charge exchanging with neutral vinyl methyl ether to produce m/z 58 which in turn reacts with neutral 1,3-butadiene to give the condensation products (see Scheme I).

Mechanism. The reaction of the vinyl methyl ether cation radical and neutral 1,3-butadiene conducted at low pressure produces principally m/z 80, which corresponds to the elimination of methanol from the adduct. This elimination is a characteristic decomposition of the 4-methylcyclohexene cation radical. Other product ions of lesser abundance also form, most notably m/z 97 from the methyl radical elimination, but minor amounts of these ions also originate from the reference compound, 4-methoxycyclohexene. Furthermore, the deuterium labeling studies of van Doorn et al. are consistent with a regiospecific 1,3 methanol elimination from both the ion–molecule adduct and the 4-methoxycyclohexene cation radical.[4] These observations are strong evidence for the formation of a single $C_7H_{12}O^{+\cdot}$ adduct at low pressure, which has the same structure as ionized 4-methoxycyclohexene.

In contrast to the low-pressure experiments, the products formed in a high-pressure source containing a mixture of 1,3-butadiene and vinyl methyl ether include abundant ions corresponding to the eliminations of both CH_3OH and $\cdot CH_3$ from the adduct. The stabilized ion–molecule adduct no longer bears any resemblance to the 4-methoxycyclohexene cation radical when analyzed by

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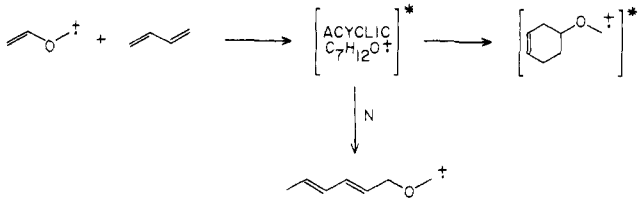
Scheme II

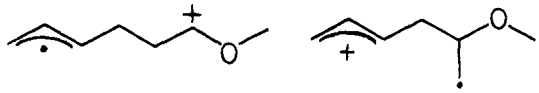


CAD spectroscopy; in this case, the loss of $\cdot CH_3$ is the most important process and the loss of CH_3OH is barely detectable.

To attribute the differences found in the decompositions of the stabilized and unstabilized adducts to different amounts of internal energy effects would be unprecedented. Usually, internal energy effects are minimal. In fact, for those cases where internal energy does affect fragmentation, the variations in relative abundance are less than a factor of 2.[14]

The observation of two different structural adducts at high and low pressure may be reconciled by invoking either parallel reactions producing two adducts or sequential reactions. If the two structures are the result of parallel reaction channels, then there should be evidence for both structures in both the high- and low-pressure experiments. However, the decompositions of the unstabilized adduct can be accounted for entirely in terms of only one structure, i.e., 4-methoxycyclohexene cation radical. Furthermore, there is little or no evidence for the 4-methoxycyclohexene cation radical in the CAD spectrum of the stabilized adduct. Alternatively, invoking a sequential mechanism permits us to consolidate the results. The cyclic structure would not necessarily be observed under conditions of high pressure if its acyclic precursor is intercepted by stabilizing collisions.

Evidence for the structure of the adduct which serves as a precursor for 4-methoxycyclohexene can be obtained from a study of its CAD spectrum. The spectrum matches well with that of 1-methoxy-2,4-hexadiene. The reaction of 1,3-butadiene with vinyl methyl ether cation radical to form precisely 1-methoxy-2,4-hexadiene cation radical is unlikely because it would require the formation of a double bond between the two reacting species. More feasible candidates are structures a and b which involve reaction at the 1-position of 1,3-butadiene. However, it is difficult



a b

to generate unambiguously these cation radicals so that their CAD spectra can be compared with that of the stabilized adduct. Thus, there remains some uncertainty in the structural assignment of the precursor for the acyclic adduct. Nevertheless, the close match between the CAD spectrum of the adduct and the 1-methoxy-2,4-hexadiene cation radical is good evidence that the initially formed adduct is acyclic.

A mechanism which accounts for these observations is proposed in Scheme II. The methyl vinyl ether cation radical reacts with 1,3-butadiene to produce an acyclic structure which, in the absence of stabilizing collisions, cyclizes to give an activated 4-methoxycyclohexene cation radical. This cyclic adduct dissipates some of its internal energy by undergoing the very characteristic loss of methanol. Under higher pressure conditions, where collisional stabilization is possible, the initially formed adduct can be observed. On the basis of the favorable comparison of its CAD spectrum with that of 1-methoxy-2,4-hexadiene, the structure of this adduct is assigned to be acyclic. The overall mechanism is a two-step cycloaddition.

