in CD_3CN clearly discriminate between the two types of $COCH_3$ groups within the acac ligand, and the Pt–O bond does not break, even at 70 °C. Lengthening of the Pt–O bond may be caused by the trans influence of the Pt–C bond across the Pt–Pt bond. Such a trans influence has been reported for some Pt(III) dimers.[10b,14]

The present two complexes further indicate that platinum(II) and platinum(III) states prefer to form a Pt–C bond where possible and that platinum complexes will provide further an interesting field even for cluster complexes in the border of classical coordination and organometallic chemistry.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 01612001) on Priority Area of "Dynamic Interactions and Electronic Processes of Macromolecular Complexes" and a Grant-in-Aid for Scientific Research (No. 01430009) from the Ministry of Education, Science and Culture, Japan. We are grateful to Professors Hiroshi Ogino and Mamoru Shimoi and Dr. Chizuko Kabuto for the measurements of the X-ray reflection data.

Supplementary Material Available: Tables of crystallographic data and details of the structural determination, atomic positional and thermal parameters, and interatomic distances and bond angles for **1** and **2** (5 pages); tables of observed and calculated structure factors for **1** and **2** (6 pages). Ordering information is given on any current masthead page.

(14) Lippert, B.; Schollhorn, H.; Thewalt, U. *J. Am. Chem. Soc.* **1986**, *108*, 525–526. Schollhorn, H.; Thewalt, U.; Lippert, B. *J. Chem. Soc., Chem. Commun.* **1986**, 258–260.

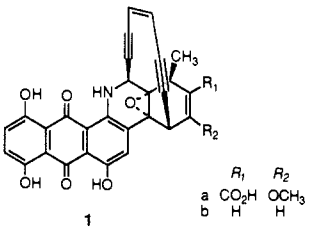
Proposal for Blending Classical and Biradical Mechanisms in Antitumor Antibiotics: Dynemicin A

James P. Snyder* and Gregory E. Tipsword

Drug Design Section, Searle R and D
4901 Searle Parkway, Skokie, Illinois 60077
Received January 25, 1990

Recently isolated antitumor antibiotics are proving to be extraordinary for their exceptional potency, unusual enediyne bicyclic structures, and remarkable biradical DNA cleaving mechanisms. The glycosylated esperamicin,[1,2] calicheamicin[3,4] and neocarzinostatin[5,6] variations were the first families extracted from widely dispersed soil samples. This year a Bristol-Myers/Cornell team presented another theme with the isolation and structure elucidation of dynemicin A, **1a**.[7] The violet compound combines the enediyne moiety and the classical anthracycline quinone chromophore. Sandwiched between the two funtionalities is a tetra-substituted epoxide.

Several questions beg for resolution. If the compound disables DNA similar to its natural enediyne congeners, which end of the molecule carries the weaponry? Can the two ends act in concert through a common trigger? What mechanistic intermediates are consistent with the actions of other antitumor antibiotics?

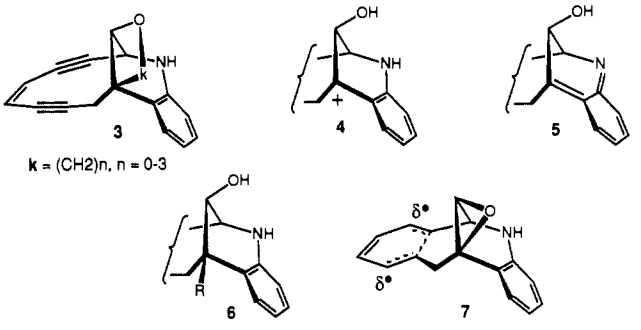


1 2

Computational methodology offers insights into and projections beyond these issues.

The force field predicted structure of dynemicin A (**1a**) is shown in Figure 1. The calculation assumes hydrogen bonding in the anthraquinone fragment leading to planarity for the extended π-system. Geometric features resemble previous enediyne X-ray structures:[8-13] r(acetylene C---C) = 3.66 Å; C≡C—C bonds are bent with predicted angles ranging from 162 to 169 °C. The molecule is an almost perfect right-angled elbow. Perched atop the bicyclic extension of the anthraquinone fragment, the epoxide ring is poised for interaction with the aromatic framework. Nothing has been reported concerning the ability of dynemicin to cleave DNA, but the compound exhibits potent antibacterial activity and extends the life span of mice inoculated with leukemia.[7] If as in neocarzinostatin the epoxide opening is a trigger for biradical formation and subsequent DNA damage,[14-17] two extreme mechanisms for ring opening are suggested: acid-catalyzed ring rupture or base-catalyzed deprotonation of the hydroquinone two-electron-reduction product[18] (**10**, Figure 2) accompanied by simultaneous epoxide cleavage to give **2a**. Both are stereoelectronically favored by the flat architecture of **1** to stabilize a carbocation or a C=C double bond, respectively.

