Table I. Stereoselectivity for Carbene Insertion

19	reactn condtns[a]	% yield	ratio (20:21)
(*E*)-19	*t*-BuOK, −78, 15 min	60	51:49
(*E*)-19	*t*-BuOK, −78, 15 min[b]	51	51:49
(*E*)-19	*t*-BuOK, 0, 10 min	63	49:51
(*Z*)-19	*t*-BuOK, −78, 20 min	60	52:48
(*Z*)-19	*t*-BuOK, 0, 10 min	65	51:49
(*Z*)-19	Et_3N, 25, 1.5 h	63	49:51

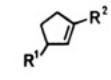
[a] Reactions were carried out in THF; temperatures are in °C. [b] The reaction was carried out in the presence of 18-crown-6 (1.3 equiv).

Elimination of alkenyliodonium salts by base treatment yielding the corresponding alkylidenecarbenes, followed by regioselective 1,5-C–H insertion, probably can explain the formation of these bicyclic compounds.[9,10]

Alkylidenecarbenes are electrophilic, as are most carbenes,[11] and hence the rate of insertion of carbenes to C–H bonds bearing electron-withdrawing substituents such as carbonyl groups on the carbon atoms should decrease considerably. In the reaction of **7** with triethylamine, in fact, competitive 1,2-rearrangement of a β-alkyl group of the resulting carbene occurred, and the insertion product, β,γ-enone **8**, and the rearranged alkyne **9** were obtained in a ratio of 67:33. Alkenyliodonium salts with β-heteroatom substituents exclusively undergo intramolecular 1,2-migration: the only isolated product from the reaction of vinyl sulfide **10** was the alkynyl sulfide **11** (72% yield). Similarly, the vinyl sulfoxide **12** produced a mixture of acetylenic sulfoxides **13** and **14** in a ratio of 79:21 (84% yield). This is presumably a result of 1,2-migration to give **13**, followed by isomerization.[12] The absence of insertion products in the reaction mixture of **10** and **12** is probably due to high migratory aptitude of phenylsulfenyl and phenylsulfinyl groups.[14]

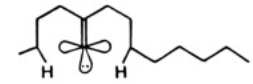
Reaction of (*E*)-vinyliodonium salt **15**[4] with triethylamine afforded 1-decyne in high yield. Since the much faster rate of cis-β-elimination compared to that of α-elimination in the dehydrohalogenation of vinyl halides yielding alkynes has been well documented,[15] both α- and β-deuteriovinyliodonium salts, **16** and **17**, were treated with triethylamine to investigate the possible reaction pathway. Surprisingly, the results shown in Scheme I clearly suggest that the alkyne-forming reaction proceeds predominantly via α-elimination affording carbenes followed by an intramolecular 1,2-hydrogen shift.

To gain some insight into the freeness of the carbenic species generated from alkenyliodonium salts, both stereoisomers of phenyl(2-butyl-1-decenyl)iodonium tetrafluoroborates ((*E*)- and (*Z*)-**19**) were synthesized in a highly stereoselective manner as shown in Scheme II. Both (*E*)- and (*Z*)-**19** were treated with *t*-BuOK or triethylamine in THF, and the ratio of the insertion products, 3-methyl-1-octylcyclopentene (**20**) and 1-butyl-3-pentylcyclopentene (**21**), was determined from the 400 MHz NMR spectra of the crude reaction mixtures (Table I).[16] The structures of these isomeric cyclopentenes were determined from their mass spectra, which showed relatively abundant fragments derived from a cleavage of allylic and vinylic carbon–carbon bonds. It seems reasonable to assume that if there is any association with the leaving group, that is, iodobenzene in the transition state for 1,5-C–H insertions such as **23**,[9e] there should be a memory effect that reflects the stereochemistry of alkenyliodonium salts (*E*)- and (*Z*)-**19** in the product ratios.[9e,11] Table I clearly indicates that the product ratios of **20** and **21** were equally about 1:1

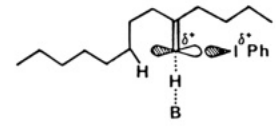


20; R^1 = Me, R^2 = n-C_8H_{17}

21; R^1 = n-C_5H_{11}, R^2 = n-C_4H_9



22



23 ; B = base

irrespective of the stereochemistry of the alkenyliodonium salts and the reaction conditions used. The complete lack of regioselectivity for the intramolecular insertion of carbenes derived from the vinyliodonium salts clearly indicates that the loss of stereochemistry of the vinyliodonium salts precedes the intramolecular insertion. Thus, these results suggest the involvement of the free carbene **22** rather than the carbenoid **23**.

