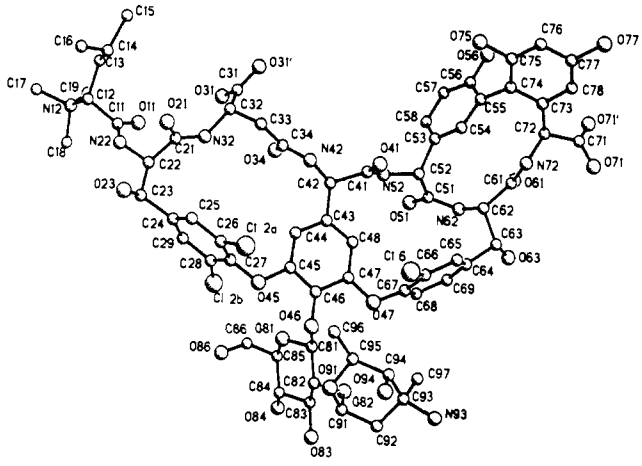
established the structural relationship of CDP-I to vancomycin.

M43A derivative **6** crystallizes as colorless prisms in the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell with the dimensions a = 14.018 (2), b = 21.460 (5), and c = 33.673 (8) Å. The calculated density is 1.33 g cm^{-3}. A total of 5809 unique reflections with 2θ less than 116.0° were measured on an automated four-circle diffractometer with monochromatic copper radiation. Crystals of vancomycin CDP-I[6] have the same space group and very similar unit cell dimensions. It was assumed that the two structures are nearly isomorphous and a difference electron density map was calculated by using positions reported for vancomycin CDP-I and structure factors for **6**. The difference map clearly showed two additional peaks in the correct positions for methyl groups (C18 and C19 in **7**).



The structure was refined by the least-squares method with anisotropic temperature parameters for all the non-hydrogen atoms of **6**. A difference electron density map showed 28 additional peaks which seemed to be at reasonable positions for water molecules. Eight of these were included in the refinement as oxygen atoms with full occupancy factors and isotropic temperature parameters. The other 20 putative water molecule oxygen atoms were given fixed isotropic temperature parameters, and their occupancy factors were allowed to refine. Of the 78 hydrogen atoms in **6**, 68 were included in the refinement at calculated positions with isotropic temperature parameters. Because of a persistent unexplained peak in the electron density map, we were able to show that chlorine atom 2 in **7** is disordered and exists in approximately 90% of the molecules in position 2a and the other 10% in position 2b. This supports earlier work[7,8] that suggested that in vancomycin the phenyl ring C to which this chlorine is attached flips approximately 180° when forming the CDP-I **5**. It would appear that, as in the case of vancomycin,[7] the chlorine atoms in M43A are on opposite sides of the molecule. The final R factor was 0.127 for 5297 observed reflections. Figure 2 shows an ORTEP plot of the molecule.

Amycolatopsis orientalis M43-05865 also produced trace amount of M43B. As in the case of vancomycin CDP-I **5**, the rearranged product **6** eluted in HPLC as two peaks with retention times 7.77 and 11.71 min, respectively. This is due to the fact that **6** exists as a mixture of two atropisomers as shown by the above X-ray data. In solution, both CDP-I[8] and **6** exist as an equilibrium mixture of atropisomers in which the chlorine-containing aromatic ring is slowly rotating with a half-life of several hours, resulting in separation of the atropisomers by HPLC. However, M43B elutes as a single peak with a retention time of 13.13 min. The new metabolite, M43B, had the same molecular weight and elemental composition as the rearranged M43A derivative **6** by FABMS peak match experiment.[9] Both compounds, M43B and **6** showed fragments with identical masses of 1334 and 1172 in the FABMS by cleavages of vancosaminyl and vancosaminyl-*O*-glucosyl moieties, respectively. These data suggest that M43B has the unrearranged desamido structure **4**.