The acid-promoted cationic route was evaluated with structures **3–6** by the MM2//PRDDO protocol for calculating ΔE^*(TS–GS) described previously.[13,19]



3 4 5 6 7

(1) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C. Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466.
(2) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468.
(3) Golik, J.; Clardy, J.; Dubay, G. Groenewold, G.; Kawaguchi, H.; Konishi, M.; Kirshnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462.
(4) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Kirshnan, B.; Ohkuma, H.; Saitoh, K.-i; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464.
(5) Kappen, L. S.; Ellenberger, T. E.; Goldberg, I. H. *Biochemistry* **1987**, *26*, 384–390.
(6) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212–7214.
(7) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449–1452.
(8) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462.
(9) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866–4868.
(10) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 6890–6891.
(11) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921–6923.
(12) Schoenen, F. J.; Porco, J. A.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765–3768.
(13) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630–7632. ΔE^*(TS–GS) is the PRDDO energy difference between ground-state enediyne and the corresponding biradicaloid transition state.
(14) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198–1201.
(15) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697–699.
(16) Hawley, R. C.; Kiessling L. L.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1105–1109.
(17) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6808–6890.
(18) Boldt, M.; Gaudiano, G.; Haddadin, M. J.; Koch, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 2283–2292.
(19) MM2 force field parameters for epoxides and carbenium ions were developed for this work and will be reported in due course. The epoxide values are similar to a set recently published (Podlogar, B. L.; Raber, D. J. *J. Org. Chem.* **1989**, *54*, 5032–5035). Bridgehead carbocations are likewise well-described by MM2 molecular mechanics (cf.: Müller, P.; Mareda, J. *Helv. Chim. Acta* **1987**, *70*, 1017–1029).

0002-7863/90/1512-4040$02.50/0

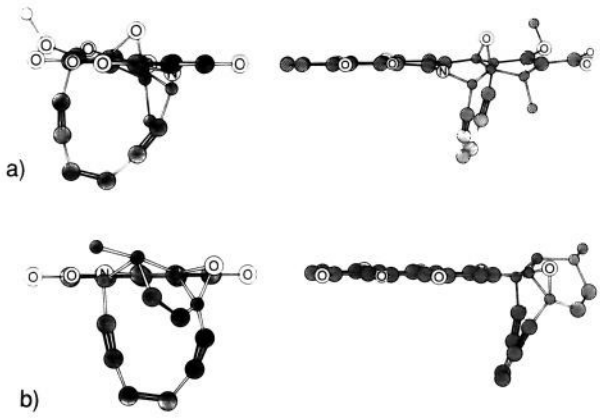


Figure 1. The MM2 optimized structures for dynemicin A (**1**) (a) and the anthraquinone-supplemented form of **11** (b). The two views of each emphasize the positioning of the epoxide ring relative to the anthraquinone moiety. Hydrogen atoms have been eliminated for clarity.

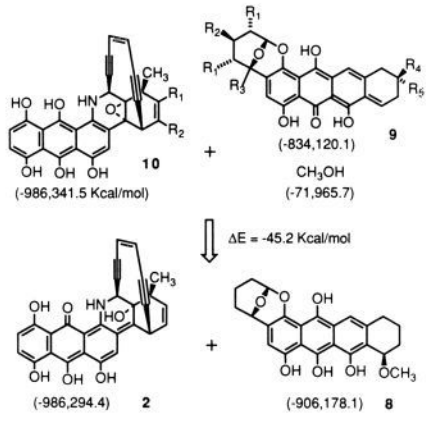


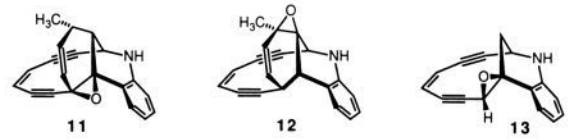
Figure 2. An isodesmic reaction for comparing the relative ease of converting dynemicin and menogaril hydroquinones **10** and **8** ($R_1 = R_2 = R_3 = R_4 = R_5 = H$) to quinone methides **2** and **9**, respectively. The energies are MM2//PRDDO values predicting **2** and **8** to be favored by 45.2 kcal/mol.

