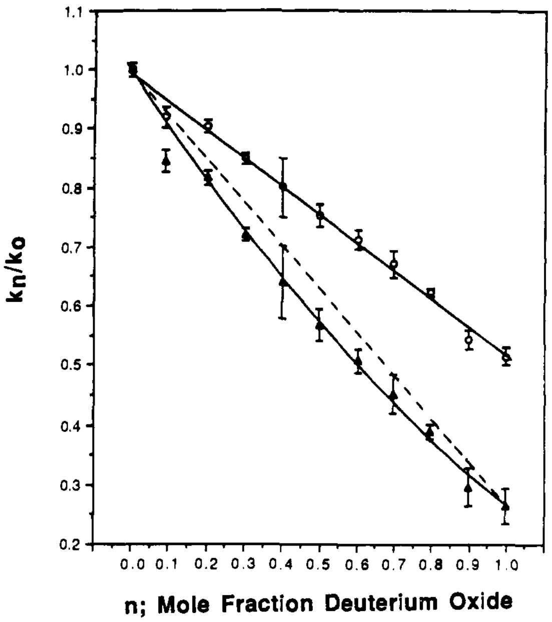

Figure 1. The pseudo-first-order rate constant for the hydrolysis of substrate **1** at kinetic saturation with bifunctional catalyst **2** in water as a function of the mole fraction of D_2O; the temperature was 25.0 °C, and the pH was adjusted to the kinetic maximum (see text). The vertical axis is the rate constant in a given medium relative to that in H_2O. The lower curve is the theoretical curve for a two-proton inventory, one with an isotope effect k_H/k_D of 2.12 and the other with $k_H/k_D = 1.90$, along with the average (2–3 runs) experimental points (▲), with error bars $\pm 2\sigma$. The dashed line is the theoretical curve for a one-proton inventory connecting the H_2O and D_2O points. The upper curve is a straight-line fit of the experimental points (○) in a plot of $(k_n/k_0)^{1/2}$, which should be linear for a two-proton inventory.

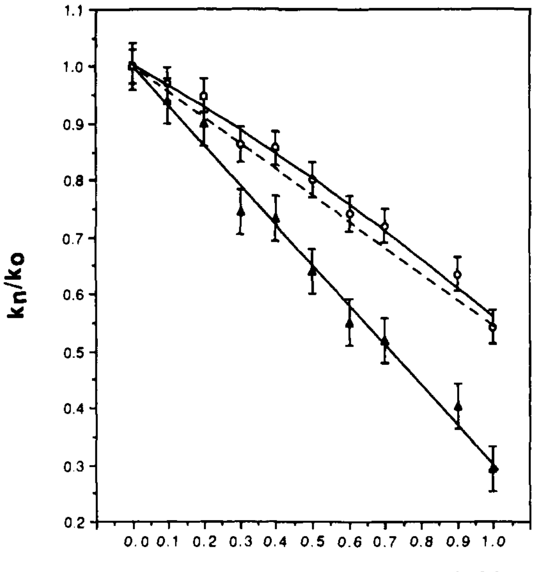

Figure 2. The pseudo-first-order rate constant for the hydrolysis of substrate **1** at kinetic saturation with monofunctional catalyst **3** in water as a function of the mole fraction of D_2O; the temperature was 25.0 °C, and the pH was adjusted to the kinetic plateau maximum (see text). The lower curve is the theoretical straight line for a one-proton inventory along with the experimental points (▲). The upper curve is a least-squares fit of the experimental points (○) in a plot of $(k_n/k_0)^{1/2}$, which should show upward curvature for a one-proton inventory. The dashed line is a straight line connecting the H_2O and D_2O points; it does not fit the points, in contrast to the $(k_n/k_0)^{1/2}$ curve of Figure 1.

can fit a theoretical curve for a two-proton isotope effect with k_H/k_D of 2.12 and 1.90, respectively; 2.12 is the measured k_{HOH}/k_{DOD} for cleavage of **1** by **2** at high pH, where the ImH^+ catalytic group is neutralized.