We believe these results bear on the interpretation of cycloadditions involving cation radicals in solution. For these condensed-phase reactions, it has been postulated[1,6a] that a concerted (4 + 1) cycloaddition mechanism[15] pertains. Indeed, in this case, the principal precursor for the gas-phase cycloaddition is the ionized olefin rather than the ionized diene. However, the gas-phase cycloaddition is *not* concerted but rather proceeds by formation of an acyclic intermediate which, in the absence of stabilizing collisions, cyclizes to give the 4-methoxycyclohexene cation radical.

Experimental Section

Mass Spectrometry. The CAD spectra and the mass spectra of the ions formed in the 13–390-mtorr pressure range were recorded by using a Kratos MS-50 triple analyzer mass spectrometer of EBE design, which has been described previously.[7] Ion–molecule reactions were run in a commercially available (Kratos Scientific Instruments) chemical ionization source which was operated at ambient temperature to reduce arcing. Source pressures were estimated by using an ion gauge located in the source-pumping manifold. A linear calibration was obtained by plotting pressure data obtained with a Hastings gauge vs. that of the ion gauge. The Hastings gauge was mounted on a probe which abutted against the CI source entrant. This calibration was tested by recording the methane spectrum at various pressures and matching the i_{41}/i_{43} ratios to those reported earlier.[16] The corresponding pressures were compared and found to agree within 30%. Thus, ion gauge values of 1×10^{-5} and 5×10^{-4} torr corresponded to source pressures of approximately 3 and 500 mtorr, respectively.

The 1,3-butadiene (Matheson instrument grade) and the carbon disulfide (Matheson, Coleman, and Bell reagent grade) were admitted to the mass spectrometer through a commercially available (Kratos Scientific Instruments) reagent gas inlet system. Vinyl methyl ether (Matheson) was admitted to the mass spectrometer through a custom-fabricated all-glass heated inlet system operated at 100 °C.

Fourier transform mass spectra were recorded by using a home-built mass spectrometer operated in the heterodyne mode,[11] controlled by a Nicolet FTMS 1000 data system and associated electronics. Both 1,3-butadiene and vinyl methyl ether were admitted to the spectrometer by using a heated inlet system. Typical operating pressures were 5×10^{-7} torr for experiments involving only one reagent and 1×10^{-6} torr for experiments conducted by using a 1:1 mixture of the two. The pressure values reported are uncorrected ion gauge measurements. Time-delay experiments were performed by acquiring spectra at 50-ms intervals at delay times varying from 1 to 501 ms. The ion abundances of interest were obtained by integration of the observed peaks.

Reference Compounds. The reference compounds which were synthesized were characterized by mass spectrometry (Kratos MS-50 triple analyzer)[7] and NMR spectroscopy (Varian EM-390 90-MHz spectrometer).

1-Methoxy-2,4-hexadiene. This compound was obtained from sorbyl alcohol (2,4-hexadien-1-ol) by using the method of Paquette, Zon, and Taylor.[17] The sorbyl alcohol was prepared by a lithium aluminum hydride reduction of methyl sorbate and was the generous gift of Dr. W. Zeller. The methyl ether was purified by using preparative gas chromatography (2 m, 5% SE-30 column, column temperature 90 °C, and flow rate 60 mL/min). NMR (90 MHz, $CDCl_3$): δ 6.33–5.39 (m, 4, =C*H*), 3.90 (d, 2, CH_2), 3.29 (s, 3, OCH_3), 1.73 (d, 3, CH_3).

3-Methoxy-1,5-hexadiene. This compound was prepared from 1,5-hexadien-3-ol (Aldrich Chemical Co.).[17] The methyl ether was purified by preparative gas chromatography (2 m, 5% SE-30 column, column temperature 115 °C, and flow rate 55 mL/min). NMR (90 MHz, $CDCl_3$): δ 5.93–5.49 (m, 2, =C*H*), 5.23 (br s, 1, =C*H*), 5.11 (br d, 2, =CH_2), 4.95 (br s, 1, =C*H*), 3.58 (br q, 1, C*H*), 3.27 (s, 3, OCH_3, 2.32 (br t, 2. CH_2).

4-Methoxycyclohexene. This compound was prepared from 3-cyclohexen-1-ol.[17] 3-Cyclohexen-1-ol was prepared by the method of Staroscik and Rickborn[18] starting with 1,4-cyclohexadiene (Aldrich). The methyl ether was purified by preparative gas chromatography (2 m, 5% SE-30 column, column temperature 80 °C, and flow rate 60 mL/min). NMR (90 MHz, $CDCl_3$): δ 5.58 (br s, 2, =C*H*), 3.43 (m, 1, C*H*), 3.35 (s, 3, OCH_3), 2.38–1.50 (complex, 6, CH_2).

3-Methoxycyclohexene. 2-Cyclohexenone (Aldrich) was reduced in diethyl ether by using lithium aluminum hydride. The resulting 2-cyclohexenol was converted to 3-methoxycyclohexene.[17] The product ether was purified by fractional distillation: bp 128–133 °C/ambient pressure. NMR (90 MHz, $CDCl_3$): δ 5.54 (br s, 2, =C*H*), 3.58 (br t,

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1, CH), 3.23 (s, 3, OCH_3), 2.08-1.40 (complex, 6, CH_2).