The antibacterial activity of M43 factors A and D is similar, if not identical, to that of vancomycin suggesting that the state of methylation of the leucine residue does not affect their antibacterial activity. However, M43B is about 20–40 times less active than vancomycin. The corresponding unrearranged desamido analogue of vancomycin, designated M43F (**8**) is about ten times less active than vancomycin.[10] The rearranged M43A compound **6** and CDP-I **5** are completely devoid of antibacterial activity. *Clearly, the negative charge on the aspartate strongly depressses antibacterial activity in* **4**, **5**, **6**, and **8**. The presence of the negative carboxyl group in M43B, M43F, **5**, and **6**, near the binding site, and the change in the conformational geometry[8] in the rearranged **5** and **6** for the binding of D-Ala-D-Ala-carboxyl terminus of UDP-*N*-acetylmuramylpentapeptide to the N-terminal *N*-methylleucine contribute to the diminution in the biological activity in compounds M43B, M43F, **5**, and **6**, respectively. Details of the structure activity relationships of the M43 factors, the rearranged compound **6**, and other vancomycin derivatives will be discussed elsewhere.[11]

Supplementary Material Available: Tables of HPLC retention times and FABMS and ^{1}H NMR spectral data for vancomycin, M43A, and M43D and the atomic coordinates and temperature factors, bond lengths, bond angles, anisotropic temperature factors, and hydrogen coordinates and temperature factors for the M43A derivative **6** (11 pages). Ordering information is given on any current masthead page.

(8) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915–6922.

(9) Fast atom bombardment peak match for **6**: MH$^+$ = 1477.4524. Calculated for $C_{68}H_{79}N_8O_{25}Cl_2$ = 1477.4534.

(10) Nagarajan, R.; Merkel, K. E., unpublished results.

(11) Nagarajan, R. *Antimicrob. Agents Chemother.*, manuscript in preparation.

^{1}H NMR Evidence for a Non-Chair Conformation for the Six-Membered Ring Attached Apical Equatorial to Pentacovalent Phosphorus. Potential Implications for Enzyme-Catalyzed Reactions of Cyclic Nucleotides

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Pentacovalent phosphorus derivatives, of long standing interest in their own right,[1] are likely key intermediates in the enzymatic reactions of biologically important phosphates including nucleoside cyclic 3′,5′-monophosphates.[2] We recently concluded from an NMR study of **1** ⇄ **2**[3] that enzyme–substrate binding energy would be sufficient to convert the normal chair form phosphate ring of a cAMP or cGMP into the twist conformation. Consideration of twist conformations for *pentacovalent* cyclic nucleotide adducts in enzymic systems also was suggested.

Little is known about the conformational properties of six-membered rings attached to *pentacovalent* phosphorus. The ^{1}H NMR techniques successfully applied to **1** ⇄ **2**,[3] the corresponding tricoordinate phosphite system,[4] and to P(IV) 2-oxo- and 2-

(1) Holmes, R. R. *Pentacoordinated Phosphorus*; American Chemical Society: Washington, D.C., 1980; Vol. I, II; ACS Monograph No. 175, 176.

(2) Van Haastert, P. J. M.; Dijkgraaf, P. A. M.; Konijn, T. M.; Abbad, E. G.; Petridis, G.; Jastorff, B. *Eur. J. Biochem.* **1983**, *131*, 659. Burgers, P. M. J.; Eckstein, F.; Hunneman, D. H.; Baraniak, J.; Kinas, R. W.; Lesiak, K.; Stec, W. J. *J. Biol. Chem.* **1979**, *254*, 9959. van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 79. van Ool, P. J. J. M.; Buck, H. M. *Eur. J. Biochem.* **1982**, *121*, 329. van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 119. de Wit, R. J. W.; Hekstra, D.; Jastorff, B.; Stec, W. J.; Baraniak, J.; van Driel, R.; van Haastert, P. J. M. *Eur. J. Biochem.* **1984**, *142*, 255.

(3) Nelson, K. A.; Bentrude W. G.; Setzer, W. N.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 4058.

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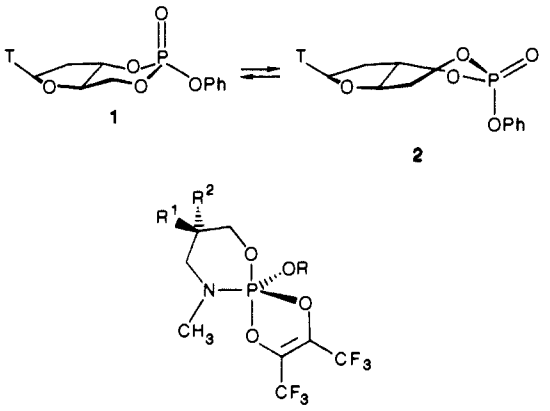
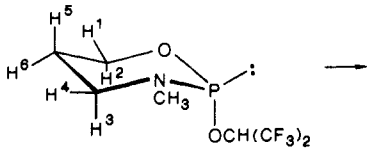