Strong bases like alkyllithiums or drastic reaction conditions are required to generate carbenic species from vinyl halides, thus precluding the presence of many functional groups in the substrate. Our new method produces alkylidenecarbenes under mild conditions, making the reaction compatible with a variety of functional groups.

Supplementary Material Available: Synthetic procedure for **4**, **7**, **10**, **12**, **16**, and **17** and spectral data for **1**, **2**, **4**, **5**, **7**, **10**, **12**, **18**, **19**, **20**, and **21** (4 pages). Ordering information is given on any current masthead page.

(9) For generation of carbenoids from α-elimination of vinyl halides, see: (a) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142. (b) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086. (c) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745. (d) Fischer, R. H.; Baumann, M.; Köbrich, G. *Tetrahedron Lett.* **1974**, 1207. (e) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035. (f) Harada, T.; Nozaki, Y.; Yamaura, Y.; Oku, A. *J. Am. Chem. Soc.* **1985**, *107*, 2189.

(10) For generation of RCOCH=C: from gas-phase thermolysis of α-alkynones, see: (a) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852. (b) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13.

(11) For excellent reviews of alkylidenecarbenes, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348.

(12) Reaction of **13** with *t*-BuOK in THF at −78 °C for 10 min gave the sulfoxide **14** in 82% yield.[13]

(13) Cf. O'Connor, D. E.; Lyness, W. I. *J. Am. Chem. Soc.* **1964**, *86*, 3840.

(14) The facile 1,2-migration of acyloxy groups of alkylidenecarbenes yielding alkynyl carboxylates has been proposed.[6]

(15) Cristol, S. J.; Whittemore, C. A. *J. Org. Chem.* **1969**, *34*, 705.

(16) Isomerization of **19** was not observed under the reaction conditions employed.

Experimental Support for Asp-52's Importance in Lysozyme Using a Carbohydrate-Based Enzyme Model. Acetal Hydrolysis Catalyzed by a "Stereoelectronically Correct" Carboxylate Group

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Theories concerning the mechanism of action of lysozyme and the testing of those theories by enzyme modelling efforts are amongst the most thoroughly documented in the bioorganic literature. The function of lysozyme's Glu-35 as a general acid catalyst has been extensively modelled; rate enhancements of acetal hydrolysis as high as 10^6 have been observed.[1] By comparison, much smaller (2–100-fold) accelerations have been attributed to the presence of an adjacent ionized carboxylate group;[2,3] a large acceleration would provide support for the proposed role of lysozyme's Asp-52 residue as either an electrostatic or nucleophilic catalyst. These small rate effects have prompted more than one author to conclude that Asp-52 contributes little or nothing to

(1) For a summary of work by several labs on g.a.c. in acetal hydrolysis, see: Sinnott, M. I. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; pp 417–420.

(2) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 6693.

(3) Loudon, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 465.

