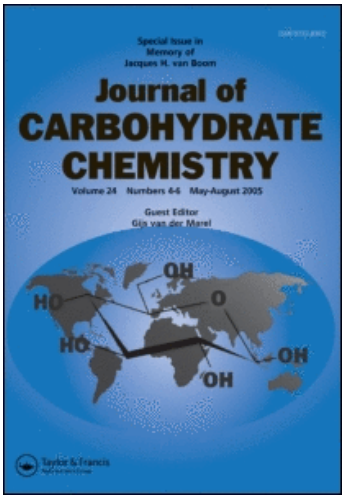

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REARRANGEMENT OF 3-ACYL DERIVATIVES OF L-ASCORBIC ACID

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ABSTRACT

Evidence of rearrangement of 3-acyl derivatives of ascorbic acid to 2-acyl derivatives has been found for carbon and phosphorus acyl groups. The observations are consistent with intramolecular rearrangement through a cyclic intermediate in which the acyl group is bonded to both the 2- and 3-oxygen atoms of ascorbic acid. A rate of rearrangement has been measured for the 3-diphenylphosphinate ester. Calculated results indicate an increase in negative atomic charge at O-2 in the 3-acyl esters but a decrease in the charge of O-3 in the 2-acyl esters.

INTRODUCTION

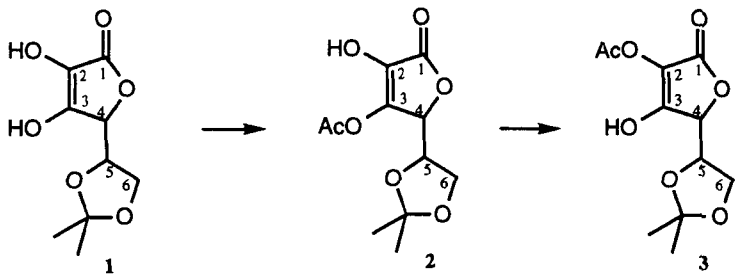
Ascorbic acid has four hydroxyl groups which can be acylated. By working with **1**, the 5,6-isopropylidene derivative of ascorbic acid, IAA,[1,2] the situation is simplified in that only the 2- and 3-hydroxyls remain unblocked. Since the acidity of ascorbic acid, pK_a of about 4, is due to ionization of the 3-hydroxyl, many investigators have expected that acylation would occur preferentially at that position. Acylation of IAA has yielded both 2- and 3-ascorbyl esters. In some cases, there have been problems with identification of isomers because the method of synthesis has led investigators to conclude that the product is the 3-ester. For example, the sulfate, which is a derivative found naturally,[2] was shown to be identical to the synthesized sample. The method of synthesis favored a 3-derivative

and for some years this compound was thought to be a 3-sulfate. Subsequent studies demonstrated that the synthesized ascorbate sulfate was an O-2 derivative.[3,4] The phosphate derivative has a similar history.[5] It is therefore of considerable interest to understand how the 2-acylated ascorbates are formed.

An initial report of the synthesis of the 3-acetyl derivative of 5,6-isopropylidene-L-ascorbic acid[5] was later shown by Paulssen, et al.,[6] to be another case of mistaken identity. They found evidence for acetylation at the O-3 position with acetic anhydride in water, but the initially formed 3-ester **2** hydrolyzed and underwent rearrangement to the 2-ester **3** as shown in the scheme below. The latter reaction was predominant over pH range 4-7. This suggests that rearrangement of 3-esters could account for the formation of 2-esters in organic solvent.

RESULTS AND DISCUSSION

We have reported methods for unambiguous spectroscopic identification of the point of acylation and have suggested why certain methods give 3-esters and others give 2-esters.[7] In organic aprotic solvent, methods which involve acylation of the anion appear to give 3-esters, while methods that involve acylation of the neutral ascorbate give 2-esters. This contrasts with results in basic aqueous solution where 2-O derivatives are found while the 3-O is relatively unreactive due to delocalization into the enonolactone ring. [1]



1 2 3

Although pK_as and ultraviolet spectroscopy over a range of pHs in aqueous solution give unambiguous structural assignments,[1] infrared spectroscopy or NMR of the isopropylidene moiety provides a quick and quantitative way to identify products and estimate product mixtures of 2- and 3-esters (Table 1).[7,8] These methods have enabled us to carry out experiments which give quantitative data on 2- and 3-esters in a mixture and which provide clear evidence for the rearrangement in acylated ascorbates.

