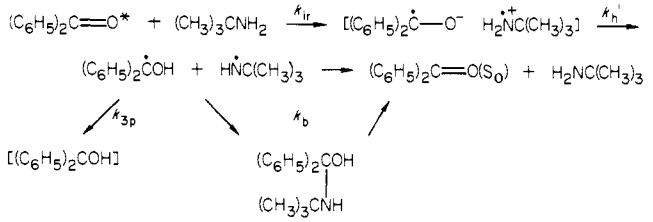
Scheme III



by naphthalene of photoreduction of benzophenone by the amines, based on $k_q = 6 \times 10^9$ M^{-1} s^{-1}. The rapid reaction of 0.06 M benzophenone, 0.1 M 2-aminobutane, 4 M TBA, and 0.1 M 1-pentanethiol led to benzopinacol, 90%, and *N*-2-butylidene-2-aminobutane,[7] 76% yield. The slow reduction of 0.06 M benzophenone by 4 M TBA did not go to completion; the reduction of 0.01 M ketone led to benzopinacol.

Reaction of benzophenone triplet with TBA forms ketyl radical with $\varphi = 0.96$.[5] However, TBA has no α H, and quantum yield for net reduction of ketone is low, $\varphi \sim 0.06$ (experiment 1, Table 1), indicating that ketyl and aminyl radicals disproportionate, either directly or after combination, much more rapidly than ketyl radicals dimerize (Scheme III). A low rate constant for aminyl coupling would lead to a high steady-state concentration of aminyl radical and contribute to a high rate of ketyl–aminyl reaction.

2-Aminobutane and diisopropylamine, containing both NH and α-CH, may lead to both α-aminoalkyl and alkylaminyl radicals (Scheme II, k_h and k'_h). The former reduces ground-state ketone and is necessary for efficient photoreduction; the latter would disproportionate with ketyl radical (Scheme III, k_b), regenerate starting materials, and reduce quantum yields.

1-Pentanethiol, which interacts directly with little of the triplet and is a very inefficient reducing agent ($\varphi \sim 0.03$, experiment 2), increases reduction by 2-aminobutane and diisopropylamine, from $\varphi = 0.79$ and 0.56 (experiments 3 and 7) to $\varphi = 1.20$ and 1.29 (experiments 4 and 8). Reduction by the tertiary amine is decreased slightly by thiol (experiments 11 and 12). When 4–5 M TBA is added to these three amines (experiments 5, 9, and 13), quantum yields are greatly decreased. Then, addition of 0.02–0.1 M 1-pentanethiol (experiments 6, 10, and 14) increases the quantum yields of the TBA-retarded reductions, tenfold in the case of 2-aminobutane, fivefold for the secondary amine, and nearly twofold for the tertiary amine.

The retardations by TBA (experiments 5, 9, and 13) are consistent with the extent to which it reacts with triplet and lead to little net reduction (Scheme III). We propose that the thiol counters this effect by catalyzing conversion of an aminyl radical to an α-aminoalkyl radical. The aminyl radical abstracts hydrogen from the thiol, and the thiyl radical abstracts hydrogen from the α-carbon of the reducing amines (eq 1 and 2a). Catalysis by thiol

$$(CH_3)_3CNH\cdot + RSH \rightarrow (CH_3)_3CNH_2 + RS\cdot \quad (1)$$

$$RS\cdot + >CHN< \underset{2b}{\overset{2a}{\rightleftharpoons}} RSH + >\dot{C}N< \quad (2)$$

in the absence of TBA (experiments 4 and 8) would be caused similarly, as alkylaminyl radicals from primary and secondary amines (Scheme II, k'_h) may be converted to aminoalkyl radicals by a sequence corresponding to eq 1 and 2a. The tertiary amine leads only to aminoalkyl radicals, and inefficient retardation is observed, via eq 2b. α-Aminoalkyl radicals are more stabilized than α-hydroxyalkyl radicals by overlap of the unpaired electron with nonbonding electrons of the heteroatom. They may abstract hydrogen from S of thiols less rapidly than do α-hydroxyalkyl radicals,[1,8] in competition with their being oxidized by ground-state ketone (Scheme I).[9,10] Thus, aromatic thiols retard photoreduction by amines, but less effectively than that by alcohols,[1] and aliphatic thiols, with stronger S–H bonds, may show very weak retardation, which is observed only with the tertiary amine (experiment 12).

