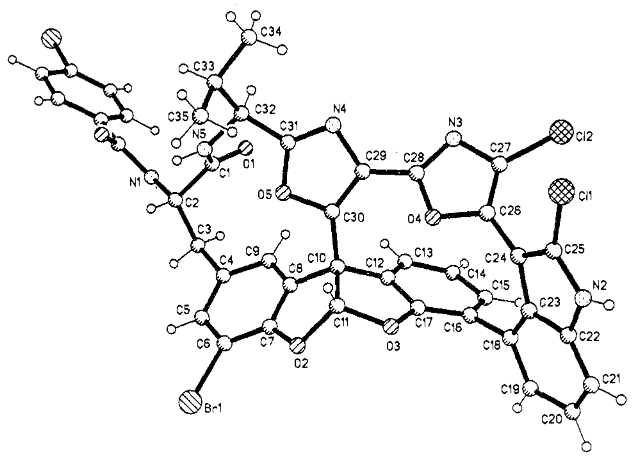

Figure 1. A computer-generated perspective drawing of **3**. The absolute stereochemistry shown was determined by using anomalous dispersion measurements in the X-ray diffraction study.

the structure of diazonamide B (**2**) from **3**, two questions had to be answered: was O2 or O3 bonded to C11, and what was the stereochemistry at C11? The hemiacetal ring involved O3 rather than O2 in diazonamide B (**2**), on the basis of a three-bond correlation observed between the C11 proton and C17. The stereochemistry at C11 proved intractable. Molecular mechanics studies[10] of the hemiacetal **2** and its corresponding aldehyde indicate a small preference (~1 kcal/mol) for the *R* configuration at C11 (OH down in the drawing) in the hemiacetal and a small preference (~1 kcal/mol) for aldehyde conformations in which the *si* face of the aldehyde faces O3, also leading to an *R* configuration at C11. But these calculated differences are too small to assign the C11 stereochemistry securely.

The similarity of ^{1}H and ^{13}C NMR data and the UV and IR spectra for diazonamide A (**1**) and B (**2**) indicated an identical polycyclic nucleus for A, except for the replacement of the C6 bromine by hydrogen. Diazonamide A (**1**) differed from B (**2**) in containing an extra valine residue. On the basis of a downfield shift of C2-H (δ 4.56 in **1** compared to δ 3.30 in **2**) and an 8.5-Hz coupling in **1** of C2-H to the amide proton at δ 7.67 in DMSO-d_6, the valine carboxyl was attached to N1. The absolute stereochemistry of this terminal valine was not determined.

Diazonamides A (**1**) and B (**2**) represent an entirely new class of halogenated, highly unsaturated cyclic peptides containing derivatives of at least three common amino acids: a 3,4,5-trisubstituted L-tyrosine (C1–C9), a tryptophan substituted at the 2- and 4-positions of the indole (C18–C27), and an L-valine (C31–C35). Carbons C28–C30 could be the partial carbon skeleton of an undetermined β-hydroxy amino acid with amine nitrogen N4 and carboxyl oxygen O4. The likely biosynthetic origin of the C10–C17 unit is not clear. These structural units have cyclized in an unprecedented manner to form an extremely rigid framework with essentially no conformational freedom for the polycyclic core.

The UV spectra of diazonamides A[6] and B[7] show little evidence of their high degree of unsaturation. The strict steric requirements of the bicyclic framework prevent any appreciable overlap of the conjugated heterocycles. In the crystal structure of diazonamide B *p*-bromobenzamide (see Figure 1), the two oxazole rings are twisted with respect to one another with a dihedral angle of 29°, the chlorooxazole and chloroindole rings have a dihedral angle of 60°, and the chloroindole ring has a dihedral angle of 74° with the C12–C17 phenol.

Diazonamide A has potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines, with IC$_{50}$ values less than 15 ng/mL. Diazonamide B is less active.

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Supplementary Material Available: Crystallographic data for diazonamide B *p*-bromobenzamide (**3**) (10 pages). Ordering information is given on any current masthead page.