The synthesis of the 3-*O*-diphenylphosphinate ester of IAA is effected readily from the acyl chloride and the monoanion of **1** generated by addition of one equivalent of triethylamine to IAA as shown in the first entry of Table 1.

Table 1. Products[a] of the reaction of 5,6-*O*-isopropylidene-L-ascorbic acid (IAA) and phosphinyl and acetyl chlorides.

In flask[b]	Added[b]	Solvent	t(min)	Temp(°C)	% 3-ester[a]	%2-ester[a]
IAA-TEA	DPC	acetone	2	25	91	5
DPC	IAA-TEA	THF	7	2	67	0
DPC	IAA-TEA	THF	15	2	55	15
DPC	IAA-TEA	THF	45	2	1	45
DPC-TEA	IAA	THF	60	2	3	45
IAA-Lutidine	DPC	acetone	20	0	-	55
IAA-TEA[c]	DPC	acetone	120	-78	-	99[c]
IAA-TEA	AC	acetone	2	25	61	-
IAA-TEA	AC	acetone	3	25	21	75[d]
IAA-TEA	AC	DMA	5	25	12	60[e]
IAA-Pyridine	AC	acetone	720	25	17	56[f]

a. Product identification based on proton NMR data for the isopropylidene methyls and IR data of lactone C1=O1 and C2=C3 data given in the experimental section. b. The first two columns give the materials in the flask with the solvent and the materials added to this mixture. TEA = triethylamine, DPC = diphenylphosphinyl chloride, THF = tetrahydrofuran, AC = acetyl chloride, DMA = dimethyl acetamide, Lutidine = 2,6-dimethyllutidine. c. Six molar equivalents of methanol were added to the reaction. d. Wet solvent, 1.1 % water. e. 28% diester. f. 37% diester.

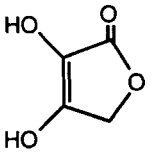
The various conditions presented here show those that lead to the 3-ester and those that give contamination with the 2-ester. While the 2-ester product may be minimized, reactions with acyl chlorides also lead to formation of 2,3-*O*-diesters. A diester could not be prepared deliberately from diphenylphosphinyl chloride and this suggests that steric requirements of the acyl group may also be an important factor towards reactivity. The absence of proton donors, such as water or methanol, is critical to the reaction outcome. If proton donors are present, 2-esters are formed under the same conditions used to generate the 3-esters. The data also indicate that prolongation of the reaction time, use of neutral IAA, protic impurities or the less basic pyridine lead to reduced formation of the 3-esters and an increase of the 2-esters. One effect of these conditions is to reduce the available monoanion of IAA. Altogether this confirms that the ionic or neutral state the O-3 and O-2 atoms in IAA and derivatives are relevant to reactivity and acylations.

In pursuing this point, theoretical calculations on 3,4-dihydroxy-5*H*-furan-2-one, **4a**, and some derivatives were undertaken to define the physical properties of the reactive

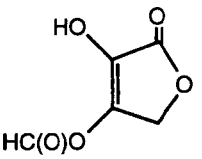
Table 2. Calculated net atomic charges for selected atoms in derivatives of **4**.

compound	O-1	O-2	O-3	C-1	C-2	C-3
4a	-0.2770	-0.1997	-0.1918	+0.3193	-0.0795	-0.0207
4b	-0.4262	-0.2194	-0.4426	+0.3562	-0.4309	+0.2525
4c	-0.2748	-0.2382	-0.1950	+0.3265	-0.1249	+0.0113
4d	-0.2798	-0.1733	-0.1830	+0.3281	-0.1030	+0.0240
4e	-0.2430	-0.1892	-0.2036	+0.3862	-0.1511	-0.0485

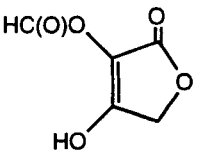
oxygen atoms. These structures resemble ascorbic acid but lack the side chain that occurs at carbon 4 of the lactone ring. Compound **4b** is the O-3 monoanion of **4a**.



