d orbital (a d_{xz}/d_{yz} combination orbital)[12] with the $2\pi_s$ orbital of the $C_5H_3Me_2$ unit. This brings the total π-electron count to six and explains, in a qualitative fashion, the observed aromatic character of **1**. A more detailed molecular orbital treatment of **1** will be forthcoming.

In summary, we conclude that iridacycle **1** is, in fact, a metallabenzene with all of the usual aromatic properties. In particular, (a) the six-membered ring is planar and the bonding is delocalized, (b) a ring current is present, causing the ring protons to be shifted significantly downfield in the ^1H NMR spectrum, and (c) the compound is very robust, surviving in refluxing benzene with no apparent decomposition.

We have begun to explore the chemical reactivity of **1** and will report the results of this study in a future communication.

Acknowledgment. Support from the National Science Foundation (Grant CHE-8520680) and a loan of $IrCl_3 \cdot 3H_2O$ from Johnson Matthey, Inc. are gratefully acknowledged. Washington University's X-ray Crystallography Facility was funded by the National Science Foundation's Chemical Instrumentation Program (Grant CHE-8811456).

Supplementary Material Available: Tables of final atomic coordinates, thermal parameters, bond lengths, and bond angles (4 pages); listings of observed and calculated structure factor amplitudes (19 pages). Ordering information is given on any current masthead page.

(12) We define the following coordinate axis system: the axial ligand lies along the z axis, while the four basal ligands, when projected onto the xy-plane, lie along the x, $-x$, y, and $-y$ axes.

The 10-Membered Ring Analogues of Neocarzinostatin Chromophore: Design, Synthesis, and Mode of Decomposition†

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The labile nonprotein chromophore[1,2] of the antitumor antibiotic neocarzinostatin (NCS), isolated from the culture filtrate of *Streptomyces carzinostaticus* by Ishida and co-workers in 1965,[3] is essentially responsible for the biological activity of NCS.[2,4] Goldberg et al. proposed that the thiol activation of the chromophore produces a free-radical intermediate which cleaves DNA via abstraction of 5′-hydrogen from DNA on aerobic incubation.[5] However, extreme instability and structural ambiguity of the chromophore hampered the establishment of precise mechanisms for its radical generation and the DNA cleavage at the molecular level. The breakthrough came in 1985: Edo and his collaborators assigned the planar structure of the NCS chromophore as an unprecedented epoxybicyclo[7.3.0]dodecadienediyne nucleus **1**,[6]

Scheme I. Myers' Proposed Mechanism for the Formation of **4**

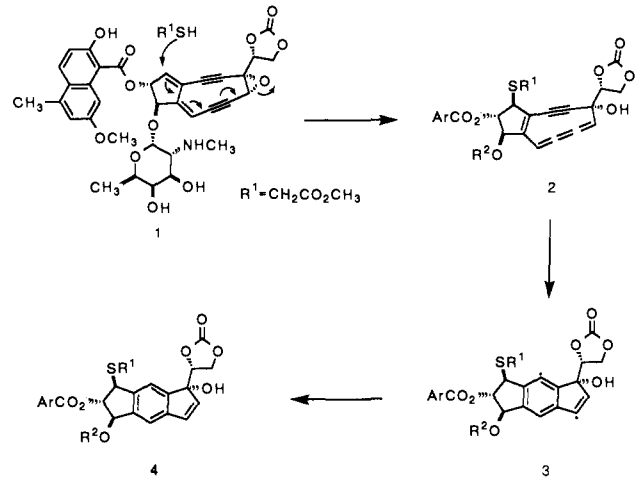
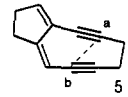
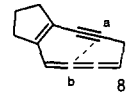
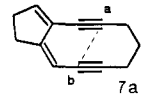
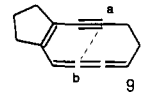


Table I. Calculated Strain Energies and Distances ab of Model Compounds **5**, **8**, **7a**, and **9**