1 2

3a: $R^1 = R^2 = H$; $R^3 = (CF_3)_2CH$
b: $R^1 = H$; $R^2 = t$-Bu; $R^3 = (CF_3)_2CH$

thio-1,3,2-oxazaphosphorinane six-membered rings[5] seem not to have been utilized in *pentacovalent* phosphorus systems. Even the presence of the necessary $^3J_{HP}$ Karplus coupling relationships is unverified for P(V). We report here a 500-MHz ^{1}H NMR investigation *which shows phosphorane* **3a** *to be in a non-chair (boat and/or twist) conformation.*

Phosphorane **3a** was prepared by the addition of **4** to equimolar, neat hexafluorobiacetyl at 0 °C. Distillation (58–59 °C, 0.3 mmHg) gave **3a** in 72% yield (96% purity by capillary GLC): δ ^{31}P NMR (C_6D_6), −48.7; structure confirmed by ^{13}C NMR, and GC–MS (70 eV) m/z, M^+ 478.9 (molecular ion).



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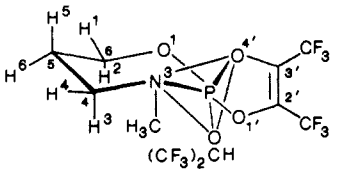


5

The coupling constants for **3a** (Table I) are accounted for by a non-chair conformation (or mixture of conformers) close to structure **7**. Proton numberings appear in structures **5**–**7**. Formation of **7** from **5** can be most readily considered in stepwise fashion. Because of the high degree of ring pucker about phosphorus in apical-equatorial[6] chair **5** ($\angle O_1$–P–$N_3 \simeq 90°$), the OR and H_2 are in close proximity (H_2···OR, ≃2.0 Å, Drieding models). (The chair form chosen is arbitrary.) Chair-to-boat interconversion (**5** → **6**) removes this *steric interaction.* The H_5···$O_{4'}$ repulsion in **6** then is relaxed by conversion to **7**. Moreover, in **7** the lone pair on presumably trigonal-planar N_3 is in the equatorial plane as is preferred for R_2N–P^V compounds.[7]

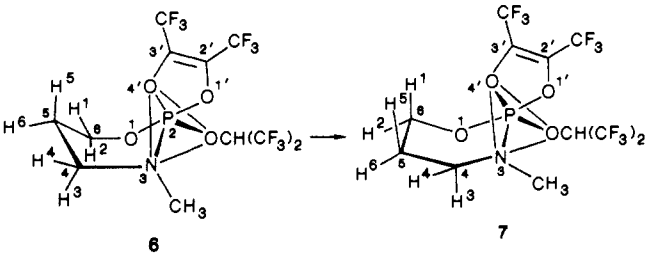
Table I. Selected ^{1}H NMR Parameters for **3a** at 500 MHz (C_6D_6), 26 °C[a]

δ_1, 3.70	δ_2, 3.36	δ_3, 2.62	δ_4, 2.05
$J_{15} = 8.66$	$J_{25} = 7.68$	$J_{35} = 11.29$	$J_{45} = 4.28$
$J_{16} = 4.59$	$J_{26} = 8.90$	$J_{36} = 3.38$	$J_{46} = 4.28$
$J_{1P} = 8.66$	$J_{2P} = 26.05$	$J_{3P} = 5.50$	$J_{4P} = 25.00$
$J_{12} = -11.00$		$J_{34} = -12.50$	

[a] Chemical shifts (δ, ppm) and coupling constants (J, Hz). Other parameters: $\delta_5 = 1.22$; $\delta_6 = 1.00$; $J_{56} = -13.37$ Hz; $\delta(CH(CF_3)_2) = 5.26$; $\delta(CH_3$–$N) = 2.32$.