For **3**(n=0)–**5** the predicted energy barriers to the corresponding biradicaloid transition states (e.g., **7**) are $\Delta E^* \geq 39$ kcal. The epoxide effectively protects the antibiotic from enediyne cyclization. A smooth reduction in the ΔE^* for cyclization with ring enlargement is instructive [**3** (n = 0–3); ΔE^* = 59.7, 37.6, 23.3, 21.9 kcal]. By the same token, structures with sp^2 bridgehead centers similar to esperamicin and calicheamicin (e.g., **4**, **5**)[1,2,13] are too strained to promote biradical formation. Capture of a nucleophile to give **6** ($R = OCH_3$), however, is predicted to alleviate bicyclic strain and promote rapid biradical formation at ambient temperature (ΔE^* = 19.1 kcal).

Alternative assisted release of the epoxide moiety is best described by reference to menogaril,[18,20] an oxygenated bicyclic analogue of the well-known anthracycline antitumor drugs daunomycin and adriamycin. Like them, the compound is believed to experience activation by reductive elimination of methoxide from hydroquinone **8** to give the reactive quinone methide[18,20-25] **9** ($R_1 = OH$, $R_2 = N(CH_3)_2$, $R_3 = R_5 = CH_3$, $R_4 = OH$; cf. Figure 2). The latter two menogaril intermediates and their counterparts for other anthracyclines have been observed spectroscopically. The quinone methides likewise capture both electrophiles and nucleophiles[18,20-22] including 2-deoxyadenosine[26] at the site of alkoxide loss. Accordingly menogaril is reduced in part to its 7-deoxy derivative (e.g., $OCH_3 \rightarrow H$ in **8**, Figure 2) in aqueous medium.[18]

A similar series of events is possible for dynemicin A with the difference that epoxide ring opening of **10** to give quinone methide alcohol **2** is equivalent to alkoxide loss from **8**. To compare the two series, isodesmic reactions[27,28] were constructed as shown in Figure 2. Each structure was optimized with MM2 and then subjected to a single-point PRDDO SCF calculation. Reduction of the dynemicin analogue **1b** to its hydroquinone **10** is calculated to be favored over the same process for menogaril by 3.9 kcal. Subsequent elimination of epoxide or methoxide giving quinone methides **2** and **9**, respectively, is favored for the dynemicin system by 45.2 kcal. Sixty percent of this strain-release value can be attributed to the three-ring moiety,[29] and the rest, to the bicyclic system. The final rearrangement of **2** to its quinone tautomer is PRDDO exothermic by 22.8 kcal. The latter (e.g., **6**, R = H) is in turn posited to cyclize to biradical readily under biological conditions, ΔE^* = 19.2 kcal.

The picture that emerges is the mechanistic linkage of the enediyne and anthraquinone fragments through an exquisitely located three-ring trigger. Other placements of the epoxide ring can be expected to effect a degree of chemical stability similar to that observed for **1a**.[7] Structures **11**–**13** are illustrative with ΔE^*'s of 64.5, 27.2, and 36.5 kcal, respectively. Removal of the four-carbon allyl bridge in **11** and **2** causes little change in the enediyne closure estimates, suggesting bioviability for simpler stable variants of the full dynemicin structure. Movement of the epoxide ring outside the antibiotic bicyclic core (e.g., **12**) engenders considerably less molecular strain. The compound would cyclize to biradical in solution below 100 °C. The stereoisomer of **3** (n = 0), i.e., **13**, is predicted to be quite stable, but it cannot, of course, accommodate the allyl bridge.



Apart from what appears to be increased bending strain in **11** and **13** relative to dynemicin, another important difference is the relationship of the three-ring system to the extended anthraquinone π-system. Neither struture presents the epoxide favorably oriented for interaction during ring opening as depicted for system **11** in Figure 1. A corresponding adjustment in biological behavior can be anticipated for molecular geometries incorporating this feature. Considerations of mechanism and strain for other antitumor agents have stimulated the synthesis of a diverse collection of novel entities.[10,11,25,30-37]

In summary, dynemicin A is structurally and energetically designed for biradical-mediated DNA capture by a cooperative interplay between anthraquinone and enediyne fragments. The