Entry	Compound	MM2 (85) Strain Energy (kcal/mol)	MM2 (85) ab (Å)	MNDO Heat of Formation (kcal/mol)	MNDO ab (Å)
1	 5	25.85	2.95	117.5	2.97
				Δ10.3	
2	 8	Δ11.02	— [a]	127.8	3.03
3	 7a	14.83	3.12	101.1	3.20
				Δ9.7	
4	 9		— [a]	110.8	3.20

[a] Calculation parameters for cumulene are not available.

which was recently supported by the elegant synthesis of the parent carbocyclic core by Wender and co-workers.[7] Furthermore, Myers proposed both the structure of the chromophore–methyl thioglycolate adduct **4** and the mechanism of its formation (Scheme I).[8,9] As a part of our studies on the mechanism of chemical and biological action of the NCS complex, we designed and synthesized the NCS chromophore analogues **6** and **7b** to answer the questions: (i) whether the ring strain inherent in the unsaturated nine-membered ring system is essential to such novel molecular transformation generating free radical and (ii) whether the epoxide functionality is also essential to it.[10]

Molecular mechanics calculations [MM2(85)] indicated that the strain energy of the 10-membered ring analogue **7a** was much less than that of the parent hydrocarbon **5** (entries 3 and 1, Table I).[11] On the other hand, the increase of heat of formation from diyne **7a** to enynecumulene **9**, a 10-membered ring analogue of Myers' intermediate **2**,[8] calculated by MNDO (entries 3 and 4)

† Dedicated to Professor Nakao Ishida.
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§ Hiroshima University.

(1) Napier, M. A.; Holmquist, B.; Strydom, D. J.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 635.
(2) Koide, Y.; Ishii, F.; Hasuda, K.; Koyama, Y.; Edo, K.; Katamine, S.; Kitame, F.; Ishida, N. *J. Antibiot.* **1980**, *33*, 342.
(3) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.
(4) Kappen, L. S.; Napier, M. A.; Goldberg, I. H. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1970.
(5) Hensens, O. D.; Dewey, R. S.; Liesch, J. M.; Napier, M. A.; Reamer, R. A.; Smith, J. L.; Albers-Schöberg, G.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 538. Kappen, L. S.; Goldberg, I. H. *Nucleic Acids Res.* **1985**, *13*, 1637.
(6) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.
(7) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909.
(8) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493.
(9) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212.
(10) (a) Koide, Y.; Ito, A.; Edo, K.; Ishida, N. *Chem. Pharm. Bull. (Tokyo)* **1986**, *34*, 4425. Edo, K.; Akiyama-Murai, Y.; Saito, K.; Mizugaki, M. *J. Antibiot.* **1988**, *41*, 1272. (b) Lee, S. H.; Goldberg, I. H. *Mol. Pharmacol.* **1988**, *33*, 396.
(11) Since strainless bond enthalpy constants of —C≡C— delocalized and =C—C≡ delocalized were assumed to be identical with those of normal bond enthalpy, the calculated strain energies themselves should be taken as indicative only, but their difference will be meaningful.

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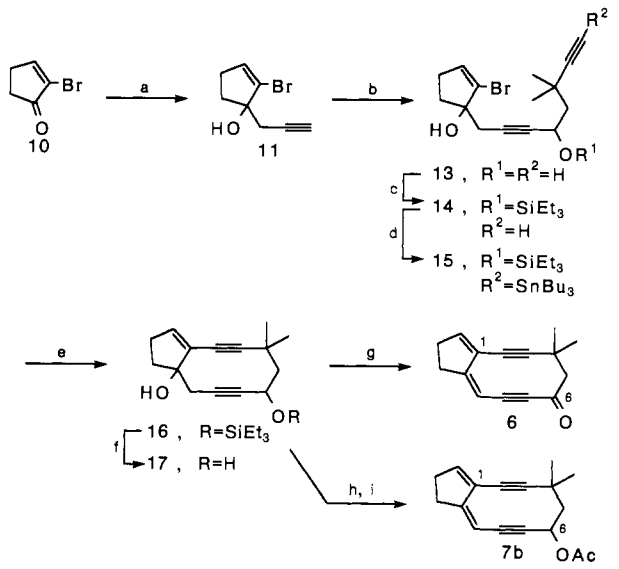
Scheme II. Synthesis of Compounds **6** and **7b**[a]



