Stereomutation of Methoxycarbenium Ions. 2. Experimental Evidence for an Inversion Process

Christopher Blackburn,[1a] Ronald F. Childs,*[1a] Dieter Cremer,*[1b] and Jürgen Gauss[1b]

Contribution from the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1, and the Lehrstuhl für Theoretische Chemie, Universität Köln, D-5000 Köln 41, Federal Republic of Germany. *Received August 31, 1984*

Abstract: The stereomutation about the C–O partial double bond of a series of 1-methoxy- (**2**/**3**) and 1-hydroxy-3-arylallyl cations (**5**) has been examined experimentally in strong acid solutions and theoretically by using HF/STO-3G calculations. The interconversions of cations **2**/**3** were shown to be intramolecular processes in FSO_3H, CF_3SO_3H, and FSO_3H/SbF_5. The rate constants of the stereomutation of these cations, which were measured by using dynamic NMR methods, were found to depend on the substituents on the aryl ring. Apart from the case where the aryl ring bears two *m*-CF_3 groups, **2g**/**3g**, the rate constants for stereomutation are linearly related to σ^+ ($\rho = -2.37$) with π donors accelerating the reaction. The calculations performed for **5** show that the lowest energy pathway for isomerization involves rotation rather than inversion. They also reveal that π-donor substituents on the aryl ring lower the barrier to rotation while raising the barrier to inversion. In both cases, the calculated barriers for substituted systems show a linear correlation with σ^+. It is concluded that the preferred pathway for stereomutation of most of these 1-hydroxy and 1-methoxyallyl cations in both strong acid solution and the gas phase involves rotation. When the aryl ring bears very strongly electron-withdrawing groups, e.g., two CF_3 groups in **2g**/**3g**, the inversion pathway would seem to be preferred. This is the first example of a methoxycarbenium ion which undergoes stereomutation by inversion rather than rotation.

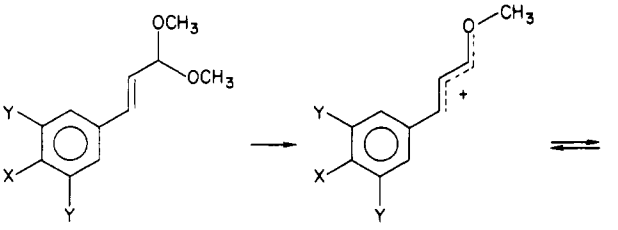
Hydroxy- and alkoxy-substituted carbenium ions are an important class of carbocations that occur widely as reaction intermediates and can be readily prepared as stable ions in nonnucleophilic media.[2] In the previous paper in this issue, we have examined the mechanisms for stereomutation about the carbon–oxygen partial double bonds of these ions and shown on the basis of calculations that a rotational process should be the principal isomerization pathway in solution.[3]

In this paper we present the results of a detailed experimental examination of the isomerization of some 3-aryl-1-methoxyallyl cations. These systems were selected as they are particularly amenable to a systematic study. The results have been coupled with further ab initio calculations and together they confirm that the mechanism of stereomutation of these ions depends on the electronic nature of the 3-aryl substituent.

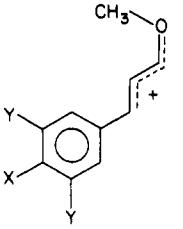
Results and Discussion

Preparation and Characterization of Cations. In order to probe systematically the effect of substituents on the barrier to stereomutation of methoxycarbenium ions, a series of 3-aryl-1-methoxyallyl cations was prepared with different substituents in the aryl rings. These cations were generated by dissolving the dimethylacetals of the corresponding cinnamaldehydes in FSO_3H or related super acids. In each case, the low-temperature ^1H NMR spectrum of the ion showed one major species to be present in addition to protonated methanol. The chemical shifts and coupling constants of the various proton resonances, Table I, were very similar to the related iminium salts[4] and completely in accord with the assigned structures **2a–g**. The *E* configuration about the CO bond is assumed on the basis that this conformation should be preferred sterically.[5]

In addition to the resonances of the major isomer, a further series of resonances of much lower intensity was detected in each case. The clearest evidence for the presence of a second species was in the O–Me region of the NMR spectrum where a further methyl resonance of some 10–15% of the intensity of the major isomer was detected. Careful examination of the rest of the spectra at 250 or 400 MHz revealed vinyl and aryl resonances which were