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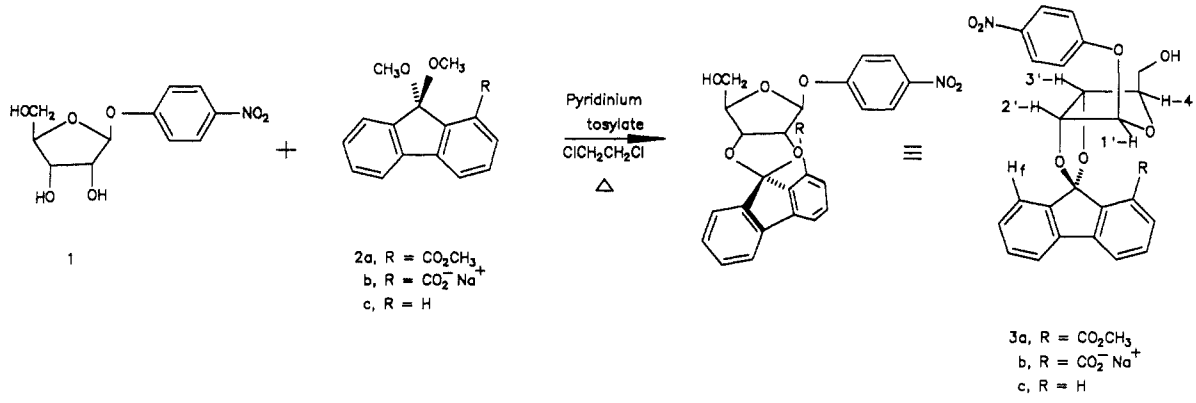
Scheme I



the energetics of the bond-breaking process. It is at least fair to say that the role of Asp-52 in lysozyme remains one of the most long-lived enigmas in enzyme mechanism chemistry. We now report that the hydrolysis of riboside ketal **3c**, slowed by steric inhibition to "backside" solvation, is accelerated by a factor of 860 upon introduction of a carboxylate group (**3b**).

Our enzyme model was prepared as shown in Scheme I. Condensation of riboside **1**[4] with ester **2a**, prepared by acid-catalyzed esterification of fluorenone-1-carboxylic acid,[5] affords endo ketal[6] **3a** in 25% yield. We have been unable to find any trace of the exo isomer, whose formation is precluded for reasons similar to those described previously.[7] For reference, ketal **3c** was prepared in the same way with 9,9-dimethoxyfluorene (**2c**). Ester hydrolyses were accomplished with NaOH in aqueous methanol, from which the sodium carboxylates (**2b** and **3b**) crystallized. Carboxylate **3b** incorporates several design elements that make it a particularly attractive lysozyme model: (1) the spiro bicyclic linkage places the carboxylate group symmetrically underneath the ribose ring oxygen, enforcing proximity to the syn lone pairs;[8] (2) the rigid fluorene framework prohibits a conformational flexure that would disengage carboxylate and ring oxygen moieties; and (3) because fluorenone ketals hydrolyze via formally antiaromatic oxonium ion intermediates, they are themselves unusually stable.[7] In addition, the presence of a ketal group on a ribose's 2′,3′-positions does not drastically affect the rate of its glycosidic hydrolysis in the pH-independent region.[9]

The results of our kinetic studies of hydrolysis (release of *p*-nitrophenol) in totally aqueous media are shown in Figure 1. The pH-independent hydrolysis of endo acid **3b** is 860 times faster than that of reference compound **3c**. That **3b** does not undergo rate-limiting fluorenone ketal hydrolysis under these conditions is confirmed in two ways: (1) the hydrolysis rate of ketal **2b** is proportional to the hydrogen ion concentration from pH 4 to 8,[10] while that for **3b** is not; and, (2) in the pH independent regions **3b** does hydrolyze somewhat faster than does **1**, which could not happen if **3b** hydrolyzed to **1** prior to glycosidic hydrolysis. As compared to reference compound **3c**,[11] endo acid **3b** exhibits the

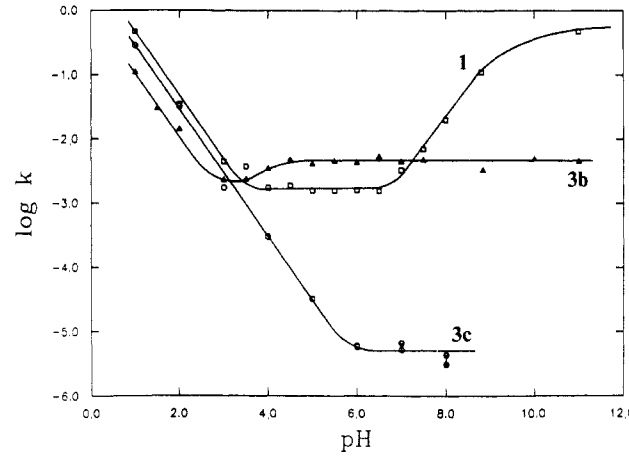


Figure 1. pH rate profiles for the hydrolyses of *p*-nitrophenylriboside derivatives at 100 °C.[15]