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Design of Self-Destructive Electron Acceptors. Highly Efficient Cleavage of C–C Bonds in Photogenerated Radical Anions[†,1]

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Unimolecular fragmentation reactions of radical ions to radicals and ions (mesolytic cleavages[3]) have recently attracted considerable attention,[4,5] especially in the context of photochemically initiated electron-transfer (ET) processes.[6] In systems where the fragmentation is rapid, it may successfully compete with energy-wasting back-electron transfer (BET) processes, yielding high quantum yields of radicals and ions.[6] The fragmentation reaction may, therefore, provide means to rapidly generate these reactive intermediates[7] or serve as a convenient probe of photoinduced electron-transfer (PET) processes.[8]

[†] Dedicated with admiration and appreciation to Professor Ronald Breslow.

(1) Presented in part at the Symposium on Photoinduced Charge Transfer, Rochester, NY, 1990.

(2) (a) The Pennsylvania State University. (b) On leave from the Technical University of Lódz (Poland). (c) Radiation Laboratory, Notre Dame.

(3) Maslak, P.; Narvaez, J. N. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 283.

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(7) An important application of such processes is rapid initiation of polymerization. See, for example: Chatterjee, S.; Davis, P. D.; Gottschalk, P.; Kurz, M.; Sauerwein, B.; Yang, X.; Schuster, G. B. *J. Am. Chem. Soc.* **1990**, *112*, 6329. Also compare: Dektar, J. L.; Hacker, N. P. *J. Org. Chem.* **1990**, *55*, 639 and references therein.

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Table I. Carbon–Carbon Bond Cleavage in Photogenerated Radical Anions

1	$\Delta G^{\ddagger}(\mathrm{AX})$,[a] kcal/mol	$E_{\mathrm{X}^\bullet}$,[b] V	ΔE,[c] kcal/mol	$\Delta G(^{\bullet-}\mathrm{AX})$,[d], kcal/mol	k_f,[e] s^{-1}	Φ_t[f]	Φ_s[f]
a	39.7	−0.81	35.9	3.8	9×10^6	0.15 ± 0.01	0.04 ± 0.01
b	38.7	−0.93	33.2	5.5	8×10^5	0.15 ± 0.01	0.04 ± 0.01
c	40.0	−0.52	42.7	−2.7	4×10^8	0.25 ± 0.03	0.08 ± 0.04
d	35.2	+0.08	56.5	−21.3	4×10^9	0.59 ± 0.07	0.25 ± 0.07
e	33.8	+0.27	60.8	−27.0	$>3 \times 10^{10}$	0.97 ± 0.12	1.00 ± 0.10

[a] Activation energies for homolysis at 300 K, assumed to be equal to the free energy change of homolysis. The homolytic cleavage of **1a–e** was carried out in decalin at 180–230 °C in the presence of excess thiophenol as radical scavenger. Under these conditions the cleavage is presumed to be irreversible.[20] [b] Oxidation potentials[21] of the corresponding α-cyanobenzyl anions ($\mathrm{X}^- = \mathbf{2}^-$) in 0.1 M $\mathrm{Et_4NClO_4}$ in DMSO vs SCE (the reduction potential of $\mathbf{3}^\bullet$ is −1.01 V).[22] [c] The difference (in kcal/mol) between the oxidation potential of the α-cyanobenzyl anions (EX^-) and the reduction potential of the acceptor[21] ($E_{\mathrm{AX}} = -2.37$ V vs SCE for all acceptors). [d] Estimated free energy of mesolysis (kcal/mol). [e] The estimated rate of C–C bond scission in the radical anions. [f] The absolute quantum efficiency[23] of fragmentation within the triplet and singlet ion pairs (Figure 1).

Fragmentation of C–C bonds in such processes is of particular interest. The radical ion precursors are stable to a variety of conditions, but may yield highly labile radical ions upon one-electron oxidation or reduction. Until now, the examples of C–C bond scission in photogenerated radical ions were limited to radical cations.[8,9] We describe here the design of self-destructive electron acceptors, radical anions[10] of which undergo rapid fragmentation on the micro- to nanosecond time scale, yielding PET systems with quantum yields approaching unity.