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Registry No. CH_2=CHCH=CH_2, 106-99-0; CH_3CH=CHCH=C-HCH_2OCH_3, 16277-66-0; CH_2=$CHCH_2CH(OMe)CH$=CH_2, 82574-81-0; methyl vinyl ether cation radical, 59123-15-8; 4-methoxycyclohexene, 15766-93-5; 3-methoxycyclohexene, 2699-13-0.

Ab Initio Calculations of the Li^+ and Na^+ Affinities of Aziridine and Ethylene Oxide Rings

A. M. Sapse,*† J. D. Bunce,† and Duli C. Jain‡

Contribution from the City University of New York Graduate Center and John Jay College, New York, New York 10019, and York College of the City University of New York, Jamacia, New York 11451. *Received October 18, 1983*

Abstract: Li^+ and Na^+ affinities of the aziridine and ethylene oxide rings are calculated at the Hartree-Fock level with 6-31G* and 6-21G basis sets, respectively. The purpose of the calculations is to investigate the possible influence of the presence of the ions on the carcinogenicity of the ethylene oxide ring and on the antitumor activity of aziridine-containing drugs, such as mitomycin. The energy of activation of the opening of the ammoniated aziridine ion under nucleophilic attack by NH_3 is found to be slightly higher than that in the case of protonated aziridine, as calculated by Kikuchi et al.[15c]

The pH dependence of the activity of some carcinostatic drugs has formed the object of several studies.[1] The mitomycins, powerful antibiotics used as antitumor therapeutic agents against many forms of cancer,[1,2] are thought to act via the opening of the aziridine ring whose presence in the drug is responsible for its activity. Mitomycins interact with DNA either by alkylation, an easily repaired event, or by interstrand cross-linking, a lethal effect to the cell. As such, the interaction with the biological target DNA is considered to be the primary event in mitomycin's activity. Two different mechanisms have been proposed for the opening of the aziridine ring. The first one consists of the opening of the ring under nucleophilic attack by one of the DNA bases (most probably the O6 of guanine).[1] In the second one, proposed by Moore,[3] the ring opens by intramolecular rearrangements, a double bond is formed, and the nucleophilic attack by DNA occurs at one of the ends of the double bond.

The latter mechanism has been supported by the experiments of Tomasz and Lipman[4] and of Kohn and Zein.[5] A theoretical determination of the activation energy for the opening of the double bond under nucleophilic attack gives a value of 12 kcal/mol.[6] Both the above-mentioned reactions recognize the fact that mitomycins belong to the class of bioreductive alkylating agents. Also, both reactions show the activation to occur at low pH. A reason for this can be found in the increased ability of aziridines to undergo opening when a proton is attached to nitrogen.[7] Even though the basicity of the aziridine ring in mitomycin C is found to be small,[8] it is still to be presumed that a positive charge attached to the nitrogen will facilitate the opening of the ring.

Another class of compounds, this time carcinogens, the ethylene oxides, also are presumed to open under nucleophilic attack, made easier by the attachment of a proton to oxygen. As such, it seems clear that a positive charge attached to either the nitrogen of the aziridine ring or to the oxygen of the ethylene oxide will have influence on their biological activity. However, at physiological pH, an acidic activation is not to be expected. In this work, we examine the possibility of replacing the proton by a metal ion such as Li^+ or Na^+. Indeed, it has been shown by Del Bene et al.[9] that many nitrogen and oxygen bases exhibit substantial Li^+ affinity, related by an almost linear relationship to their proton affinity. To those, one of us and a co-worker[10] have added the calculation of the Li^+ affinity of guanidine, found to be around 70 kcal/mol. Accordingly, we calculate the Li^+ and Na^+ affinities of aziridine and ethylene oxide and compare them to their proton affinities. We also calculate the activation energy for the aziridine ring opening under nucleophilic attack by ammonia in the presence of an ammonium ion attached to the nitrogen of the ring.

Method and Results

For the Li^+ and Na^+ affinities to be obtained, ab initio Hartree-Fock calculations are performed with the GAUSSIAN-80 program.[11] The bases (aziridine and ethylene oxide), the acids, and the Li^+ compounds are subjected to geometry optimization using the 6-31G*[12a] basis set which adds polarization functions to all the atoms except hydrogen. Indeed using a fairly large basis set will decrease the superposition error. For the Na^+ compounds, the 6-21G[12b] basis set is used. For the error of using a smaller basis set to be tested, the 6-21G basis set is also used for calculations of the bases and of the Li^+ compounds. In each case, complete optimization is performed with the exception of Na^+ compounds where only the Na-O and Na-N distances are op-

†City University of New York Graduate Center and John Jay College.
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