[a](a) $CH{\equiv}CCH_2MgBr$, Et_2O, room temperature; (b) EtMgBr, THF, 50 °C; $CH{\equiv}C{-}C(CH_3)_2CH_2CHO$ (**12**), room temperature; (c) Et_3SiCl, py, room temperature; (d) BuLi (2.1 equiv), THF, Bu_3SnCl (1.1 equiv), −78 °C → room temperature (14 h); (e) $Pd(PPh_3)_4$ (0.05 equiv), THF, 50 °C, 86 h; (f) H_2O, AcOH, THF, (1:1:1), room temperature; (g) $(COCl)_2$ (5 equiv), DMSO (8 equiv), Et_3N (16 equiv), CH_2Cl_2, −60 °C → room temperature; (h) Ac_2O (1.5 equiv), py, room temperature, 19 h; (i) MsCl (10 equiv), DMAP (2 equiv), Et_3N (20 equiv), CH_2Cl_2, 0 °C, ca. 20 min.

is smaller than that in the nine-membered ring models **5** and **8** (entries 1 and 2). Furthermore, calculated distances ab of **7a** and **9** (entries 3 and 4) are only slightly longer than those of **5** and **8** (entries 1 and 2), respectively.[12] Thus, we expected that the 10-membered ring analogues **6** and **7b** which have an electrophilic carbonyl or a leaving group at C6[10] would have far increased stability and might retain an aptitude for such molecular transformation as **1** does.

Straightforward syntheses of **6** and **7b** are summarized in Scheme II. Addition of propargyl magnesium bromide[13] to 2-bromocyclopent-2-enone[14] (77% yield)[7] and subsequent metalation followed by condensation with the aldehyde **12**[15] gave diol **13** in 71% yield. Although palladium-mediated cyclization of **13** failed,[16] alkynylstannane **15** prepared from silylether **14** coupled intramolecularly to afford the 10-membered ring compound **16** in good yield (72%).[17] Acid hydrolysis of **16** gave diol **17** (86%), and subsequent Swern oxidation with excess reagents produced directly the crystalline ketone **6** [mp 60 °C (dec) in sealed tube] in 72% yield. Monoacetylation of **17** followed by dehydration according to Wender's method[7] afforded the crystalline **7b** (mp 98–99.5 °C in sealed tube) in 68% yield. Its ORTEP drawing of X-ray crystallographic analysis is shown in Figure 1. Found distance ab of **7b** (3.10 Å) is very close to the calculated values for **7a**, particularly by MM2(85) (entry 3 in Table I).[12] These chromophore analogues are found to be air-sensitive but rather stable even under ambient light at room temperature in argon atmosphere.[1,2]

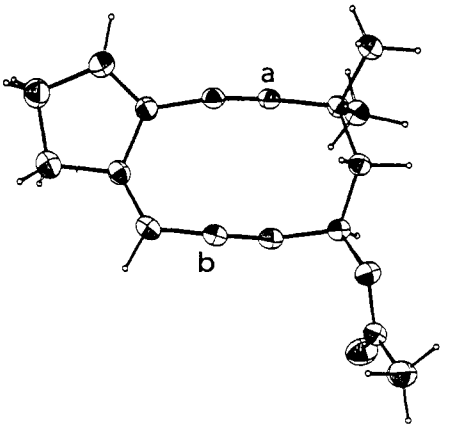
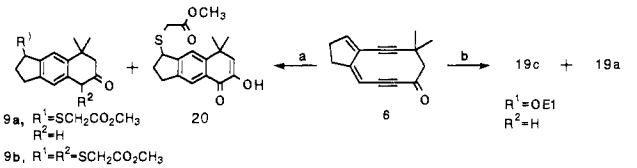


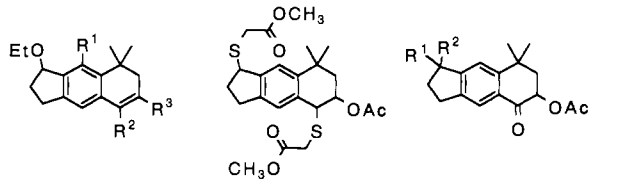
Figure 1. ORTEP of **7b**. Distance ab is 3.10 Å.