The curvature is as expected, but it is small, so we checked these conclusions. First of all, a square-root plot is straight (Figure 1), as it should be[9] for a two-proton effect. Secondly, we examined the proton inventory method with catalyst **3**, performed as above but with 10 points ranging between pH readings 6.65 (H_2O) and 6.80 (D_2O) on the high pH plateau for **3**. The data in Figure 2 show clearly that this reaction has a one-proton inventory, with a linear k_{cat} plot and upward curvature in the square-root plot. The results thus support our conclusion that the mechanism of hydrolysis of **1** by the enzyme model **2** is indeed that of Scheme I, with simultaneous proton transfers by both catalytic groups.[12]

The hydrolysis of cytidine 2′,3′-cyclic phosphate by ribonuclease A also shows a two-proton inventory, with points that can fit a curve with a k_H/k_D of 1.75 for each proton.[10] The similarity with our findings is striking; as we have described elsewhere,[4] k_{cat}/K_m for the reaction of **1** with **2** is only 230-fold smaller than that for this enzyme reaction. Thus the enzyme may well use a mechanism[6] directly analogous to that of Scheme I.

Acknowledgment. Support of this work by the NIH and the ONR and a NSF Postdoctoral Fellowship to E.A. are gratefully acknowledged.

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(12) As the scheme suggests, T. Liu in our laboratory has found that the cleavage of **1** by **2** is ca. 95% selective for the formation of the 2-phosphate, with ca. 5% of the 1-phosphate formed.

Highly Diastereoselective Coupling Reaction of Cyclopentenol Derivatives by Palladium Catalyst

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Since the pioneering works by Mizoroki[1] and Heck,[2] the palladium-catalyzed alkenylation of olefins has been utilized in a wide range of organic syntheses.[3] Although particular attention has been paid to the reaction,[4] only a few investigations concerning the diastereo- and/or enantioselective coupling have been reported, to our knowledge.[5]

In the course of our study to develop a new methodology directed toward the synthesis of prostaglandin (PG) and its analogues, we have been interested in the use of palladium as a catalyst, because the alkenylation of allyl alcohol producing γ,δ-unsaturated carbonyl compounds is regarded as an equivalent of conjugate addition to enone.

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(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581–582.

(2) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322.

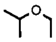
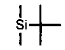
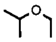
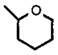
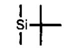
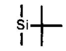
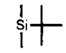
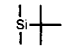
(3) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985; pp 214–242. Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, Heidelberg, New York, 1980; pp 137–152.

(4) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. *Organometallics* **1988**, *7*, 2435–2439. Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919–2922. Larock, R. C.; Gong, W. H.; *J. Org. Chem.* **1989**, *54*, 2047–2050. Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603–2606. Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915–2918. Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329–4332. Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325–4328. Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron* **1988**, *33*, 4321–4330. Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507–2508. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454–3456. Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328–2329 and references cited therein.

(5) Only chirality transfer has been reported, but the selectivity is low. Smadja, W.; Czernecki, S.; Ville, G.; Georgoulis, C. *Organometallics* **1987**, *6*, 166–169.

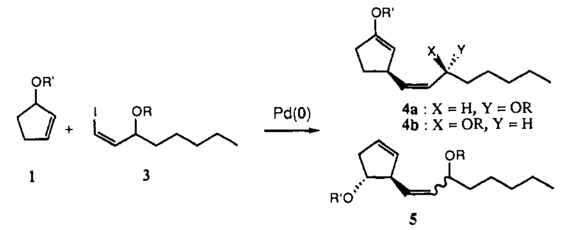
0002-7863/89/1511-8932$01.50/0

Table I. Diastereoselective Reaction with Cyclopentenol[a]

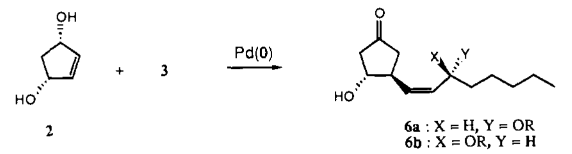
	1	3	Isolated Yield, %	
Entry	R'	R	4(a : b)[b]	5
1	H		61 (75 : 25)	13
2[c]			37 (80 : 20)	7
3	H		54 (81 : 19)	19
4	H		62 (85 : 15)	13
5[c]			78 (87 : 13)	0
6	H		57 (92 : 8)	18
7[c]			58 (92 : 8)	0

[a] Conditions: Pd(OAc)$_2$ (0.1 equiv), P(*o*-tol)$_3$ (0.2 equiv), K$_2$CO$_3$ (1.5 equiv), MeCN at reflux for 8 h. After removal of the protections by the usual manner, the yields were obtained. [b] The ratios were determined by 500-MHz ^{1}H NMR after acetylation. [c] The corresponding enol silyl ether of 4 is isolable before hydrolysis.