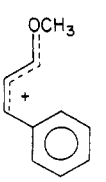
1 **2**



3

a, X=OCH_3, Y=H; **b**, X=CH_3, Y=H; **c**, X=Y=H; **d**, X=Cl, Y=H; **e**, X=CF_3, Y=H; **f**, X=NO_2, Y=H; **g**, X=H, Y=CF_3

associated with the minor methyl resonance. The positions of these resonances were very similar to those of **2**, indicating that in each case, the signals were due to a geometric isomer. The coupling constants across the C_2,C_3 position indicated that the *E* configuration was retained in these minor ions, and this was confirmed by the independent generation of the $C_2,C_3(Z)$ isomers, e.g., **4**, photochemically at low temperature.[6] It was concluded on the



4

basis of this ^1H NMR evidence and also exchange reactions to be described later that the minor isomers were the CO(*Z*) isomers **3a–g**. In the case of cation **2f**, irradiation at low temperature

(1) (a) McMaster University. (b) Universität Köln.
(2) Olah, G. A.; White, A. M.; O'Brien, D. H. *Carbonium Ions. 1968—1976* **1973**, *4* 1697–1781.
(3) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.*, preceding paper in this issue.
(4) Childs, R. F.; Dickie, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 5041–5046.
(5) If the assignment of the C,O(*E*) configuration to **2** is incorrect, it would not affect the mechanistic conclusion reached in this paper.
(6) Blackburn, C.; Childs, R. F. *J. Chem. Soc., Chem. Commun.* **1984**, 812–813. Childs, R. F.; Lund, E. F.; Marshall, A. G.; Morrisey, W. J.; Rogerson, C. V. *J. Am. Chem. Soc.* **1975**, *98*, 5924–5931.

0002-7863/85/1507-2442$01.50/0

Table I. ^{1}H NMR Data for 3-Aryl-1-methoxyallyl Cations

cation	temp, °C	chemical shift,[a] ppm						coupling constant, Hz	
		H_1	H_2	H_3	aryl H	OCH_3	CH_3	$J_{1,2}$	$J_{2,3}$
2a	−50	8.76	7.37	8.62	8.62 (d) 8.11 (d)	4.69	4.21	9.7	14.8
3a						4.52			
2b	−60	8.80	7.41	8.66	7.72 (d) 7.51 (d)	4.70	2.55	9.9	15.0
3b						4.56			
2c	−40	8.92	7.50	8.74	8.03 (d) 7.90 (t) 7.67 (s)	4.77		9.8	15.2
3c	−40	8.97	7.60	8.88		4.65		10.7	14.5
4c	−56	9.03	7.02	8.94	7.75 (m)	4.82		10.2	11.0
2d	−50	8.93	7.46	8.68	7.68 (d)	4.79		9.8	15.1
3d						4.67			
2e	+20	9.06	7.55	8.74	8.10 (m) 7.88 (d)	4.86		9.5	15.4
3e						4.76			
2f	−50	9.26	7.67	8.79	8.59 (d) 8.26 (d)	4.99		9.1	15.5
3f	−50	9.31	7.91	8.93	8.34 (m)	4.87		9.8	15.7
2g	+20	9.17	7.42	8.76	8.41 (s) 8.31 (s)	4.94		9.3	15.4
3g		9.33				4.85		9.5	

[a] All chemical shifts relative to tetramethylammonium tetrafluoroborate taken as δ 3.10. Solvent, FSO_3H; s, singlet; d, doublet; m, multiplet; t, triplet.

caused isomerization to occur predominantly about the C_1–O partial double bond, thus enriching the mixture with the less stable *Z* isomer, **3f**.

The two C,O isomers of these ions were in equilibrium under the conditions used in this study. The equilibrium constants are given in Table II. As can be seen, apart from the methoxy-substituted systems **2a**/**3a**, the magnitude of the equilibrium constant increases as electron-withdrawing groups are put on the aryl ring.

Rate Studies. The ^{1}H NMR spectra obtained for each of the sets of ions exhibited a reversible temperature dependence. In each case, at high temperatures, only a single set of resonances was present which corresponded in chemical shift to the weighted average of the shifts of the *E* and *Z* isomers. The rate constants for the stereomutations were obtained by comparison of calculated and observed spectra for the OCH_3 signals during coalescence, making due allowance for the temperature dependence of the equilibrium constants over the temperature range studied. The rate constants and free energies of activation for the stereomutations are given in Table II.