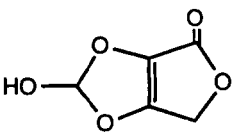
4a



4c



4d



4e

Results from semiempirical calculations using AMPAC provide useful information. This theoretical procedure was chosen because it is efficient and the AM1 basis set has been modified to reduce the tendency towards overestimation of core repulsion energies commonly found for compounds with heteroatoms.[9] As pointed out in Table 2, calculation results on 3,4-dihydroxy-5*H*-furan-2-one, **4a**, show that in the neutral species the O-2 atom has a slightly higher electron density (-0.1997) than the O-3 atom (-0.1918). These results are consistent with previous postulates that the O-2 is the more nucleophilic of the two atoms in the neutral species.[1] Further, the monoanionic species, **4b**, has the charge delocalized in the ene-diol system. Despite this the O-3 atom bears the greater charge (-0.4426) and is experimentally the nucleophilic oxygen of the anion.[7] Acylation at O-3 or O-2, **4c** and **4d**, has only a minor effect on charges at C-1, C-2, C-3 relative to **4a**.

We observed instability of the 3-esters as pure products or as product mixtures. A sample of reaction products of the acetyl esters showed 45% 3-esters, 26% diester, 26% IAA, and about 3% 2-ester upon reaction work-up. A reexamination of this mixture after standing for about 3 days in chloroform showed a distribution of 16% 3-ester, 20 % IAA and 64% 2-ester.[8] This isomerization was also observed for the 3-*O*-benzoyl ester in the

presence of 17% mole equivalent of triethylamine hydrochloride, a potential proton donor, where the ratio of 2- to 3-esters increased from 1.24 to 1.65 in five days. These findings clearly show the susceptibility of the 3-esters to rearrangement because of protic impurities and prolonged reaction time. A further example of the instability was demonstrated by the 3-*O*-(2',2',3',4',4'-pentamethyltrimethylene)phosphinate ester. As a solid, this purified phosphinate ester completely isomerizes to the 2-ester. In chloroform the 3-ester (IR bands at 1781 cm^{-1} (C1=O1), 1700 cm^{-1} (C2=C3)) is first converted to an intermediate which then becomes the 2-ester (IR bands at 1777 and 1773 cm^{-1} (C1=O1), 1679 and 1688 cm^{-1} (C-2=C3)) within 48 h, suggesting a half-life of less than 10 h. These observations led us to conclude that the initially formed 3-esters readily rearrange to the 2-esters. These findings in organic solvents are characteristic of the isomerizations in aqueous buffers at pH 2-7,[6] where the 3-*O*-acetylascorbic acid undergoes intramolecular rearrangement to 2-*O*-acetylascorbic preferentially over hydrolysis, with $k_{obs(isomer)}/k_{obs(hydrol)}$ ratio of about 7 at pH 6 where all species are monoanions.

In a test of this idea and the effect of protic impurities on the stability of the esters, the rearrangement of the 3-*O*-diphenylphosphinate ester was studied. For a sample 0.012M in chloroform with six molar equivalents of methanol, isomerization to the 2-ester was determined to have a half-life of 33 h at 25 °C ($k_{obs}=5.8\times10^{-6}$ s^{-1}). It is well known that neighboring hydroxyl groups are active as nucleophiles in monophosphate isomerizations.[10] Unimolecular isomerizations have been observed in ribonucleoside-2'-phosphate,[11] glycerol-1-phosphate and glycerol-2-phosphate[12] and in other β-hydroxy phosphate esters.[11-13]

Another factor possibly influencing the isomerization in acyl esters of ascorbic acid is that the O-2 and O-3 atoms are restricted to an eclipsed conformation due to the planar lactone ring.[16] This restricted structure should enhance the intramolecular rearrangement by nucleophilic participation of the vicinal hydroxyl group[17] group in the isomerization of the esters. With phosphinate esters, evidence suggests the rearrangement would proceed through an associative mechanism leading to a pentacoordinate intermediate.[14] Our finding of a smaller half-life for the 3-*O*-(2',2',3',4',4'-pentamethyltrimethylene)-phosphinate ester than for 3-*O*-diphenylphosphinate ester is consistent with the involvement of a pentacoordinate phosphorus intermediate. It has been shown that the ring strain in the former ester facilitates the formation of such an intermediate,[15] where the ring strain is reduced when the ring occupies apical-basal sites in the trigonal bipyramidal intermediate. The breakdown of the cyclic pentacoordinate intermediates is generally under kinetic control.[13] The lack of evidence for the formation of 2,3-diesters from the 3-*O*-diphenylphosphinate esters of IAA suggests an intermolecular isomerization is not likely. A lack of intermolecular rearrangement is also displayed by the less sterically hindered acyl

Table 3. Selective calculated π–bond orders in derivatives of **4**. The respective bond length in Å is given underneath in parenthesis.