Herein, an alkenylation of cyclopentenol derivatives **1** (eq 1) and *meso*-cyclopentene-1,3-diol (**2**) (eq 2) with the protected 3-hydroxy-1-iodo-*cis*-1-octene **3** is described. 3-Alkenylated cyclopentanone derivatives **4a** and **6a** were stereoselectively obtained in good yields. In particular, differentiation of the prochirality of the *meso*-diol **2** proceeded with high diastereoselectivity, and the stereochemical requirements on three asymmetric carbons in a PG skeleton have been satisfied by use of the asymmetric center of **3**.



(1)



(2)

At first, the envisioned palladium-catalyzed diastereoselective reaction of the vinyl iodide **3** and cyclopentenol **1** was examined under the conditions as follows: palladium acetate (10 mol %), tri-*o*-tolylphosphine (20 mol %), and potassium carbonate (1.5 equiv) under refluxing in acetonitrile. The product yield and the ratio of 3-alkenylcyclopentanones **4** and their isomers **5**[6] are shown in Table I. The isomer ratios vary sharply in terms of the size of protecting groups R' and R in **1** and **3**, respectively. The results (entries 6 and 7) reveal that the 2-methoxyisopropyl group attached to **3** plays an important role in producing **4a** preferentially and, in addition, the protecting group of **1** may suppress the formation of **5**.[7] This diastereoselective coupling is specific for the *cis*-alkenyl iodide **3**. Indeed, the reaction of the corresponding trans isomer of **3** with **1** (R' = *tert*-butyldimethylsilyl) resulted in the formation of a 1:1 mixture of diastereomers. The stereochemical outcomes of **4** have been unequivocally determined by both careful inspection of their 2D NMR spectra and a comparison with those of the authentic samples.[8b] In contrast to the stereoselective 1,4-addition of *cis*-alkenylcuprates,[8] this diastereoselective palladium-catalyzed reaction is remarkable with regard to simplicity of manipulation, yield, and selectivity.

Encouraged by the above diastereocontrolled phenomena, the *meso*-diol **2**[9] was submitted to the palladium-catalyzed alkenylation. Because of the base-labile functionality of **6**, the above conditions gave a poor yield despite high diastereoselectivity. Potassium carbonate was changed to sodium carbonate, and the absence of phosphine ligand did not affect the results. As listed in entry 3 of Table II the methoxyisopropyl group as R provided the desired product **6a** with excellent diastereoselectivity as expected. Relative stereochemistry was confirmed again as mentioned above.[10] On the other hand, another set of conditions (entry 4), employing palladium chloride at 30 °C, also gave **6a** exclusively. However, the reaction was very slow and the iodide **3** was recovered intact in 24% yield.

Since the cyclopentenol **1** has two reactive olefinic carbons, the isomer **5** is produced as a minor product. Apparently, such a problem is irrelevant to the *meso*-diol **2** and, in addition, the choice of the *meso*-diol **2** caused a very intriguing enhancement of diastereoselectivity. Therefore, the correlation of the ratio of **6a** to **6b** with that of **4a** to **4b** for each protective group looks square. Thus, the ratio 75:25 (entry 1 in Table I) increased to 86:14 in the case of **2** (entry 1 in Table II), which is almost equal to the value $75^2:25^2 = 90:10$. Similarly, the isomer ratios 85:15 and 92:8 observed for entries 4 and 6 in Table I are led to the calculated values 97:3 and 99:1, respectively. These are quite consistent with the observed isomer ratios 98:2 and 99:1 for the corresponding protective groups (entries 2 and 3 in Table II). This accumulative induction might be ascribed to a cooperative effect of the two hydroxy groups of the *meso*-diol.[13]

Although an excellent strategy to attain high optical purity has been reported in a combination of enantioselective reaction and kinetic resolution for σ-symmetrical substrates,[14] the present

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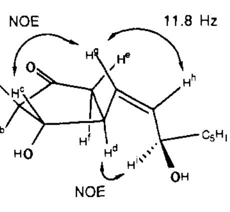
(6) After acetylation, it was revealed that the olefin partially isomerized to trans (J = 15 Hz). Such an isomerization sometimes occurs, e.g.: Heck, R. F. *Org. React.* (*N.Y.*) **1982**, *27*, 345–390. Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083–1090. Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1982**, *23*, 4517–4520.

(7) Such an increase of selectivity by using allyl silyl ether is known. Hirao, T.; Enda, J.; Ohshiro, Y.; Agawa, T. *Chem. Lett.* **1981**, 403–406.