In reduction by alcohols, direct abstraction from α C occurs, and alkoxyl radicals are generally not formed. In reduction by amines, the charge-transfer mechanism and the lower bond energy of N–H vs. O–H allow formation of alkylaminyl radicals from primary and secondary amines, which then may regenerate starting material. However, H· is readily abstracted from S of thiols, even by triphenylmethyl radical,[11] and the unstabilized aminyl radicals may also do this rapidly (eq 1) in competition with disproportionation with ketyl. Thiols have unusual properties in that although H· may be abstracted very rapidly from S the resulting thiyl radicals are highly reactive, notably, but not only, in abstracting H·, in this case from α C of amines, forming stabilized α-aminoalkyl radicals (eq 2a). Such hydrogen transfers from and to sulfur compete effectively with other possible hydrogen abstractions and with radical combination.[12] They may lead to inhibition,[2] or to change of products,[13] as in photoreduction by alcohols, or to catalysis, as in the change of identity of radicals[14] and in the decarbonylation of aldehydes.[15] In the present case, catalysis by the sequence of hydrogen transfers is further favored, as combination of thiyl and ketyl radicals and thiyl and α-aminoalkyl radicals regenerates thiol, and disulfide is reduced by ketyl radical to thiol and thiyl radical.[8]

Acknowledgments. This work was supported by the National Science Foundation Grant CHE 78-09333.

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(9) Cohen, S. G.; Stein, N. *J. Am. Chem. Soc.* **1969**, *91*, 3690.
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(11) Colle, T. H.; Lewis, E. S. *J. Am. Chem. Soc.* **1979**, *101*, 1810.
(12) Cohen, S. G. *Organosulfur Chem.* **1967**, 33.
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(14) Cohen, S. G.; Wang, C. H. *J. Am. Chem. Soc.* **1957**, *79*, 4104.
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Ion–Molecule Complexes in Unimolecular Fragmentations of Gaseous Cations. Cyclization of Unsaturated Carbocations in the Gas Phase

Sir:

The cyclization exemplified by reaction 1 constitutes a major pathway in terpene biosynthesis.[1] This intramolecular electrophilic addition represents an endocyclic closure,[2] since both sp^2 carbons at the unsaturated terminus of cation **1** are incorporated into the

(1)

ring that is formed. Although there are some exceptions,[3] most of the reported examples form six-membered ($n = 3$) or larger rings, a result that has led to the suggestion that endocyclic attack of double bonds is disfavored for shorter chain lengths.[2] A major

(1) Coates, R. M. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 73–230.
(2) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
(3) Exceptions not noted in ref 2 include the biosyntheses of the cuparane and kaurane skeletons (ref 1) and a recently reported synthetic route to cyclopentanones: Cookson, R. C.; Smith, S. A. *J. Chem. Soc., Chem. Commun.* **1979**, 149–150.

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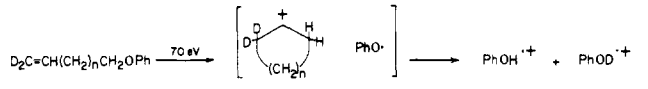
Table I. Percent Ionization (of $m/z \geq 39$) of Phenol-d_1 and Phenol-d_0 Fragment Ions from Deuterated Analogues of of Compounds 1-3



	% Σ_{39}	
n = 2	33	1.9
n = 3	35	2.0
n = 4	41	0.8

piece of evidence derives from solvolysis studies, which show that precursors of 4-pentenyl cations (**1**, where $n = 2$) exhibit no rate enhancement relative to saturated analogues under conditions where the next higher homologue ($n = 3$) exhibits appreciable rate enhancement.[4]

We have initiated a program to investigate rearrangements of ions in the gas phase and wish to report relative rates of cyclization for cations that formally pass through structure **1** ($n = 2$–4). We have previously shown[5] that molecular ions of phenoxyalkanes decompose via ion–molecule complexes (reaction 2) that are

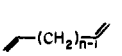
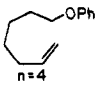
$$\mathrm{ROPh} \xrightarrow{70\ \mathrm{eV}} \text{molecular ion} \rightarrow \underset{\text{ion–molecule complex}}{[\mathrm{R}^+\ \mathrm{PhO}\cdot]} \rightarrow \underset{m/z\ 94}{\mathrm{PhOH}^{+}\cdot} + \text{olefins} \quad (2)$$

composed of cations, R^+, electrostatically bound to phenoxyl radicals. The ultimate products from these ion–molecule complexes arise via proton transfer from the carbocation to the relatively basic phenoxyl radical. Within ion–molecule complexes, alkyl cations (R = propyl, butyl, or neopentyl) live sufficiently long to undergo the same hydride and methyl shifts that are seen from solution phase studies.[5]

The intermediacy of ion–molecule complexes has also been inferred for ion–molecule reactions[6] and for unimolecular fragmentation of oxonium ions.[7] In previous studies,[5,8] we have ruled out virtually all reasonable alternatives to reaction 2 in olefin production from 70-eV electron bombardment of phenoxyalkanes. If we presume that this mechanism can be generalized to other phenyl ethers, then reaction 2 provides a method for examining carbocations that are free from counterion and solvent effects. We describe here results consistent with this hypothesis for terminally unsaturated phenoxyalkenes.