Compound	C1=O	C1- C2	C3=C2	C3-O3	C2-O3	ΔH_f (Kcal)
4a	0.8749 (1.222)	0.0728 (1.483)	0.7632 (1.364)	0.1246 (1.357)	0.1026 (1.361)	-136.5386
4b	0.7215 (1.238)	0.2289 (1.430)	0.3155 (1.418)	0.6970 (1.247)	0.0763 (1.369)	-185.9783
4c	0.8755 (1.222)	0.0700 (1.484)	0.7753 (1.362)	0.1283 (1.358)	0.0916 (1.364)	-165.3262
4d	0.8722 (1.223)	0.0762 (1.481)	0.7583 (1.366)	0.1466 (1.352)	0.0943 (1.368)	-161.4721
4e	0.9080 (1.218)	0.0805 (1.459)	0.7617 (1.377)	0.1294 (1.371)	0.0872 (1.383)	-150.9839

esters. Here, rearrangement of the 3-acetyl esters to the 2-ester showed no increase in the amount of 2,3-diester.

The isomerizations observed in this study all show the 3-esters rearranging to the 2-esters. No evidence for the reverse process was detected for either the carbonyl or phosphinate esters. The uniqueness in this finding is in marked contrast to the phosphate rearrangement of ribonucleosides-2'- and 3'-phosphates and glycerol-1- and 2-phosphates, where a respective equilibrated ratio of 6.7 to 1 was found for the glycerolphosphates.[12b,c] In view of this evidence of isomerizations on these different systems, we again turned to molecular mechanics[9] for further analysis of **4a-4e.** While calculations do not assimilate experimental conditions, they provide a theoretical description of the effects of substitution on the structure. Tables 2 and 3 give the atomic charges, bond order, and bond lengths.

The calculated bond lengths in Table 3 for the neutral and monoanionic forms of the model compound **4a** and **4b** agree well with crystallographic data for ascorbic acid, its monoanion and 2-*O*- and 3-*O*-esters, in Table 4. The calculated π-bond orders of **4a** and **4b** also indicate clearly that upon ionization the bond order increases at C3-O3 and C2-C1 while it decreases at C3=C2 and C1-O1. This is expected as a result of delocalization of the charge at O-3 in the unsaturated lactone system. As evident from crystallographic data, Table 4, delocalization of a charge at O-3 causes C1-C2 to shorten and C2=C3 to lengthen.

In contrast, crystallographic data indicates that esterification at O-3 causes shortening of the C2=C3 bond while lengthening the C1-C2 bond. Calculations also show that acylation at O-3, **4c**, causes a slight increase in the π-bond order of C3=C2 (+0.0121)

Table 4. Selected bond lengths of ascorbic acid and ascorbates.

Compound	r(C1=O1) (Å)	r(C1-C2) (Å)	r(C2=C3) (Å)	Ref.
ascorbic acid	1.216 (std.)	1.452 (std.)	1.338 (std.)	16
monoanion	1.233 (+.017)	1.416 (-.036)	1.373 (+.035)	17
3-$R_2P(O)$-	1. 186 (-.030)	1.472 (+.020)	1.313 (-.025)	18
2-$(C_6H_5)_2P(O)$-	1.176 (-.040)	1.480 (+.028)	1.331 (-.007)	19

a. Values are in angstroms; Δ values are relative to ascorbic acid. b. R is morpholino.

relative to **4a**. This is consistent with reduced delocalization of the lone pairs of O-3 with the ascorbate conjugated system due to the interaction of the O-3 with the acyl group. The 2-ester, **4d**, has approximately the same C2=C3 bond length as ascorbic acid. Calculations show a decrease in π-bond order (-0.0049) relative to **4a.**