(20) Fisher, J.; Abdella, B. R. J.; McLane, K. E. *Biochemistry* **1985**, *24*, 3562–3571.
(21) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 2380–2387.
(22) Ramakrishnan, K.; Fisher, J. *J. Med. Chem.* **1986**, *29*, 1215–1221.
(23) Land, E. J.; Mukherjee, T.; Swallow, A. J.; Bruce, J. M. *Br. J. Cancer* **1985**, *51*, 515–523.
(24) Anne, A.; Moiroux, J. *Nouv. J. Chim.* **1985**, *9*, 83.
(25) Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648–4650.
(26) Egholm, M.; Koch, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 8291–8293.
(27) Darrah, T. T.; Carroll, T. X.; Siggel, M. R. F. *J. Org. Chem.* **1988**, *53*, 1812–1815.
(28) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley and Sons: 1986; New York, pp 298–308.
(29) Benson, S. W. *Thermochemical Kinetics*; 2nd ed.; John Wiley and Sons: New York, 1976; pp 276.
(30) Moore, H. W. *Science* **1977**, *197*, 527–532.
(31) Moore, H. W.; Czernick, R. *Med. Res. Rev.* **1981**, *1*, 249–280.
(32) Carter, P. A.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 1626–1628.
(33) Danishefsky, S. J.; Yamashita, D. S.; Mantlo, N. B. *Tetrahedron Lett.* **1988**, 4681–4684.
(34) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631–633.
(35) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, 433–436.
(36) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, 4217–4220.
(37) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, 851–854.

chemical lability of the intervening epoxide and the overall molecular strain induced by bridgehead O-oxidation appears to be an essential element for the antibiotic's function. Epoxide relocation offers novel opportunities to examine and alter it.

Acknowledgment. Thanks to Professor Kosta Steliou (University of Montreal) for providing continuing stimulation on this problem. Professor Lester Mitscher (University of Kansas) kindly brought us in touch with key citations in the literature.

Registry No. 1a, 124412-57-3.

Cooperative Reactivity in Photogenerated Radical Ion Pairs: Photofragmentation of Amino Ketones

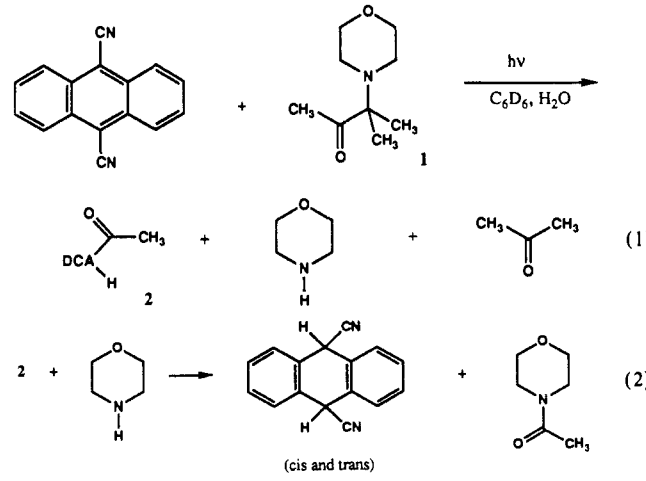
William R. Bergmark* and David G. Whitten*

Department of Chemistry, University of Rochester Rochester, New York 14627

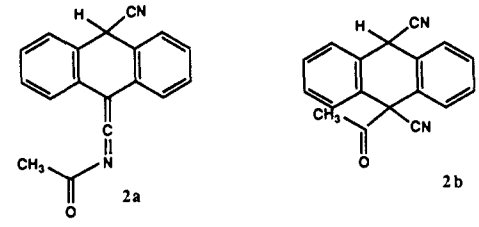
Received January 29, 1990

A number of instances of fragmentation (or cleavage) have recently been noted for certain electron donors when activated by photoinduced single electron transfer (SET) reactions.[1-6] In some cases the occurrence of fragmentation is attributed chiefly to a greatly reduced carbon–carbon bond energy in the donor cation radical compared to the corresponding neutral molecule.[2,7] Studies in our laboratories have focused on electron-transfer quenching of excited singlet acceptors by amino alcohols and diamines in nonpolar solvents. For the former we have shown that moderately efficient (in some cases) and chemically clean reaction occurs in nonpolar solvents within contact ion pairs in which *both* donor cation–radical (dcr) and acceptor anion–radical (aar) play important roles. The crucial step competing with reaction-limiting back electron transfer is the concerted fragmentation and deprotonation of the dcr with the aar acting as a base. Herein we report a novel reaction in which scission of a strong carbon–carbon bond in an unexcited donor can be brought about via quenching of an excited acceptor. In this case, the aar seems to function as a nucleophile in a displacement within the contact ion pair; the net reaction involves a chemically clean and yet unprecedented ketone to amide interconversion. This kind of reactivity fits well into an emerging pattern of contact ion pair reactivity.