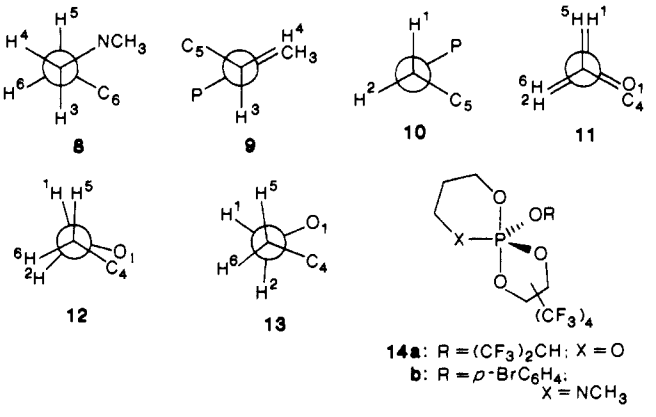
This *stereoelectronic* effect probably accounts for the population of **7** rather than the boat form with C_6 and N_3 at the bowsprit positions (not shown).[6]

Evidences for **7** are several. *First*, the P–N_3–C_4–C_5 geometry in **7** is very similar to that in chairs **4** and **5**. (C_4–C_5 bond projection given by **8**.) The large $^3J_{35}$ proton coupling required is indeed found (11.3 Hz). The other couplings between H_3–H_6, as predicted for **7**, are very similar to those of the chair-form ring of **4**.[8] Furthermore, $^3J_{4P}$ is large (25.0 Hz), and $^3J_{3P}$ is small (5.50 Hz) as expected from the Newman formula **9** (C_4–N_3 bond of **7**) if indeed *a classical Karplus-like relationship of* $^3J_{HP}$ *to dihedral angle HCNP is operative. Secondly*, the geometry on the C_5–C_6–O_1–P side of the ring in **7** (projection **10**) is such that H_2 has become pseudoequatorial with a close to antiperiplanar relationship to phosphorus. Thus $^3J_{2P} = 26.1$ Hz. By contrast for



6 7

pseudoaxial H_1, $^3J_{1P}$ is only 8.7 Hz. *Most importantly*, H_2 has a relatively large coupling to *both* H_5 *and* H_6 which completely excludes a gauche arrangement of H_1, H_2, H_5, and H_6 as in chair



8 9 10 11

12 13

14a: R = $(CF_3)_2CH$; X = O
b: R = *p*-BrC_6H_4; X = NCH_3

5 or even boat **6**. Indeed, the large values and near-equality of J_{26} and J_{15} are in accord with structure **7** as is the 4.6-Hz value for J_{16}. (Newman, C_5–C_6 bond projection, **11**.) However, J_{25} (7.7 Hz) > J_{16} (4.6 Hz) contrary to **7**. This is accommodated readily by twisting boat **7** about the C_5–C_6 bond as in **12**. Alternatively, equilibrium **11** ⇄ **13** would increase the value of J_{25} and not greatly reduce J_{16}. (J_{HP} values are little affected by these C_5–C_6 bond rotations.) *Regardless, 3a clearly populates a non-chair conformation.* Population of more than a few percent of a chair conformation like **5** would strongly average J_{1P}(increase) and J_{2P}(decrease), although the couplings for H_3 and H_4 would be little changed.

Thirdly, in chair **4** the chemical shift order is $\delta H_3 > \delta H_4$ and $\delta H_2 > \delta H_1$. For **3a** $\delta H_3 > \delta H_4$ as with **4**, but now $\delta H_1 > \delta H_2$.

(4) Nelson, K. A.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 7752.
(5) E.g. see: (a) Bajwa, G. S.; Bentrude, W. G.; Pantaleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602. (b) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *Ibid.* **1982**, *104*, 6385. (c) Bentrude, W. G.; Day, R. O.; Holmes, J. M.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *Ibid.* **1984**, *106*, 106. (d) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *Ibid.* **1985**, *107*, 2083. (e) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P. *Ibid.* **1986**, *108*, 6669. (f) Gorenstein, D. G.; Rowell, R.; Findlay, J. *Ibid.* **1980**, *102*, 5077. (g) White, D. W.; Gibbs, D. E.; Verkade, J. G. *Ibid.* **1979**, *101*, 1937. (h) Roca, C.; Kraemer, R.; Majoral, J.-P.; Navech, J.; Brault, J. F.; Savignac, P. *Org. Magn. Reson.* **1976**, *8*, 407.
(6) Bone, S. A.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Perkin Trans 1* **1977**, 80.
(7) (a) Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047. (b) Szobota, J. S.; Holmes, R. R. *Inorg. Chem.* **1977**, *16*, 2299 and references therein.
(8) For **4**: $J_{35} = 11.7$ Hz; $J_{36} = 3.4$ Hz; $J_{45} = 4.7$ Hz; $J_{46} = 3.3$ Hz.