largest rate acceleration yet reported for carboxylate-catalyzed acetal hydrolysis by any mechanism.[12] Furthermore, the acceleration observed significantly exceeds the 100-fold limit suggested by the key work of Fife.[2]

It seems initially surprising that endo acid **3b** and **1** itself hydrolyze at nearly the same pH-independent rate. In fact, it is the very slow[13] hydrolysis of the reference compound **3c** that affords the bulk of the carboxylate acceleration. Intriguingly, this finding suggests a role for Asp-52 that does not dictate carboxylate catalysis in flexible model systems at all. Comparing acid **3b** with reference compound **3c** is directly analogous to comparing lysozyme to an Asp-52 → Ala-52 mutant enzyme. Such a site-specific mutation would be expected to diminish the catalytic activity because of an inability to solvate the oxonium ion intermediate, a role that Asp-52 accomplishes. Ironically, it is at least possible that Asp-52 serves not so much to accelerate acetal hydrolysis as to prevent it from decelerating after transport from solution

(4) Honma, K.; Nakazima, K.; Uematsu, T.; Heimada, A. *Chem. Pharm. Bull.* **1976**, *24*, 394.
(5) Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1935**, *57*, 2174.
(6) Homonuclear NOE experiments reveal that the methyl ester group of **3a** is near ribose protons H-1′ (2.5%) and H-4′ (3.3%) and not H-2′ and H-3′. X-ray structure determination of a derivative proves the endo stereochemistry.
(7) Bakthavachalam, V.; Lin, L.-G.; Cherian, X. M.; Czarnik, A. W. *Carbohydr. Res.* **1987**, *170*, 124.
(8) Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169.
(9) At pH 5 and 100 °C, glycosidic hydrolysis of 2′,3′-isopropylidene-7-methylguanosine is only 13 times slower than that of 7-methylguanosine (Sweger, R. this lab, unpublished results). Similarly, the hydrolysis of 2′,3′-isopropylidene-NAD$^+$ is only 4.5 times slower than that of NAD$^+$ at 80 °C and below pH 7 (Johnson, R. W.; Marschner, T. M.; Oppenheimer, N. J. *J. Am. Chem. Soc.* **1988**, *110*, 2257).
(10) Unpublished results, this laboratory.
(11) Because the carboxylate group of **3b** is so far from the anomeric center (six bonds), it cannot exert a large polar inductive effect on the glycosidic hydrolysis reaction. In any case, the inductive effect of a carboxylate group would be to *decelerate* the hydrolysis as compared to a hydrogen substituent; we observe the opposite result.
(12) The mechanistic possibilities include the following: charge stabilization of the TS; anchimeric (nucleophilic) assistance; ground-state desolvation of the carboxylate; lone pair exchange repulsion.[14] The pK_a of acid **3b** was determined by UV (followed at 240 nm) to be 3.5 ± 0.5, which is within the range expected for a simple aromatic carboxylic acid. This finding implies that there is no unusual hindrance to hydration of the carboxylate group, and therefore that ground-state desolvation as proposed by Vernon for lysozyme is not a likely mechanism for catalysis in model **3b**.
(13) After 200 h at 100 °C and pH 7, glycosidic hydrolysis of reference compound **3c** has occurred to only about 8%. At pH's 6, 7, and 8, another reaction begins to consume **3c**; the two data points at each of these pH's in Figure 1 represents upper and lower limits for the rate constant at that pH.
(14) Bakthavachalam, V.; Czarnik, A. W. *Tetrahedron Lett.* **1987**, *28*, 2925.
(15) Buffers (50 mM) used: pH 1–2, HCl/KCl; 3–5.5, potassium phthalate; 6–7.5, potassium phosphate; 8.8–10, sodium borate; 11, CAPS/NaOH.

into a desolvated active site. Such a proposition is fully consistent with the "electrostatic stabilization" mechanism, with the caveat that carboxylate does no better a job of stabilizing an oxonium ion than does bulk water.