We have examined the products of reaction 2 for R = 4-pentenyl (**2**), 5-hexenyl (**3**), and 6-heptenyl (**4**). Our methodology employs two techniques: mass spectrometry of deuterated analogues and collection of neutral products from a specially constructed electron bombardment flow (EBFlow) reactor.[8] Mass spectrometry is used to examine the ionic product of reaction 2, phenol molecular ion, which results from proton transfer to the phenoxyl radical. The production of phenol-d_1 fragment ions (m/z 95) in the mass spectra of the deuterated compounds shown in Table I indicates that cyclization occurs.[9]

Table II. Neutral $C_{n+3}H_{2n+2}$ Isomers Recovered from 70-eV Radiolyses of ω-Phenoxy-1-alkenes at 10^{-5}–10^{-4} torr

SUBSTRATE	FRACTION OF RECOVERED $C_{n+3}H_{2n+4}$		
			other linear dienes
2  n=2	0.08	0.25	0.65
3  n=3	0.28	0.16	0.37
4  n=4	0.04	0.24	0.43

In forming the ion–molecule complex, the carbocation rearranges via cyclization (reaction 1) or hydride shift (reaction 3).

$$\mathbf{1} \rightarrow \mathrm{H_2C{=}CH(CH_2)_{n-1}\overset{+}{C}HCH_3} \rightarrow \mathrm{H_2C{=}CH(CH_2)_{n-2}\overset{+}{C}HCH_2CH_3} \rightarrow \text{etc.} \quad (3)$$

If cyclization were to take place in every ion, then $PhOH^{+}\cdot$ and $PhOD^{+}\cdot$ would be observed to equal extents from the reaction shown in Table I (neglecting the deuterium kinetic-isotope effect, which in other systems has a value $k_H/k_D = 1.3$[5,11]), provided that scrambling does not occur in the cyclized cation. From solution NMR studies[12] and solvolysis experiments,[13] however, it is known that cycloalkyl cations rapidly undergo unimolecular scrambling. Mass spectrometry, therefore, gives a lower limit for the extent of cyclization, since scrambling will diminish the likelihood that a deuteron will be transferred to phenoxyl.

From the proportions of $PhOD^{+}\cdot$ in Table I, cyclization occurs in at least 5–10% of the ion–molecule complexes, but the data may result not only from the α,ω closure (reaction 1) but also from the closure of hydride-shifted cations (e.g., the secondary cations shown in reaction 3) to form smaller rings. A definitive analysis can be obtained only by examination of the neutral products from reaction 2. From the mass spectrometric result for $n = 2$, we predict (neglecting the possibility of scrambling) that the bulk of recovered neutral C_5H_8 from ionization of 1-phenoxy-4-pentene (**2**) should be linear dienes but that a fraction on the order of one-tenth will be cyclopentene. EBFlow radiolysis with 70-eV electrons shows this very result, as summarized in Table II. Although it is conceivable that some of the recovered products may have come from other sources (e.g., cyclization of 4-pentenyl radicals[14] or free C_5 cations), the congruence of the mass spectrometric and EBFlow results for **2** points to an ion–molecule complex as the source of cyclopentene.

The observation of cyclopentene from **2**, cyclohexene from **3**, and cycloheptene from **4** confirms that reaction 1 takes place.[15]