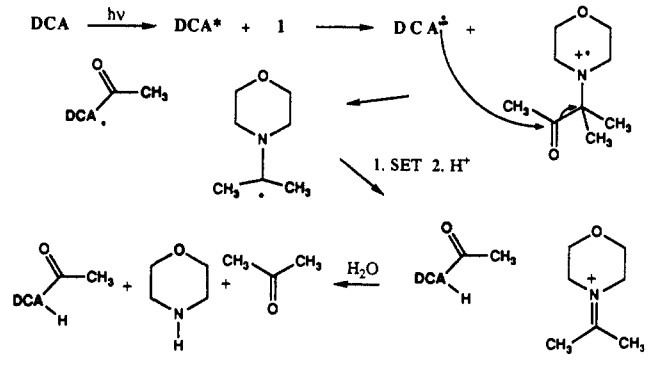
Irradiation (with a high-pressure mercury lamp filtered to pass light from 400 to 440 nm) of 9,10-dicyanoanthracene (DCA) in the presence of amino ketone **1** in deuterated benzene (freeze–pump–thaw vacuum degassed solution) with a trace of water (0.011%) leads to a bleaching of the long-wavelength absorption of DCA together with formation of photoproducts, which are indicated by NMR and GC–MS analysis to be acetone, morpholine, and an acylated form of DCA (eq 1). In a subsequent dark reaction over several hours, **2** and morpholine undergo further reaction to produce 4-acetylmorpholine and 9,10-dihydro-9,10-dicyanoanthracene, $DCAH_2$ (eq 2). The overall result of the



reaction is a net two-electron reduction of DCA concurrent with an oxidative conversion of the amino ketone to an amide and a ketone. The reaction occurs relatively cleanly with the indicated stoichiometry and overall 90% chemical yield and a modest quantum efficiency ($\Phi = 0.038$) under conditions where quenching of the fluorescence of DCA is nearly complete. The initial photolysis produces a singlet at 1.69 ppm in the NMR spectrum, consistent with either structure **2a** or **2b**.



A reasonable mechanism for the overall conversion described in eq 1 is given below: The initially formed amino radical has



a low oxidation potential and would be expected to undergo a second electron transfer.[4,8]

While an unassisted cleavage of $1^{\bullet+}$ could be proposed to yield the same products, thermochemical cycle estimation of the carbon–carbon bond energy in $1^{\bullet+}$ of ca. 30 kcal/mol suggests that the aar-assisted path is more probable.[8]

In contrast to the amino alcohol cleavage processes mediated by photoinduced electron transfer which occur in a wide range of solvents, the present reaction has been found to occur cleanly in benzene, but in more polar solvents, such as acetonitrile and methanol, both the quantum yield and the chemical yield are decreased. Thus, in the present case, the reaction is evidently governed both by the generation of reactive partners as a contact ion pair or exciplex and also by the absence of appreciable solvent stabilization of the potential nucleophile and substrate. Other

(1) Chatterjee, S.; Gottschalk, P.; Davis, P. D.; Schuster, G. *J. Am. Chem. Soc.* **1988**, *110*, 2326-2328.
(2) Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P.; Mattes, S. L. *J. Am. Chem. Soc.* **1989**, *111*, 8973-8975.
(3) *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Parts A-D.
(4) (a) Ci, X.; Lee, L. Y. C.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 2536. (b) Ci, X.; Whitten, D. G. In *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Part C, p 553. (c) Kellett, M. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 2314. (d) Haugen, C. H.; Whitten, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 7281. (e) Ci, X.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 7215.
(5) (a) Arnold, D. R.; Maroulis, A. *J. Am. Chem. Soc.* **1976**, *98*, 5931. (b) Arnold, D. R.; Lamont, L. J. 1989 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, Dec 17-22, 1989; Organic Abstract 2.
(6) Sankararaman, S.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 6448-6449.
(7) Wayner, D. D. M.; Griller, D. *From Atoms to Polymers*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers, Inc.: New York, 1989; Chapter 3.

(8) The bond-dissociation energy for the radical cation was taken to be equal to the ionization potential of the radical (5.7 eV: Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132) minus the ionization potential of the neutral (7.9 eV) plus the bond-dissociation energy of the neutral (81 kcal/mol).

0002-7863/90/1512-4042$02.50/0