This reversal is consistent with the axial or pseudoaxial proton being downfield of its equatorial or pseudoequatorial counterpart in both **4** and **7(3a)**.

The above is fully reinforced by the ^1H NMR parameters for the 5-*t*-Bu analogue **3b** (major diastereomer) which evidently has the *t*-Bu (which replaces H_6) in a pseudoequatorial position.[9] $^3J_{HH}$ and $^3J_{HP}$ values are close to those for **3a**. As we have noted previously for P(IV) *5-tert*-butyl-2-oxo-1,3,2-oxazaphosphorinanes,[5a-e] the combination of large J_{2P} (29.4 Hz) *and* J_{25} (7.3 Hz) found for **3b** can only be reconciled if the conformer populated is a boat or twist. The P(IV) systems require a group such as *tert*-butyl at C_5 in order for the steric or electronic property of a group on phosphorus to express itself in population of a twist or boat. *By contrast destabilization of either chair conformation of* ***3a*** *(****5*** *or its alternative) by the above-described steric repulsions appears to be an intrinsic property of P(V) ring systems attached apical equatorial.*

Compounds **14a**[10] and **14b**[11] were shown by X-ray crystallography to possess six-membered rings in non-chair conformations. The nitrogen lone pair of **14b** is in the equatorial plane. To our knowledge our ^1H NMR results present the first clear evidence for the population of a phosphorinane ring on P(V) in a non-chair form *in solution.*

*The idea that boat or twist conformations for the pentacovalent intermediates in enzymic reactions of nucleoside cyclic 3′,5′-*monophosphates *should receive serious consideration finds support in the present NMR study and also in the X-ray results.* The findings in the model systems of course do not define what actually *does* occur in the enzyme system.

Acknowledgment. Support of this work by Grant CA 11045 from the National Cancer Institute of the Public Health Service is gratefully acknowledged. We thank Dr. Alan E. Sopchik for obtaining the 500-MHz spectra for **3a** and **3b**.

Supplementary Material Available: Table of ^{13}C NMR data for **3a** and ^1H NMR data for **3b** (1 page). Ordering information is given on any current masthead page.

(9) Yu, J. H., unpublished results from this laboratory.
(10) Schomburg, D.; Hacklin, H.; Roeschenthaler, G. V. *Phosphorus Sulfur* **1988**, *35*, 241.
(11) Barlow, J. H.; Bone, S. A.; Russell, D. R.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 1031.

The Bicyclobutyl Anion: An Alkyl Carbanion

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Alkyl anions in the form of organometallic compounds are extremely important reagents and have been extensively studied in solution.[1] In the gas-phase alkyl carbanions (R^-) are exceedingly difficult or even impossible to generate for any substantial period of time. This is the result of their high reactivity and low, or in some cases even negative, electron affinities.[2] Despite these formidable experimental problems, acidities of a variety of alkanes have been determined by an ingenious kinetic technique which does not require the free R^-.[3] More recently,

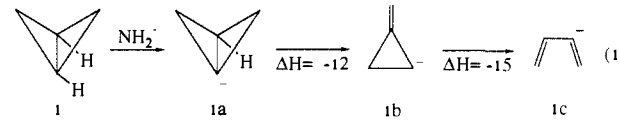
Table I. Summary of Results for Bracketing Experiments

ref acid	ΔH_{acid}[a]	proton transfer[b] ref acid	proton transfer[b] conjugate base	EA (eV)	electron transfer[b]
NH_3	403.6	–	+		
$EtNH_2$	399.3	+ (slow)	+		
n-$PrNH_2$	398.4	+	+		
i-$PrNH_2$	397.3	+	+		
Me_2NH	396.2	+	+ (slow)		
H_2O	390.7	+	–		
SO_2				1.10[c]	+[d]
O_2				0.44[e]	–[f]

[a] Acidities are in kcal mol^{-1} and come from Lias et al. (see ref 9a). [b] A "+" indicates the occurrence and a "–" denotes the absence of the indicated reaction. The conjugate base column corresponds to reaction of **1** with the conjugate base of the reference acid. [c] Nimlos, M. R.; Ellison, G. B. *J. Phys. Chem.* **1986**, *90*, 2574. [d] Additional products are observed at m/z 49 (HSO^-) and 117 (adduct). [e] Celotta, R. J.; Bennett, R. A.; Hall, J. L.; Siegel, M. W.; Levine, J. *J. Phys. Rev.* **1972**, *A6*, 631. [f] No reaction with O_2 is observed.