Scheme III. Decomposition of **6** in the Presence of **18**[a]



[a](a) $HSCH_2CO_2CH_3$ (**18**), AcOH, EtOH, air, 20 °C, 2 h; (b) **18**, AcOH, EtOH, Ar, 18 °C, 2 weeks.

Decomposition of **6** (0.01 M) in 0.1 M ethanolic acetic acid in the presence of methyl thioglycolate **18**[5,9] (0.1 M, 10 equiv) at 20 °C under aerobic conditions was complete within 2 h to give a mixture of tetrahydrobenzindans **19a** (28%), **19b**[18] (7%), and **20** (10%, Scheme III). Under similar but deoxygenated conditions, however, **6** decomposed slowly ($t_{1/2} \approx 2$ days), and the ethanol adduct **19c**[19] was obtained as a major product (24% after 14 days) besides **19a** (7%). These results suggest that **19a**, **19b**, and **20** might be principally produced via free-radical addition of **18** promoted by $^3O_2$ leading to transannular cyclization and that **19c** would originate from Myers' type of nucleophilic conjugate addition (Scheme I).[8] These two modes of decomposition were more clearly observed in the reaction of **7b**. When refluxed with **18** (10 equiv) in deoxygenated 0.1 M ethanolic acetic acid for 112 h, **7b** gave the ethanol adducts **21a–21c** (3, 0.5, and 3%, respectively), which all lost the acetoxy group via the Myers' vinylogous S_N2' mechanism, besides the thioglycolate adduct **22**[18] (6%). Under the aerobic conditions (25 °C, 22 days) no ethanol adduct was detected, but the oxidation product **23a** (5%) and the thioglycolate adduct **23b**[18] (5%) were isolated. The products **22**, **23a**, and **23b** retained the acetoxy group, which supports the free-radical addition mechanism.



21a, $R^1=R^2=R^3=H$ 22 23a, $R^1, R^2=O$

21b, $R^1=SCH_2CO_2CH_3$ $R^2=R^3=H$

23b, $R^1=SCH_2CO_2CH_3$ $R^2=H$

21c, $R^1=R^3=H$ $R^2=SCH_2CO_2CH_3$

These results demonstrate that even the dienediyne systems exempt from severe ring strain, such as ketone **6** and acetate **7b**, can undergo the radical- and nucleophile-initiated molecular

(12) These differences of ab distance, however, could be significant. For the intriguing discussions on the crucial distance for spontaneous cyclization of conjugated enediyne, see: Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

(13) Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462.

(14) Sondheimer, F.; Wolovsky, R.; Ben-Efraim, D. A. *J. Am. Chem. Soc.* **1961**, *83*, 1686.

(15) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewsky, A. R.; Takeda T.; Waldner, A.; Williard, P. G.; Zutter, U. *J. Am. Chem. Soc.* **1986**, *108*, 1039.

(16) Oxidatively coupled product of alkyne was mainly obtained under several conditions (Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467, and also see ref 7).

(17) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.

(18) Diastereomeric mixture as indicated by NMR spectroscopy.

(19) Similar addition of methanol to **1** has been observed by Mizugaki and his co-workers. Mizugaki, M., private communication.

transformations to benzenoids and suggest the importance of free-radical triggering mechanism in the aromatization of **1**.

Acknowledgment. We thank Dr. Chizuko Kabuto (Instrumental Analysis Center for Chemistry) for assistance in X-ray crystallographic analysis. We are grateful to Prof. Kiyoto Edo (Tohoku University) and Takashi Takahashi (Tokyo Institute of Technology) for their stimulating discussions.