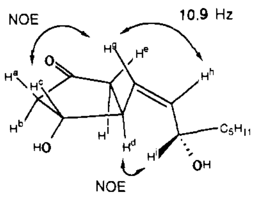
(8) (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 9256–9258. (b) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755–3759. (c) Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774–6775. (d) Lūthy, C.; Konstantin, P.; Untch, K. G. *J. Am. Chem. Soc.* **1978**, *100*, 6211–6217. Application to steroid syntheses: Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261–5263. Takahashi, T.; Okumoto, H.; Tsuji, J.; Harada, N. *J. Org. Chem.* **1984**, *49*, 948–950. Takahashi, T.; Okumoto, H.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 1925–1928. Kinetic resolution of *cis*-vinylcuprate: Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276.

(9) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876–877.

(10) Every correlation on COSY, DQCOSY,[11] and HETCOR (C-H COSY) is completely consistent with the expected structure. J values of olefinic protons indicate retention of cis geometries, which can be verified by ROESY[12] showing a NOE between H^d and H^i. A reasonable NOE between H^g and H^c appeared on ROESY, to show the trans relationship of the 4-hydroxy and the side chain, which is also supported by the mechanistic consideration.



6a



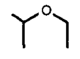
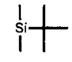
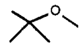
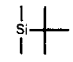
6b

(11) Shaka, A. J.; Freeman, R. *J. Magn. Reson.* **1983**, *51*, 169–173.

(12) Kessler, H.; Griesinger, C.; Kerssebaum, R.; Wagner, K.; Ernst, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 607–609. Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207–213.

(13) Such a cooperativity in asymmetric inductions with C_2 symmetrical substrates has been described. Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1981**, *103*, 2104–2105; **1982**, *104*, 1742–1744; **1984**, *106*, 3806–3810; **1985**, *107*, 4589–4590. Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343–3345. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507–4510.

Table II. Diastereoselective Reaction with Cyclopentene-1,3-diol[a]

Entry	**3** (R)	Yield, **6**	**6a** : **6b** [b]	(**4a**[2] : **4b**[2]) [c]
1		71	86 : 14	(90 : 10)
2		83	98 : 2	(97 : 3)
3 [d]		42	99 : 1	(99 : 1)
4 [e]		41	>99 : 1	

[a] Conditions: $Pd(OAc)_2$ (0.1 equiv), Na_2CO_3 (1.5 equiv), MeCN at reflux for 24 h. [b] After deprotection with acid, isomers were separated by column chromatography. [c] See Table I. [d] The dehydrated enone was isolated in 10% yield. [e] $PdCl_2$ (0.05 equiv), AcONa (1.25 equiv), Bu_3N (0.3 equiv), DMF at 30 °C for 100 h.

methodology consists of a combination of diastereoselection and differentiation of a meso substrate. This combination resulting in high stereoselectivity may offer another highly efficient strategy for organic synthesis. The recognition of the prochiralities of meso substrates is a current topic of synthetic methodology for asymmetric reactions, wherein only differentiation of the enantiotopic groups is attempted.[15] Our result is the first example of the incorporation of new chiralities with differentiation of the prochirality in a meso structure.[16]

Acknowledgment. We thank the SC-NMR Laboratory of Okayama University for obtaining 500-MHz NMR spectra, and we are grateful for partial financial support by a Teijin Award in Synthetic Organic Chemistry, Japan, and a Grant-in-Aid for Scientific Research (No. 01649512) from the Ministry of Education, Science and Culture.

Supplementary Material Available: Experimental procedures and characterization data (IR, ^1H NMR, ^{13}C NMR, copies of 2D NMR spectra, HRMS, and COSY pulse sequence spectra) for **4** and **6** (22 pages). Ordering information is given on any current masthead page.

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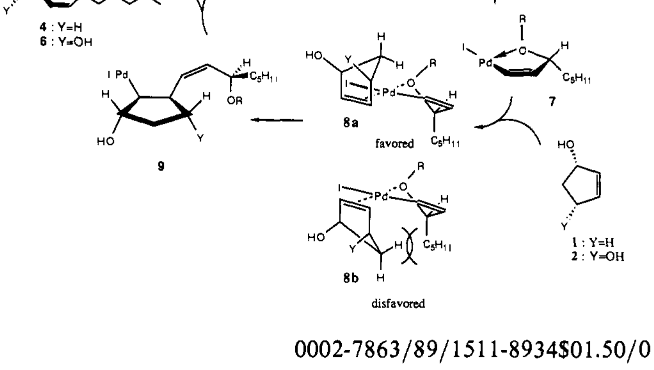
(14) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529. Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585-3588.

(15) Scheffold, R. *Modern Synthetic Methods*; Salle Sauerlander: Frankfurt am Main, 1980; Vol. 2, pp 91-350.