As we have shown recently, mesolytic cleavages have activation energies that are only slightly larger than thermodynamic barriers.[3,11] The free energy for mesolysis ($\Delta G(^{\bullet-}\mathrm{AX})$) can be estimated from a thermodynamic cycle:[3,12] $\Delta G(^{\bullet-}\mathrm{AX}) = \Delta G(\mathrm{AX}) - \Delta E$, where $\Delta G(\mathrm{AX})$ is the free energy of homolysis and ΔE is the difference between the reduction potentials of the radical anion precursor (E_{AX}) and one of the radicals produced ($E_{\mathrm{X}^\bullet}$ or $E_{\mathrm{A}^\bullet}$, whichever is easier to reduce). If the cleavage reaction is to have a small or negative $\Delta G(^{\bullet-}\mathrm{AX})$, the radical anion precursors must have a weak bond (homolytically) and a high reduction potential, but the anion produced (A^- or X^-) must be as stable as possible.

Using these guidelines, we have prepared a series of acceptors **1a–e** as radical anion precursors[13] and estimated their free energies for mesolysis (Table I). These compounds quenched fluorescence of *N,N,N′N′*-tetramethylbenzidine[14] (TMB) with near-diffusion-limited rates (1.2 (±0.2) × 10^{10} $\mathrm{s^{-1}\,M^{-1}}$). Irradiation[15] of TMB in $\mathrm{CH_3CN}$ in the presence of **1a–e** led to efficient fragmentation of these acceptors. The photoinduced reaction was catalytic in TMB. The products of the reaction were consistent with radical anion cleavage. For example, **1a** yielded α-methylbenzyl nitrile **2a** (68% yield), α-methyl-*p*-cyanostyrene (**4**, 78%), and 4,4′-dicyanobicumene (7%). Analogous fragments were produced in 75–90% yields from **1b**,**c**. In the case of **1d**,**e** the styrene fragment was recovered in 85–90% yield but the fate of α-cyanobenzyl nitrile was not determined. Apparently, styrene **4** is formed by a proton loss from the corresponding cumyl cation, which in turn is produced via the oxidation of the *p*-cyanocumyl radical ($\mathbf{3}^\bullet$) by $\mathrm{TMB}^{\bullet+}$. In agreement with this proposal, in MeOH the styrene (**4**) was replaced by 2-methoxy-2-(4′-cyanophenyl)-propane as the major product (80% yield).

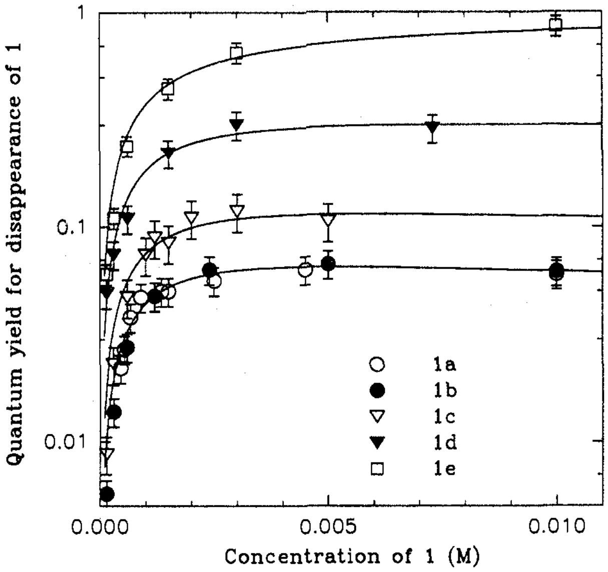

Figure 1. The quantum yield for disappearance of **1** as a function of [**1**]. TMB (0.003 M) in $\mathrm{CH_3CN}$ was irradiated at 305 ± 5 nm in the presence of **1**. The lines represent the best fit, using independently determined lifetimes and quenching rates for the triplet and singlet states of TMB (compare ref 14). The fit parameters, Φ_s and Φ_t, represent absolute efficiencies of fragmentation within singlet and triplet ion pairs. The equation[17] used: $\Phi = \Phi_s k_{qs}[\mathbf{1}]/(1/\tau_s + k_{qs}[\mathbf{1}]) + \Phi_t k_{ic} k_{qt}[\mathbf{1}]/[(1/\tau_s + k_{qs})(1/\tau_t + k_{qt}[\mathbf{1}])]$, where $k_{qs} = 1.2 \times 10^{10}$ $\mathrm{s^{-1}\,M^{-1}}$ (singlet quenching), $\tau_s = 11$ ns (singlet lifetime), $k_{ic} = 6.3 \times 10^7$ $\mathrm{s^{-1}}$ (intersystem crossing), $k_{qt} = 1.5 \times 10^8$ $\mathrm{s^{-1}\,M^{-1}}$ (triplet quenching), and $\tau_t = 5.0$ μs (triplet lifetime).