(4) Bartlett, P. D.; Closson, W. D.; Cogdell, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 1308–1314.
(5) Morton, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 1596–1602.
(6) See, for example: Stewart, J. H.; Shapiro, R. H.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 7650–7653.
(7) Bowen, R. D.; Williams, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 2752–2756, and references contained therein.
(8) Burns, F. B.; Morton, T. H. *J. Am. Chem. Soc.* **1976**, *98*, 7308–7313.
(9) Compounds **2** and **3** were prepared from phenoxide attack on the tosylates of the corresponding, commercially available alcohols. Compound **3** was prepared from **2** by hydroboration and workup with basic hydrogen peroxide, followed by oxidation with pyridinium chlorochromate to 6-phenoxyhexanal, which was converted to **4** via a Wittig reaction with methylenetriphenylphosphorane. The deuterated analogues in Table I were prepared from their next lower homologues by the same procedure by use of methylene-d_2-triphenylphosphorane. All materials were purified by preparative GLC on a 1.5 m × 0.25 in. 15% FFAP on 60/80 Chrom W/AW-DMCS column.
(10) The phenol molecular ion is the base peak in all of the compounds studied, and high-resolution mass spectrometry was required to separate $PhOD^{+}\cdot$ from the natural abundance $PhOH^{+}\cdot$–^{13}C. The percent ionization of ions $m/z \geq 39$ (%Σ_{39}) reported in Table I was determined by correcting the $PhOD^{+}\cdot$ intensity for a small fraction of $PhOH_2^{+}$ that cannot be resolved from it (but which occurs in the mass spectra of undeuterated analogues at an intensity approximately one-seventieth of the base peak).
(11) Benoit, F. M.; Harrison, A. G. *Org. Mass Spectrom.* **1976**, *11*, 599–608.
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(14) Watkins, K. W.; Olsen, D. K. *J. Phys. Chem.* **1976**, *76*, 1089–1092.

Other cyclized isomers are recovered from **2** and **3** besides those listed in Table II. Two pathways account for this, ring contraction of cycloalkyl cations and cyclization of secondary cations from reaction 3. Ring contraction of cyclohexyl to 1-methylcyclopentyl and of cycloheptyl to 1-methylcyclohexyl cations occurs rapidly (such that cyclohexyl and cycloheptyl have never been seen by NMR in solution[12]), and we recover the anticipated neutrals[16] in the EBFlow experiments, 1-methylcyclopentene from **3** (0.06 of the C_6H_{10} yield) and 1-methylcyclohexene plus methylenecyclohexane from **4** (0.09 and 0.03 of C_7H_{12}, respectively). We also recover products expected from cyclization of secondary cations: 3- and 4-methylcyclopentene (0.04 or C_6H_{10}; we do not separate these two isomers on our GLC column) from **3**; 3- and 4-methylcyclohexene (0.07 and 0.04 of C_7H_{12}, respectively) from **4**.

Our results not only provide positive evidence of reaction 1 for $n = 2$–4 but also permit us to estimate relative rates of cyclization. In every case, hydride shift (reaction 3) is in competition with cyclization (reaction 1). For the 5-hexenyl case, hydride shift is roughly two times faster; for 4-pentenyl, hydride shift is ten times faster (relative rates are based on the neutral product distributions). If we assume that a 2,1-hydride shift has the same rate constant for all of the cations studied, the implication is that endocyclic electrophilic attack to form a six-member ring is only four to five times faster than to form a five-member ring and that closure to form a seven-member ring is less than twice as fast as to form a five-member ring.

This study quantifies the notion of favoritism for endocyclic closures of the parent cation **1**. In addition, it illustrates how the mechanism of reaction 2 can be used to build a bridge between the realm of mass spectrometry and that of solution chemistry. The analogy between the chemistry of gaseous ion–molecule complexes and solvolysis chemistry seems apt and is the basis of continuing investigations.

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Supplementary Material Available: Mass spectra of compounds **2**–**4** and their d_2 analogues and product distributions from EBFlow radiolyses of compounds **2**–**4** (7 pages). Ordering information is given on any current masthead page.

(15) Standard control runs (see ref 5) rule out production of the observed products from filament pyrolysis. In an ancillary study, we find that 70-eV electron bombardment of phenoxycyclohexane produces cyclohexene as ≥95% of the C_6H_{10} yield, with methylcyclopentene isomers constituting most of the remaining C_6H_{10}.

(16) Marinelli, W. J.; Morton, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 3536-3539; **1979**, *101*, 1908.

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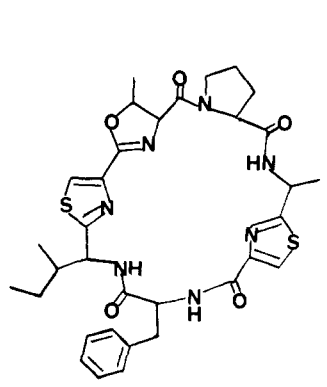
Ulicyclamide and Ulithiacyclamide, Two New Small Peptides from a Marine Tunicate