Calculations results also indicate that the acyl moiety at O-3 in **4c**, the 3-*O*-formyl ester, enhances the electron density at the O-2. This finding is apparent from data in Table 2, by a comparison of **4c** to the neutral and unsubstituted **4a**. As indicated by atomic charges, upon acylation at O-3, the O-2 atom undergoes a 19% increase in electron density (-0.2382) relative to the same site in the neutral **4a** (-0.1997). This acylation only causes a slight increase in electron density at O-3 (1.7%) and a decrease at O-1 (less than -1 %). In contrast, a comparison of **4d**, 2-*O*-formyl ester, to **4a** reveals the reverse trend. The presence of an acyl group at O-2 causes a marked decrease in atomic charge at O-2 (-13.2%), the very site of acylation. Charges at both O-3 and O-1 remain nearly unchanged. In **4e**, where the formyl group spans the O-2,O-3 atoms to form a cyclic bridge between the oxygens, the atomic charge at O-2 decreases (-5.3%) while that of O-3 increases (6.2%). The preference of 2- to 3-esters can thus be understood on the basis of increased atomic charge at O-2 in 3-esters, a decrease in charge at O-3 in 2-esters, and the conjugated system of the of the O-3 atom with the lactone ring.

EXPERIMENTAL

Preparation Of Compounds. Analytical reagent grade solvents and amines are available commercially. These were all dried and distilled under nitrogen prior to use. The phosphinyl chlorides were prepared according to procedures in literature. The various methods of acylation of IAA are entered in Table 1 of the results. Variations in these entries reflect the way the reactants (IAA, an amine base, and acyl chloride, protic donor) were combined. In a typical reaction, 0.562 g (2.60 mmol) of IAA[1] and the appropriate

equivalents of the other reactants were combined in 20 mL of solvent. The reactions were conducted under dry N_2 atmosphere and cold reaction temperatures were generated with an external cold bath. The work-up of the reaction mixture included filtering the amine hydrochloride salt on a glass Buchner funnel with frit under vacuum and then concentrating the filtrate to a powder or oil on a roto-vap at room temperature. This facile work-up provided compounds of sufficient purity for product distribution analysis with Varian XL-200 NMR and Perkin-Elmer 1500 FT-IR spectrometers. Quantitative yield and product distribution of 2-acyl and 3-acyl esters[7] is easily established by ^1H NMR of the isopropylidene methyls in $CDCl_3$. NMR data (PPM): IAA: 1.412, 1.372; 2-$P(O)(C_6H_5)_2$ ester: 1.261, 1.213; 3-$P(O)(C_6H_5)_2$ ester: 1.302, 1.255; 2-$C(O)CH_3$ ester: 1.406, 1.378; 3-$C(O)CH_3$ ester: 1.386, 1.366; 2-$C(O)C_6H_5$ ester: 1.382, 1.356; 3-$C(O)C_6H_5$ ester 1.391, 1.363; 2-$P(O)C_3(CH_3)_5$ ester: 1.380, 1.273; 2,3-$(C(O)CH_3)_2$ diester: 1.394, 1.359; 2,3-$(C(O)C_6H_5)_2$ diester: 1.426, 1.374. IR data in $CDCl_3$ or $CHCl_3$ for lactone *C-1*=O-1 and C-2=*C3*, respectively, in cm^{-1}: IAA: 1699, 1604; 2-$P(O)(C_6H_5)_2$ ester: 1776, 1682; 3-$P(O)(C_6H_5)_2$ ester: 1784, 1701; 2-$C(O)CH_3$ ester: 1781, 1687; 3-$C(O)CH_3$ ester: 1784, 1708;2-$C(O)C_6H_5$ ester: 1778, 1688; 3-$C(O)C_6H_5$ ester: 1784, 1704; 2-$P(O)C_3(CH_3)_5$ ester: 1777, 1679 and 1688; 3-$P(O)C_3(CH_3)_5$ ester: 1781, 1700; 2,3-$(C(O)CH_3)_2$ diester: 1794, 1711; 2,3-$(C(O)C_6H_5)_2$ diester: 1784, 1708.

Kinetic NMR Study. A sample of 2.99 mg (42.5 μmol) of 3-*O*-diphenylphosphinate ester of IAA was placed in a 5 mm NMR tube. To this was then added 5.9 mol eq (ca 1.7 μL) of methanol and the volume was then brought to 0.6 mL by adding sufficient purified deuterated chloroform. The tube was then sealed and placed in a Haake water bath at 30 °C. The tube was periodically removed and ^1H NMR spectra were collected using a Varian XL-200 spectrometer.

Theoretical Calculations. Theoretical calculations were carried out on compounds **4a-4e** using AMPAC. Version 3.01 of the AM1 Hamiltonian was used. The default SCF was replaced by 0.0000001, PRECISE, and complete optimization of all geometric parameters was observed. In each case the results were fully optimized and the Fletcher-Powell SCF field was achieved.