The cleavage pattern of radical anions was confirmed by direct observation of the fragments in a pulse radiolysis experiment. Thus, $\mathbf{2}^-$ and $\mathbf{3}^\bullet$ were directly detected[16] by transient absorption

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(8) See, for example: (a) Sankararaman, S.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 6448. (b) Sankararaman, S.; Haney, W. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5235, 7824. (c) Maslak, P.; Chapman, W. H., Jr. *J. Chem. Soc., Chem. Commun.* **1989**, 1809. (d) Maslak, P.; Chapman, W. H., Jr. *J. Org. Chem.* **1990**, *55*, 6334.

(9) For examples of photogenerated radical cations undergoing C–C bond scission, see: (a) Okamato, A.; Snow, M. S.; Arnold, D. R. *Tetrahedron* **1986**, *42*, 6175 and references therein. (b) Reichel, L. W.; Griffin, G. W.; Muller, A. J.; Das, P. K.; Ege, S. N. *Can. J. Chem.* **1984**, *62*, 424. (c) Davis, H. L.; Das, P. K.; Reichel, L. W.; Griffin, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 6968. (d) Eaton, D. F. *Pure Appl. Chem.* **1984**, *56*, 1191. (e) Masnovi, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 6781. (f) Ci, X.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 7215. (g) **1989**, *111*, 3459 and references therein. (h) Albini, A.; Mella, M. *Tetrahedron* **1986**, *42*, 6219. (i) Popielarz, R.; Arnold, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 3068. (j) Maslak, P.; Chapman, W. H., Jr. *Tetrahedron* **1990**, *46*, 2715.

(10) There are examples of reductive cleavage of C–C bonds involving metal reductions: (a) Grovenstein, E., Jr.; Bhatti, A. M.; Quest, D. E.; Sengupta, D.: VanDerveer, D. *J. Am. Chem. Soc.* **1983**, *105*, 6290 and references therein. (b) Staley, S. W. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: 1972; Vol. 2, p 309. (c) Walsh, T. D. *J. Am. Chem. Soc.* **1987**, *109*, 1511. (d) Maslak, P.; Narvaez, J. N. *J. Chem. Soc., Chem. Commun.* **1989**, 138. (e) Maslak, P.; Narvaez, J. N.; Kula, J.; Malinski, D. S. *J. Org. Chem.* **1990**, *55*, 4550. (f) Lagendijk, A.; Szwarc, M. *J. Am. Chem. Soc.* **1971**, *93*, 5359. (g) Walsh, T. D.; Megremis, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 3897. (h) House, H. O.; Snoble, K. A. J. *J. Org. Chem.* **1976**, *41*, 3076. (i) Taylor, R. T.; Galloway, J. G. *Tetrahedron Lett.* **1982**, *23*, 3147. Radical anions of cyclopropyl derivatives generated in photostimulated chain reactions ($\mathrm{S_{RN}1}$) also undergo C–C bond scission: (j) Russell, G. A.; Dedolph, D. F. *J. Org. Chem.* **1985**, *50*, 2378.

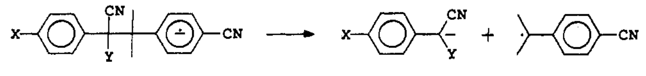
(11) Maslak, P.; Kula, J.; Narvaez, J. N. *J. Org. Chem.* **1990**, *55*, 2277.

(12) Compare: Griller, D.; Simões, A. M.; Mulder, P.; Sim, B. A.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1989**, *111*, 7872.

(13) The acceptors (*p*-cyanophenyl moiety) are electronically identical. The remote substitution has no effect on redox potentials or quenching of TMB excited states.

(14) TMB has well-characterized excited states: (a) Das, P. K.; Muller, A. J.; Griffin, G. W.; Gould, I. R.; Tung, C.-H.; Turro, N. J. *Photochem. Photobiol.* **1984**, *39*, 281. (b) Turro, N. J.; Tung, C.-H.; Gould, I. R.; Griffin, G. W.; Smith, R. L.; Manmade, A. *J. Photochem.* **1984**, *24*, 265. (c) Alkaitis, S. A.; Grätzel, M. *J. Am. Chem. Soc.* **1976**, *98*, 3549.