Acknowledgment. We acknowledge the technical assistance of Robert Hrouda for the preparation of ketal **2a** on a large scale. FT-NMR spectra were obtained by using equipment funded in part by NIH Grant no. 1 S10 RR01458-01A1. One of us (X. M.C.) thanks the Government of India for providing a National Fellowship. We thank Merck and Company for making a postdoctoral fellowship available that greatly facilitated this research. The financial support of the American Cancer Society is acknowledged with gratitude.

The Degenerate 21-Homododecahedryl Cation

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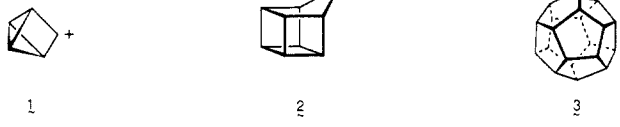
Those rearrangement processes that leave the starting material and product identical except for constitutional realignment of individual atoms and bonds have held the fascination of chemists for years. Such transformations have been observed in neutral molecules[2] and carbocations,[3] the most notable and interesting examples exhibiting *multiple degeneracy*. In the cation area, those $(CH)_n^+$ ions derived from monohomologated polyhedra have given evidence of spectacular levels of degenerate isomerization. The homotetrahedryl species **1**[4] is,in principle, capable of 5!/2 or 60

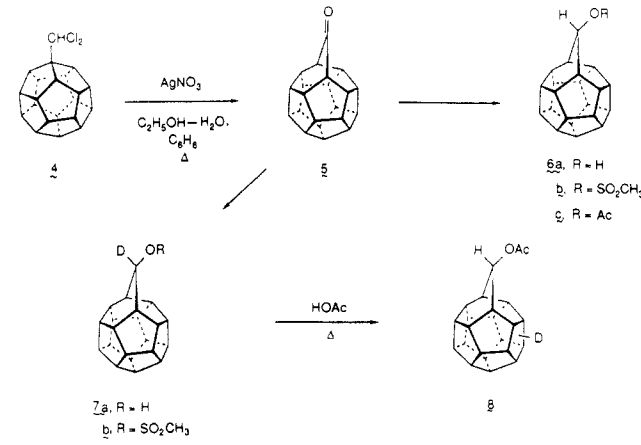


1 2 3

possible arrangements if each C–H could somehow be uniquely tagged. The multiplicity of realizable structures understandably increases with molecular size as reflected in the 9-homocubyl cation (**2**).[5] The progression from $(CH)_5^+$ to $(CH)_9^+$ carries with it the enormous potential of making 9!/2 or 181 440 degenerate isomers of **2** available.

A still more remarkable entity is the 21-homododecahedryl cation (**3**). In common with its smaller congeners, **3** possesses the latent capacity for exchanging the position of all its carbon–hydrogen units uniquely by means of simple Wagner–Meerwein 1,2-carbon shifts. Should full equivalency materialize in this instance, the number of possible different arrangements is truly vast: 21!/2 or 2.56×10^{19}. We report here, in the context of ongoing research in the dodecahedrane area,[6] a synthetic approach

Scheme I



to **3**, which when generated solvolytically is shown indeed to possess degenerate characteristics.