Supplementary Material Available: Spectral data (^{1}H NMR, IR, and MS) for all new compounds, X-ray data for **7b**, and experimental details for the syntheses of **6** and **7b** (25 pages). Ordering information is given on any current masthead page.

Identification of Protonated β-Hydroxycarbonyl Compounds by Reactive Collisions in Tandem Mass Spectrometry

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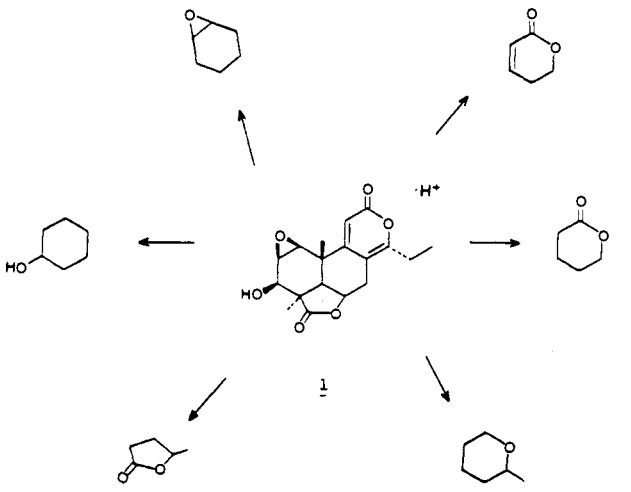
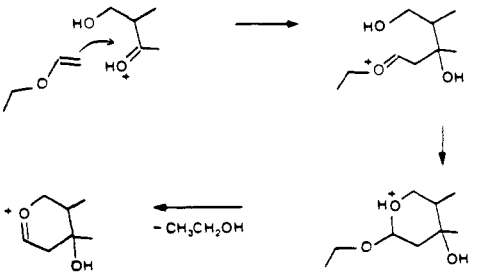
The special complications associated with mass spectrometric characterization of complex organic ions, e.g., biomolecules, have attracted much interest recently.[1,2] It is now evident that conventional ion activation methods often do not deposit high enough energies to cause decomposition of large organic ions in the microsecond time scale typical for tandem mass spectrometers.[2,3] The use of selective bimolecular reactions to identify specific functional groups is a potential solution to some of these problems. However, while reactive collisions have been successfully used to distinguish small isomeric ions,[4] few neutral reagents are known that would undergo predictable, structurally diagnostic reactions with ions containing a specific functional group.[5,6] We report here the first known bimolecular gas-phase reaction that shows a significant degree of selectivity toward a specific arrangement of functional groups in *mono- as well as polyfunctional* organic cations and discuss the mechanism of the reaction in the light of current evidence.

Our study was prompted by the discovery[7] that some complex organic ions (e.g., **1**, Scheme I) give a curious, abundant product ion upon low-energy collisions with ethyl vinyl ether[8] in the center quadrupole of a triple quadrupole mass spectrometer. This product ion formally corresponds to exchange of one of the protons of the reactant ion to a vinyl group, while ethanol is eliminated. We decided to study the nature of this previously unknown reaction by examining the reactivity of a number of mono- and polyfunctional cations toward ethyl vinyl ether, including ions containing functional groups present in the complex-protonated molecules (Scheme I) that were earlier found[7] to undergo the reaction of interest. The experiment[7,9] involves protonation of the sample molecules in the ion source of a triple quadrupole mass spectrometer (isobutane chemical ionization), followed by mass-selection of these ions with the first quadrupole mass filter for reactions occurring in the center quadrupole (ion kinetic energy 0.5 eV, nominal ethyl vinyl ether pressure 2 mTorr). The products were analyzed by scanning the third quadrupole. We discovered that only those model ions that contain *a carbonyl group and a hydroxy group in close proximity* undergo the reaction of interest. For example, protonated diacetone alcohol and protonated 4-hydroxy-3-methyl-2-butanone undergo "vinylation" and collision-induced dehydration as the only primary reactions, the product of the former reaction consisting of up to 40% of the total product ion distribution.