The small equilibrium concentration of the *Z* isomer in the case of the nitro-substituted system introduced somewhat larger errors in fitting procedures. The barrier to stereomutation was verified by warming a mixture of **2f** and **3f** which had been photochemically enriched in *Z* isomer **3f**. At −36 °C, the initial equilibrium was reestablished, and a rate constant could be obtained for the process by following the change in intensity of the ^{1}H NMR signals of the two ions. The rate constant corresponded to an activation free energy for the conversion of **3f** to **2f** of 17.1 kcal/mol^{-1}, which is in good agreement with the value obtained from the NMR coalescence measurements.

To check for intermolecular effects, the stereomutations of some of the ions were measured in weaker, CF_3SO_3H,[7] and stronger, FSO_3H/SbF_5,[8] acid media. The rate constants obtained for the interconversion in these acids were the same as those measured in FSO_3H, indicating that the reactions are intramolecular.[4,6]

It can be seen from the data in Table II that the barrier for stereomutation of the C-O bond of these cations is dependent upon the aryl substituent. Electron-donating substituents facilitate isomerization, whereas withdrawing groups raise the barrier to stereomutation. Apart from the **2g**/**3g** pair, the log values of the rate constants for the conversion of **3** to **2** correlate well with σ^+, Figure 1 (correlation coefficient 0.998).[9] The slope ($\rho = -2.37$) is negative and moderately large, indicating that in the transition state for the stereomutation, more positive charge resides in the aryl ring.

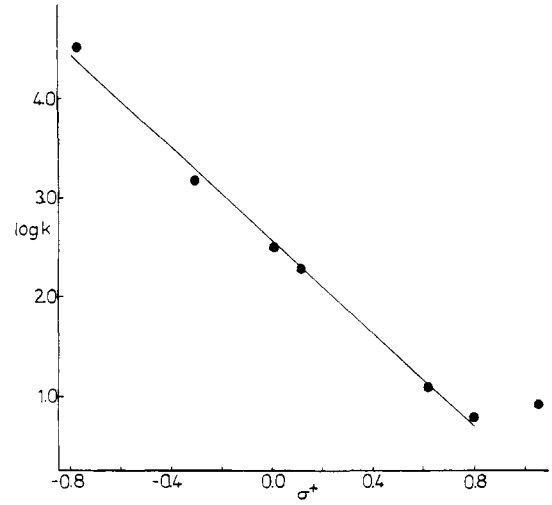


Figure 1. Correlation of log *k* for stereomutation of **2**/**3** vs. σ^+.

The direction and magnitude of the substituent dependence of the barrier to the interconversion of **2** and **3** strongly suggests that this process is occurring by a rotation mechanism. As we showed in the previous paper in this issue,[3] there is a net transfer of positive charge onto the carbon framework during the rotation process, and the barrier to stereomutation by this process should show the substituent dependence noted above.

In the case of **2g**/**3g**, the deviation from the σ^+ correlation is far outside the expected error margins for the reported σ^+ constant[9] or the experimental errors associated with the measurement of the rate constants. At the very least, it must be concluded that the stereomutation of **2g**/**3g** involves a different mechanism than

(7) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Science* (*Washington, D. C.*) **1979**, *206*, 13–20.
(8) Gillespie, R. J.; Peel, T. E. *J. Am. Chem. Soc.* **1973**, *95*, 5173–5178.
(9) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35. Value of σ^+ for $(CF_3)_2$ substituents (**2g**/**3g**) taken as 1.04, cf. Arnett, E. M.; Hofelich, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2889–2895. And: Gassman, P. G.; Fentiman, A. F., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 2549–2551.

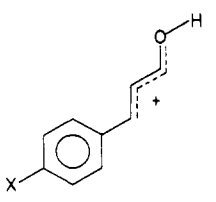
Table II. Equilibrium and Rate Constant Data[a]