Earlier, the readiness with which dodecahedrane reacts with dichlorocarbene, generated under phase-transfer conditions, to give **4** was described.[7] Heating of **4** with silver nitrate in a solvent system composed of 25% aqueous ethanol and benzene (4:1) resulted in efficient (93%) ring expansion to give **5** (Scheme I). Clear colorless crystals of **5**, mp > 280 °C, were subjected to X-ray analysis.[8] The C_{2v} point group symmetry adopted by **5**, a direct consequence of crystallographically imposed *mm* symmetry, generates two mirror planes and causes this ketone to be structurally similar to secododecahedranes,[9,10] although with less distortion of the spherical framework. For example, the two envelope-shaped five-membered rings bonded to the carbonyl group adopt a flap angle of 23.9°, significantly less than those seen in monoseco derivatives (35–37°). The six-membered rings that incorporate the ketonic center adopt an approximate half-chair conformation with the C–CO–C angle being 112.6°, entirely similar to that in 2-adamantanone.[11] On the other hand, the ^{13}C shift of the carbonyl carbon in **5** (228.2 ppm) appears considerably downfield of that in 2-adamantanone (216.9 ppm), and the weighted split carbonyl absorption for **5** is located at 1690 cm^{-1} and not at 1727 cm^{-1}.[12] Since MNDO and AM1 calculations on the 2-adamantanyl and homododecahedryl cations provide no indication of any differences that would explain these spectroscopic anomalies,[13] chemical shielding tensor changes and Fermi resonance effects brought on by orbital interaction and vibrational mixing with other sectors of the molecule are thought to be operational in **5**.

Mesylate **6b** was prepared conventionally ($NaBH_4$, CH_3OH; CH_3SO_2Cl, py). Preparative acetolysis of **6b** in hot, unbuffered

(1) The Ohio State University Postdoctoral Fellow, 1986–1988.

(2) (a) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715. (b) Schröder, G.; Oth, J. F. M.; Merenyi, R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 752. (c) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981.

(3) Leone, R. E.; Barborak, J. C.; Schleyer, P. von R. In *Carbonium Ions, Volume IV*; Olah, G. A., Schleyer, P. von R., Eds.; Wiley-Interscience: New York, 1973; Chapter 33.

(4) (a) Masamune, S.; Fukumoto, K.; Yasunari, Y.; Darwish, D. *Tetrahedron Lett.* **1966**, 193. (b) Stohrer, W.-D.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 1661. (c) Masamune, S.; Sakai, M.; Ona, H.; Jones, A. J. *Ibid.* **1972**, *94*, 8956. (d) Masamune, S. *Pure Appl. Chem.* **1975**, *44*, 861.

(5) Schleyer, P. von R.; Harper, J. J.; Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Am. Chem. Soc.* **1967**, *89*, 698.

(6) (a) Paquette, L. A. In *Strategies and Tactics of Organic Synthesis*; Lindbergh, T., Ed.; Academic Press: 1984; pp 175–200. (b) Paquette, L. A.; Miyahara, Y.; Doecke, C. W. *J. Am. Chem. Soc.* **1986**, *108*, 1716. (c) Santos, I.; Balogh, D. W.; Doecke, C. W.; Marshall, A. G.; Paquette, L. A. *Ibid.* **1986**, *108*, 8183. (d) Paquette, L. A.; Miyahara, Y. *J. Org. Chem.* **1987**, *52*, 1265. (e) Paquette, L. A.; Weber, J. C.; Kobayashi, T. *J. Chem. Soc.* **1988**, *110*, 1303. (f) Olah, G. A.; Prakash, G. K. S.; Kobayashi, T.; Paquette, L. A. *Ibid.* **1988**, *110*, 1304.

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(8) Gallucci, J. C., unpublished results.

(9) Christoph, G. G.; Engel, P.; Usha, R.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 784.

(10) Allinger, N. L.; Geise, H. J.; Pyckhout, W.; Paquette, L. A.; Gallucci, J. C. *J. Am. Chem. Soc.*, in press.

(11) Calculated by means of the equation

$$\nu(cm^{-1}) = 1278 + 68k - 2.2\phi$$

where ϕ is the C–CO–C angle in deg and $k = 10.244$ to accomodate satisfactorily the fit for acetone. Consult: Halford, J. O. *J. Chem. Phys.* **1956**, *24*, 830.

(12) (a) Foote, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 1853. (b) Schleyer, P. von R. *Ibid.* **1964**, *86*, 1854.

(13) Schleyer, P. von R.; Bremer, M., private communication.

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