(15) The acceptors, **1a–e**, do not absorb light above 300 nm and remain unchanged if the samples are irradiated without TMB. Irradiation of acetophenone, a triplet sensitizer, in the presence of **1a–e** gave no reaction, excluding an energy-transfer process as a mode of C–C bond scission. ET between TMB^1 (3.60 eV) or TMB^3 (2.73 eV) and **1** is exergonic. The driving force for BET within the $\mathrm{TMB}^{\bullet+}\mathbf{1}^{\bullet-}$ pair is ca. 2.69 eV.



1a-e$^{\bullet-}$ 2a-e^{-} 3$^{\bullet}$

a: X = H Y = Me
b: X = OMe Y = Me
c: X = CF$_3$ Y = Me
d: X = OMe Y = CN
e: X = H Y = CN

spectroscopy. These data also indicated that the radical anions decay at a submicrosecond time scale[16] (see below).

A Stern–Volmer analysis[17] of the quantum yield for disappearance of **1a–e** is shown in Figure 1. At low concentrations of **1**, only TMB[3] is quenched, yielding triplet ion pairs (TMB$^{\bullet+}$,**1**$^{\bullet-}$). The fragmentation of **1**$^{\bullet-}$, or ion separation (see below), competes with BET. Since the BET is spin-forbidden, the overall reaction is relatively efficient. At higher concentrations of **1**, more excited state molecules of TMB are quenched, but an increasing fraction of them is in the singlet state. This fraction gives singlet ion pairs, within which BET is more efficient. The overall efficiency of the photoreaction, therefore, does not increase linearly with increasing concentration of **1**.

The reactions are efficiently quenched by *p*-dicyanobenzene (DCB). The quenching is due to two processes. The first one involves direct quenching of excited states of TMB, which can be independently measured and corrected for. The second process, assumed to be diffusion-limited,[18] corresponds to electron transfer from **1**$^{\bullet-}$ to DCB. Thus, the ratio of the corrected to the measured quantum yield ($\Phi_{corr}/\Phi_m - 1$) as a function of DCB concentration provides a measure of the radical anion cleavage rates[17] (Table I). Approximately 50% of **1a**$^{\bullet-}$ and **1b**$^{\bullet-}$ are intercepted by 0.04 mM and 0.4 mM DCB, respectively. **1c–e**$^{\bullet-}$ cannot be intercepted even by 5 mM DCB, implying a rate of cleavage faster than 10^8 s^{-1}.

The quantum yields for disappearance of **1a,b** are identical (Figure 1), but the measured rates of mesolysis for **1a**$^{\bullet-}$ and **1b**$^{\bullet-}$ differ by a factor of 10. This observation requires that the measured quantum yields for these compounds reflect a competition between BET and ion separation. The rate of ion separation[19] in acetonitrile is ca. 5×10^8 s^{-1}, confirming this analysis and indicating a BET rate within the triplet ion pairs[17] of 3×10^9 s^{-1}. The quantum yield for disappearance of **1c** is higher than that for **1a,b**, which requires that the rate of cleavage of **1c**$^{\bullet-}$ be comparable to the rate of ion separation. Assuming that the rates of BET are the same for all radical anions,[13] the rate of mesolysis of **1c**$^{\bullet-}$ can be estimated to be 4×10^8 s^{-1}, indeed, very close to the rate of ion separation. In a similar fashion, the cleavage rates of **1d,e**$^{\bullet-}$ can be estimated (Table I).

In summary, the design of self-destructive acceptors based on thermodynamic considerations has proven very successful, leading to photoreactions with overall efficiencies approaching unity for acceptors with highly negative free energies of mesolysis. The rates of cleavage confirmed our earlier conclusion[3,11] that the "intrinsic" barriers in mesolytic reactions are quite low, even for near-thermoneutral reactions. The prepared acceptors are convenient molecular clocks for probing ET reactions and ion-pairing phenomena in photoinduced charge-transfer processes.

Acknowledgment. This research was supported by grants from the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society. The work at the Notre Dame Radiation Laboratory (Contribution No. NDRL-3331) was sponsored by the Office of Basic Energy Science of the Department of Energy.