REFERENCES

1. J. Tolbert, M. Downing, E. Baker, R. Carlson, and M. Knight, *Ann. N. Y. Acad. Sci.*, **258**, 48 (1972); X. Wang, W. Qian, and P. Seib, *J. Carbohydr. Chem.*, **14**, 53 (1995); J. Tolbert and B.Ward, *J. Adv. Chem. Ser.*, **200**, 101 (1982).
2. A. Bond, F. Finamore, B. McCleland, and J. Einstein, *Arch. Biochem. Biophys.*, **153**, 207 (1972).
3. R. Mumora, A. Verlangieri, and W. Weber, *Carbohydr. Res.*, **19**, 127 (1971) .

4. T. Radford, J. Sweeny, and G. Iacobucci, *J. Org. Chem.*, **44**, 658 (1979).
5. C. Vestling and M. Rebstock, *J. Biol. Chem.*, **152**, 585 (1944).
6. R. Paulssen, D. Chatterji, T. Higuchi, and J. Pitman, *J. Pharm Sci.*, **64**, 1300 (1975).
7. J. Cabral and Paul Haake, *J. Org. Chem.*, **53**, 5742 (1988).
8. J. Cabral, Ph.D. Thesis, Wesleyan University, 1987.
9. M. Dewar, E. Zoebisch, E. Healy, and J. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); M. Dewar and D. Storch, *J. Am. Chem. Soc.*, **107**, 3898 (1985). AMPAC calculation using AM1 Hamiltonian and precise geometry optimization.
10. D. Lipkin, P. T. Talbert, and M.Cohn, *J. Am. Chem. Soc.*, **76**, 2871 (1954); T. Bruice and T. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962); B. Hansen, *Acta Chem. Scand.*, **17**, 1375 (1963); L. Larsson and G. Wallerberg, *Acta Chem. Scand.*, **20**, 1247 (1966); for a review, see A. J. Kirby, *Adv. Phys. Org. Chem.*, **17**, 183 (1980).
11. D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 44 (1952); *ibid.*, 52 (1952).
12. a) M. Bailly, *Cmpt. Rend.*, **206**, 1902 (1938); *ibid.*, **208**, 443, 1820 (1939); b) E. Chargaff, *J. Biol. Chem.*, **145**, 455 (1942); c) T. Ukita, N. A. Bates, and H. E. Carter, *J. Biol. Chem.*, **216**, 867 (1955).
13. D. Brown and D. Usher, *J. Chem. Soc.*, 6558 (1965); D. Usher and M. Kates, *Nature (London)*, **228**, 663 (1979); D. Usher, D. Richardson, and D. Oakenfull, *J. Am. Chem. Soc.*, **92**, 4699 (1970); H. Abrash, C. Cheung, and J. Davis, *Biochemistry*, **6**, 1298 (1967); C. Deakyne and L. Allen, *J. Am. Chem. Soc.*, **101**, 3951 (1979); E. Baer and M. Kates, *J. Biol. Chem.*, **175**, 79 (1948); D. Brown and D. Usher, *J. Chem. Soc.*, 6547 (1965); D. Brown, G. Hall, and H. Higson, *J. Chem. Soc.*, 1360 (1958).
14. J. Downs and R. Johnson, *J. Chem. Phys.*, **22**, 143 (1954); E. L. Muetterties and R. Schunn, *Quart. Rev. Chem. Soc.*, **20**, 245 (1966); F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); R. Cook, P. Turley, C. Diebert, A. Fierman, and P. Haake, *J. Am. Chem. Soc.*, **94**, 9260 (1970).
15. P. Haake, R. D. Cook, W. Schwarz, and D. R. McCoy, *Tetrahedron Lett.*, 5251 (1968); P. Haake, R. D. Cook, T. Koizumi, P. S. Ossip, W. Schwartz, and D. A. Tyssee, *J. Am. Chem. Soc.*, **92**, 3828 (1970).
16. J. Hvoslef, *Acta Crystallogr., Sect. B*, **24**, 23 (1968); J. Hvoslef, *Adv. Chem. Ser.*, **200**, 37 (1982).
17. W. P. Jencks, *Brookhaven Symp. Biol.*, **15**, 143 (1962).
18. J. Jernow, J. Blount, E. Oliveto, A. Perrota, P. Rosen, and M. Toome, *Tetrahedron*, **35**, 1483 (1979).
19. K. Kessler, B.A. Thesis, Wesleyan University, 1982.