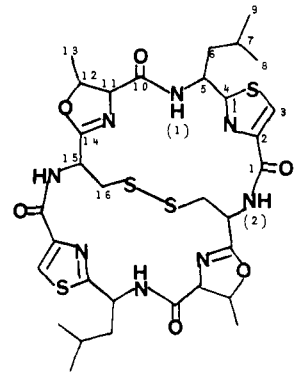
Sir:

Current interest in small peptides, many of which possess antimicrobial or neurophysiological properties,[1] prompts us to report isolation and structure of two new peptides which we encountered in our research into the molecular basis of marine symbiosis.[2]

MeOH extraction of the ascidian *Lissoclinum patella*[3,4] (freeze-dried, 82 g) from Palau, Western Caroline Islands, furnished 0.7 g of residue. Chromatography on Sephadex LH-20 (CH_2Cl_2/hexane, 4:1) and then BisSil A (EtOAc/aqueous NH_3, 95:5) yielded 40 mg of ulicyclamide (**1**) and 35 mg of ulithiacyclamide (**2**) as colorless oils, in addition to several minor constituents.



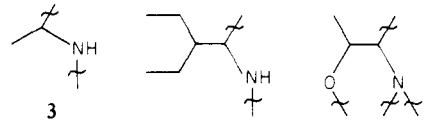
1



2

Ulicyclamide (**1**) has a molecular formula $C_{33}H_{39}N_7O_5S_2$: $[\alpha]^{25}_D$ +35.7° (*c* 2.3, CH_2Cl_2); UV λ_{max} (MeOH) 248 nm (ϵ 7900); high-resolution mass spectroscopy (HRMS), calcd, 677.2439;[7] found, 677.2446. The electron-impact mass spectroscopy (EIMS) exhibited additional peaks at m/z 620 ($M^+ - C_4H_9$) and 586 ($M^+ - C_7H_7$). The IR spectrum was transparent in the OH and COOR regions but showed intense absorptions at 3300, 1670, and 1650 cm^{-1}, indicating peptide linkages. A cyclic peptide was suggested by the lipophilic nature of **1**.

The ^{13}C NMR spectrum of ulicyclamide (Table I) exhibited signals for all 33 carbons. Four singlets between δ 171.9 and δ 170.5 denote a tetrapeptide. Signals for phenylalanine and proline were readily assignable. The olefinic region contained signals for two thiazole rings [161.1 (s), 160.5 (s), 151.4 (s), 148.9 (s), 124.3 (d), and 123.8 (d)]. The 220-MHz ^1H NMR spectrum (Table I), including spin–spin decoupling experiments, confirmed the phenylalanine and proline assignments and exhibited signals at δ 8.08 (1 H, S) and δ 8.03 (1 H, s) for the two thiazole rings, and exhibited signals for three isolated spin systems assignable to part structures **3** [δ 9.06 (1 H, d, J = 5 Hz), 5.38 (1 H, dq, J = 7, 5 Hz), 1.71 (3 H, d, J = 7 Hz)], **4** [δ 7.85 (1 H, d, J = 10 Hz), 5.26 (1 H, dd, J = 10, 7 Hz), 2.60 (1 H, m), 1.20 (2 H, m), 0.85 (3 H, t, J = 7 Hz), 0.75 (3 H, d, J = 7 Hz)], and **5** [δ 4.82 (1 H, dq, J = 4, 7 Hz), 4.26 (1 H, d, J = 4 Hz), 1.44 (3 H, d, J = 7 Hz)].



3 4 5

Hydrolysis of ulicyclamide in refluxing 6 N HCl overnight followed by treatment with C_6H_5COCl and CH_2N_2 yielded *N*-

(1) See, e.g.: *Amino-acids, Pept., Proteins*, **1978**, *9*, 395-416, and previous volumes.

(2) Ireland, C.; Scheuer, P. J. *Science (Washington, D.C)* **1979**, *205*, 922-923.

(3) Eldredge, L. G. *Micronesica* **1966**, *2*, 161-259.

(4) Family Didemnidae, order Enterogona, class Ascidiacaea, subphylum Urochordata (tunicates), phylum Chordata.

(5) The animal was first collected by Mark Yunker in August 1977 and was identified by Dr. Ralph Lewin.

(6) *Uli* in Hawaiian denotes a dark color, as the deep blue of the ocean or the green of vegetation. This ascidian is dark green.

(7) Electron-impact mass spectra were determined on a Varian MAT 311 instrument. The high-resolution mass spectra were measured at the University of Illinois. NMR data (100 MHz ^1H and 25.4 MHz ^{13}C) were determined on a Varian XL 100 spectrometer; proton data at 220 MHz were measured at the facility at the University of California, San Diego.

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