Supplementary Material Available: The Stern–Volmer kinetic scheme and DCB quenching data (3 pages). Ordering information is given on any current masthead page.

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[16] For a description of the experimental setup, see: Chateauneuf, J. E. *J. Phys. Chem.* **1990**, *94*, 7177. At 3×10^{-4} M **1** in CH$_3$CN, the fragments are produced with 10^6–10^7 s^{-1} rates (limited by concentration of **1**). Radical **3**$^{\bullet}$ absorbs (λ_{max}) at ca. 295 nm, and the anions absorb at 325 nm (**2a**$^-$), 370 nm (**2c**$^-$), and 300 nm (**2d,e**$^-$). In the latter case the anions and the radical can be distinguished by their different decay rates. The measurements of the absolute rates of C–C bond scission are in progress.

[17] The kinetic scheme used in the Stern–Volmer analysis and DCB quenching data are provided in the supplementary material.

[18] The ET between **1**$^{\bullet-}$ and DCB is exothermic by 17 kcal/mol.

[19] The rate of separation of aromatic radical ions in CH$_3$CN is structure insensitive: (a) Gould, I. R.; Moser, J. E.; Ege, D.; Farid, S. *J. Am. Chem. Soc.* **1988**, *110*, 1991. (b) Gould, I. R.; Ege, D.; Mattes, S. L.; Farid, S. *J. Am. Chem. Soc.* **1987**, *109*, 3794. (c) Gould, I. R.; Ege, D.; Moser, J. E.; Farid, S. *J. Am. Chem. Soc.* **1990**, *112*, 4290.

[20] Compare: Zamkanei, M.; Kaiser, J. H.; Brikhofer, H.; Beckhaus, H.-D.; Rüchardt, C. *Chem. Ber.* **1983**, *116*, 3216.

[21] The required reversible redox potentials for **1a–e** and **2a–e**$^-$ were obtained by using a modified cyclic voltammetry method (Klingler, R. J.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 4186) or by a second-harmonic ac voltammetry technique (Arnett, E. M.; Harvey, N. G.; Amarnath, K.; Cheng, J.-P. *J. Am. Chem. Soc.* **1989**, *111*, 4143. Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 344).

[22] Sim, B. A.; Milne, P. H.; Griller, D.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1990**, *112*, 6635.

[23] Quantum yields were measured by using ferric oxalate actinometry: Parker, C. A. *Proc. R. Soc. (London)* **1953**, *A220*, 104.

Lack of a Secondary β-Deuterium Kinetic Isotope Effect in the Solvolysis of 2-Chloro-3-hydrosqualene. A Case of Extended π-Participation and Indication of Concerted Biomimetic Polycyclization

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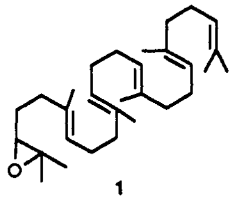
We report herein about an extended participation involving at least two double bonds in a biomimetic solvolytic reaction of a squalene derivative.

In nature, steroid hormones arise from 2,3-epoxysqualene (**1**) in an enzymatic, probably concerted, polycyclization reaction.[1,2] In the biomimetic counterpart of this reaction (Lewis acid epoxy-ring opening with **1**), tricyclic products derived from carbocation **2** are formed.[3] As with other biomimetic cyclizations, the question arises as to the reaction mechanism: is the (poly)cyclization a "stepwise" or a "concerted" process, and if the latter is operative, how many double bonds are involved in the rate-determining step?



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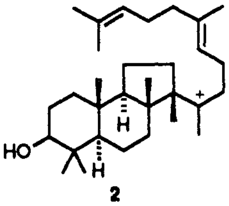

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Unfortunately, the product composition in this case as in other cases of biomimetic cyclizations is not very indicative of the reaction mechanism. A stepwise (poly)cyclization can yield acyclic and (poly)cyclic products. If the reaction is concerted and proceeding through a (nonclassical) carbonium ion, the extensive delocalization of the positive charge allows for nucleophilic attack on several centers yielding the same products as in the stepwise process.

Of the two pioneers in this field, Johnson[4] considers that the concerted mechanism is possible while in the opinion of van Tamelen[1,5] only monocyclization might be a concerted process and

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[1] (a) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111–120; (b) **1975**, *8*, 152–158.

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