Squires and Graul have described the generation of a few alkyl carbanions by collision-induced dissociation of carboxylates in a flowing afterglow–triple quadrupole instrument.[4] We now wish to report the first deprotonation of an alkane to generate the corresponding alkyl anion.

Bicyclobutane (**1**) is a well-known, thermally stable but highly strained hydrocarbon.[5] Its rigid ring structure results in the bridgehead carbon–hydrogen bonds having a high degree of s-character (40% s).[6] This is reflected in the unusually large ^{13}C–^1H coupling constant, 202 Hz, and leads to enhanced acidity in solution.[5] The gas-phase behavior was examined in a flowing afterglow device,[7] where it was found that NH_2^- reacts with **1** by proton abstraction to readily afford a $(P\text{-}1)^-$ ion (m/z 53). Simple deprotonation would lead to the bicyclobutyl anion (**1a**), but ring opened structures (**1b** and **1c**) are thermodynamically favored and could arise from an allowed electrocyclic process (eq 1).[8,9]



(4) Graul, S. T.; Squires, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 607.
(5) Wiberg, K. B. *Advances in Alicylic Chemistry*; Hart, H., Karabatsos, G., Eds.; Academic Press: New York, 1968; Vol. 2, pp 185–205.
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(7) All experiments were carried out with He buffer gas at 298 ± 2 K and at pressures of 0.35–0.40 T. The technique has previously been described and has recently been reviewed. See: (a) Ferguson, E. E.; Fehsenfeld, F. C.; Schmeltekopt, A. *Adv. At. Mol. Phys.* **1969**, *5*, 1. (b) Smith, D.; Adams, N. C. *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Chapter 1. (c) DePuy, C. H.; Bierbaum, V. M. *Acc. Chem. Res.* **1981**, *14*, 146. (d) Graul, S. T.; Squires, R. R. *Mass Spect. Rev.* **1988**, *7*, 263. Our particular apparatus will be fully reported on in a subsequent publication.
(8) For a general discussion on electrocyclic ring openings of cyclopropyl anions, see: (a) Staley, S. W. *Organic Chemistry. Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. 1, pp 199–264. (b) le Noble, W. J. *Reactive Intermediates*; Jones, M., Jr., Moss, R., Eds.; John Wiley and Sons: New York, 1978; Vol. 1, pp 27–67. (c) Dewar, M. J. S.; Nelson, D. J. *J. Org. Chem.* **1982**, *47*, 2614 and references therein. Examples of cyclopropyl anions which do not undergo ring opening in the gas phase are given in the following: (d) Andrist, A. H.; DePuy, C. H.; Squires, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 845. (e) Dawson, J. H. J.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Phys.* **1980**, *334*, 3.
(9) Heats of reaction given in eq 1 come from the heats of formation of the anions which are given by $\Delta H_f(A^-) = \Delta H_{acid}(AH) - \Delta H_f(H^+) + \Delta H_f(AH)$. The quantities used (in kcal mol^{-1}) are $\Delta H_f(H^+) = 365.7$ (ref a), $\Delta H_f(\mathbf{1}) = 51.90$ (ref b), ΔH_{acid}(methylenecyclopropane) = 390 ± 3 (ref c), ΔH_f(methylenecyclopropane) = 47.92 (ref b), ΔH_{acid}(1,3-butadiene) = 397 ± 6 (ref d), and ΔH_f(1,3-butadiene) = 26.11 (ref b). (a) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Supplement 1. (b) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970. (c) Kass, S. R.; DePuy, C. H., unpublished data. (d) Grabowski, J. J.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2565.

(1) See: March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985; pp 151–162, and references therein.
(2) (a) Schleyer, P. v. R.; Spitznagel, G. W.; Chandrasekhar, J. *Tetrahedron Lett.* **1986**, *27*, 4411. (b) Leroy, G.; Wilante, C.; Peeters, D.; Uyewa, M. M. *J. Mol. Struct.: Theochem* **1985**, *124*, 107. For experimental evidence see ref 3 and 4.
(3) DePuy, C. H.; Bierbaum, V. M.; Damrauer, R. *J. Am. Chem. Soc.* **1984**, *106*, 4051. For an alternative view, see: Tumas, W.; Foster, R. F.; Brauman, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 2714 and references therein.

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