Scheme I



Scheme II



Several bond-making, bond-breaking steps must be involved in the complex series of events ultimately resulting in addition of C_2H_2 in protonated β-hydroxy carbonyl compounds ("vinylation") upon collisions with ethyl vinyl ether. In Scheme II, a reasonable mechanism is presented that is supported by a variety of experimental results, including the following: (i) The yield of the reaction shows a first-order dependence on ethyl vinyl ether pressure. (ii) The reaction proceeds rapidly only for reactant ions with a hydroxy group in β-position with respect to a carbonyl group, e.g., protonated 3-hydroxy-2-butanone does not react. (iii) The use of methyl vinyl ether results in an ionic product with the same m/z value as is obtained for ethyl vinyl ether. (iv) Deuterium-labeling experiments indicate that one of the hydroxyl hydrogens of the protonated hydroxycarbonyl compound is lost in ethanol. (v) When both the hydroxyl hydrogens of the reactant ion are replaced by deuteriums, the production retains one deu-

(1) See, for example: (a) McLafferty, F. W. *Science* **1981**, *214*, 280. (b) Rinehart, K. L., Jr. *Science* **1982**, *218*, 254. (c) Burlingame, A. L.; Baillie, T. A.; Derrick, P. J. *Anal. Chem.* **1986**, *58*, 165R.

(2) (a) Tomer, K. B.; Crow, F. W.; Gross, M. L.; Kopple, K. D. *Anal. Chem.* **1984**, *56*, 880. (b) Cody, R. B., Jr.; Amster, L. J.; McLafferty, F. W. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6367. (c) Occolowitz, J. L. *Spectra* **1987**, *11*, 11.

(3) (a) Bricker, D. L.; Russell, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6174. (b) McCreary, D. A.; Peake, D. A.; Gross, M. L. *Anal. Chem.* **1985**, *57*, 1181.

(4) See, for example: (a) Lehman, T. A.; Bursey, M. M. *Ion Cyclotron Resonance Spectrometry*; John Wiley & Sons: New York, 1978. (b) DePuy, C.; Grabowski, J. J.; Bierbaum, V. M. *Science* **1982**, *218*, 955. (c) Levsen, K. *Fundamental Aspects of Organic Mass Spectrometry*; Verlag Chemie: New York, 1978. (d) Holmes, J. L. *J. Org. Mass Spectrom.* **1985**, *20*, 169.

(5) (a) Staley, R. H.; Corderman, R. R.; Foster, M. S.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1260. (b) Kass, S. R.; Filley, J.; Van Doren, J. M.; DePuy, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 2849. (c) Kenttämaa, H. I.; Pachuta, R. R.; Rothwell, A. P.; Cooks, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 1654.

(6) Tolf, B.-R.; Jiang, X.-Y.; Wegmann-Szente, A.; Kehres, L. A.; Bunnenberg, E.; Djerassi, C. *J. Am. Chem. Soc.* **1986**, *108*, 1363.

(7) Pachuta, R. R.; Kenttämaa, H. I.; Cooks, R. G.; Zennie, T. M.; Ping, C.; Chang, C.-j.; Cassady, J. M. *Org. Mass Spectrom.* **1988**, *23*, 10.

(8) For reactions of ionized methyl and ethyl vinyl ethers, see, for example: (a) Ferrer-Correia, A. J. V.; Jennings, K. R. *Org. Mass Spectrom.* **1976**, *11*, 867. (b) Keough, T. *Anal. Chem.* **1982**, *54*, 2540.

(9) For other studies of ion-molecule reactions in a triple quadrupole mass spectrometer, see, for example: (a) Bates, J. H.; Tedder, J. M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1263. (b) Fetterolf, D. D.; Yost, R. A. *Int. J. Mass Spectrom. Ion Processes* **1984**, *62*, 33. (c) Tabet, J. C.; Guenat, C. *Adv. Mass Spectrometry, Part B* **1985**, 831. (d, Kinter, M. T.; Bursey, M. M. *J. Am. Chem. Soc.* **1986**, *108*, 1797.

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