(16) Further investigations along this methodology are in progress. The following mechanism is plausible. In principle, insertion of olefin to alkenylpalladium takes place in cis fashion, and β-elimination of palladium hydride also proceeds by abstraction of the syn proton.[2-5] Thus, the alkenylpalladium species **7** generated by the oxidative addition of the alkenyl iodide **3** to Pd(0) undergoes insertion via the coordination from the less crowded face of the olefin of **1** and **2**. Therefore, the intermediate **8a** is favored for steric reasons. The alkylpalladium **9** collapses into **4** and **6** by picking up the syn proton.



Pulsed-Laser-Ionization High-Pressure Mass Spectrometry: A New Route to Gas-Phase Metal Ion–Ligand Thermochemistry

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Received July 31, 1989

The chemistry of bare metal ions and metal clusters has been the subject of extensive study with the advent of pulsed-laser ablation to generate gas-phase metal species. Using techniques of ion cyclotron resonance,[1,2] flowing afterglow,[3] and pulsed molecular beams,[4] many valuable insights into the dynamics of metal ion binding with neutral substrates has been realized. Despite these valuable efforts, relatively little absolute quantitative experimental data for metal ion–substrate binding energies has been obtained.

High-pressure mass spectrometry has previously been demonstrated as a precise method for obtaining ion–neutral clustering energetics.[5] In the present communication, we report the adaptation of pulsed-laser metal ion ablation to high-pressure mass spectrometry as a means of obtaining metal ion–ligand thermochemical data.

The modifications of a conventional high-pressure mass spectrometer system[6] to permit laser ionization experiments are shown in Figure 1. A Lumonics HyperEX 400 excimer laser operated at 308 nm (XeCl) was used to generate ions. Approximately 5 mJ of laser light (10-ns pulse width) was focused on a metal target mounted inside the gas-tight high-pressure region by a 5-cm lens mounted on the source housing. Metal ions generated by the laser pulse are rapidly thermalized by collisions (over 10^8 s^{-1}) with the flowing 5 Torr of buffer gas (typically Ar or N_2) present in the source. Ions diffuse slowly throughout the source under electric field free conditions until they either are discharged at the walls or exit through a 150-μm aperture into the main vacuum housing. The small fraction of ions that exit the ion source are focused, accelerated to 2 kV, and mass analyzed with a magnetic sector mass spectrometer. The laser pulse is also used to gate a multichannel analyzer, which then monitors the mass selected ion beam intensity as a function of ion residence time in the ion source. Intensities can be monitored for as long as 20 ms following the laser pulse before the ion signal decays to 0 as a result of diffusion to the walls. This time is sufficient for $>10^6$ collisions of ions with the bath gas to occur and ensures that the ions have reached thermal equilibrium with the bath gas. If small amounts of substrate with which the metal ions can either react or associate are added, the time evolution of these reaction products can also be readily monitored. If, at sufficiently long times, the time intensity profile of an ion and its association product become parallel, this is an indication that ion–molecule equilibrium has been established. From the steady state ion intensity ratio and the known substrate partial pressure, the clustering equilibrium constant may be calculated. A typical example of the establishment of metal ion–substrate clustering equilibrium is shown in Figure 2a for aluminum ions generated in a 150 °C bath of N_2 to which a small amount of acetone is added. After <1 ms, the intensities of $[Al(CH_3COCH_3)]^+$ and $[Al(CH_3COCH_3)_2]^+$ become parallel. The intensity of Al^+ has decayed rapidly to 0

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† A. P. Sloan Foundation Fellow, 1988–1990.

(1) Freiser, B. S. *J. Am. Chem. Soc.* **1982**, *104*, 3565. Freiser, B. S. *J. Am. Chem. Soc.* **1983**, *105*, 5197.

(2) Jones, R. W.; Staley, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3794. Jones, R. W.; Staley, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2296. Jones, R. W.; Staley, R. H. *J. Phys. Chem.* **1982**, *86*, 1669.

(3) Tonkyn, R.; Weisshaar, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7128. Tonkyn, R.; Ronan, M.; Weisshaar, J. C. *J. Phys. Chem.* **1988**, *92*, 92.

(4) Dietz, T. G.; Duncan, M. A.; Powers, D. E.; Smalley, R. E. *J. Chem. Phys.* **1981**, *74*, 6511.

(5) Kebarle, P. *Annu. Rev. Phys. Chem.* **1977**, *28*, 1445.

(6) Szulejko, J. E.; Fisher, J. J.; McMahon, T. B.; Wronka, J. *Int. J. Mass. Spectrom. Ion Processes* **1988**, *83*, 147.

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