cations	aryl substituent	σ^+	equilibrium const K	equilibrium const temp, °C	rate constant[b] $3 \rightarrow 2$, s^{-1}	rate constant[b] temp, °C	$\Delta G^{\ddagger}$, kcal/mol	mean,[d] kcal/mol
2a ⇄ **3a**	OCH_3	−0.78	5.4	−60	15	−48	11.8	
					28	−42	11.9	
					56	−40	11.7	
					88	−38	11.6	
					(3.3×10^4)	40		11.8
2b ⇄ **3b**	CH_3	−0.31	4.9	−60	9	−19	13.7	
					15	−11	13.9	
					45	1	13.9	
					90	5	13.8	
					(1.5×10^3)	40		13.8
2c ⇄ **3c**	H	0.0	6.1	−50	15	5	14.7	
					30	11	14.6	
					60	20	14.8	
					80	26	14.9	
					(3.1×10^2)	40		14.8
2c ⇄ **3c** (FSO_3H/SbF_5)	H	0.0	6.1	−50	12	7	15.1	
					18	14	15.1	
					43	20	14.9	
					98	30	15.0	15.0
2c ⇄ **3c** (CF_3SO_3H)	H	0.0	6.1	−50	18	14	15.1	
					37	17	14.9	
					43	20	15.0	15.0
2d ⇄ **3d**	Cl	0.11	6.2	−40	19	14	15.1	
					31	18	15.1	
					44	22	15.1	
					56	26	15.1	
					(191)	40		15.1
2e ⇄ **3e**	CF_3	0.61	8.6	−21	7	35	16.9	
					14	40	16.7	
					21	45	16.7	
					36	55	16.9	
					(12)	40		16.8
2f ⇄ **3f**	NO_2	0.79	10.5	−50	10	42	17.0	
					20	57	17.4	
					60	67	17.2	
					(6)	40		17.2
					7.3×10^{-4}	−36.5[c]	17.1	
2g ⇄ **3g**	$(CF_3)_2$	1.04	8.8	−50	8	40	17.2	
					12	45	17.1	
					20	50	17.0	
					(8)	40		17.1
2g ⇄ **3g** (SbF_5/FSO_3H)	$(CF_3)_2$	1.04	6.7	0	8	42	17.2	
					16	46	17.0	
					20	50	17.0	
					32	55	17.0	17.1

[a] All reactions in FSO_3H unless otherwise stated. Values in parentheses are extrapolated values. [b] Errors in rate constants are ∓7% for **2a**/**3a** and **2b**/**3b**, ∓10% for **2c**/**3c** and **2d**/**3d**, and + 12% for the remaining cations. [c] Rate constant obtained by observing slow disappearance of peaks due to **3f**. [d] In view of the magnitude of the energy in the rate constants, the mean $\Delta G^{\ddagger}$ quoted is the arithmetic mean of the individual values obtained at different temperatures.

the rotation process suggested for the remaining ions in this series. It is possible that the interconversion of **2g**/**3g** involves an inversion process.

Ab Initio Barriers for 3-Aryl-1-hydroxyallyl Cations. In order to substantiate the conclusions reached from the experimental results, we have carried out ab initio calculations for several 3-aryl-1-hydroxyallyl cations (**5**). These cations can be considered



5

a, X=OCH_3; **b**, X=CH_3; **c**, X=H; **d**, X=F; **e**, X=CF_3; **f**, X=NO_2

as appropriate model systems for the corresponding methoxy cations **2**.

The geometry of the allyl moiety of **5** has been determined as described in the previous paper in this issue[3] while the geometry of the aryl moiety has been taken from the work of Hehre et al.[10]

Table III. HF/STO-3G Stabilization Energies of *p*-XC_6H_4—CH=CHCHOH$^+$[a]

ion	X	min energy form	rotat TS	inversion TS
5a	OCH_3	4.7	5.8	4.1
5b	CH_3	2.3	2.8	2.1
5c	H	0	0	0
5d	F	−0.1	0.1	−0.2
5e	CF_3	−4.2	−4.8	−3.8
5f	NO_2	−10.4	−11.8	−9.7

[a] Stabilization energies in kilocalories/mole are given relative to C_6H_5—CH=CHCHOH$^+$ according to XC_6H_4—CH=CHCHOH$^+$ + C_6H_6 → C_6H_5—CH=CHCHOH$^+$ + XC_6H_5.

The benzene ring has been assumed to be coplanar with the allyl moiety for all cations considered. Due to the size of **5**, Hartree–Fock (HF)/6-31G* calculations, as used in the previous paper in this issue, were not feasible. Therefore, we have constrained calculations to the minimal STO-3G basis set.[11]

(10) Hehre, W. J., Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 1496–1504.
(11) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657–2664.

Table IV. Theoretical Stereomutation Barriers[a]

ion	HF/STO-3G abs energy	HF/STO-3G rotation	HF/STO-3G inversion	HF/6-31G* rotation	HF/6-31G* inversion
CH_2=CHCHOH$^+$ (**6**)	−188.692 74	27.0	33.5	20.1	24.5
p-XC_6H_4—CH=CHCHOH$^+$ (**5**)					
X = OCH_3 (**5a**)	−527.896 76	20.9	36.3	(13.9)	(27.3)
X = CH_3 (**5b**)	−454.062 51	21.5	35.9	(14.5)	(26.9)
X = H (**5c**)	−415.475 11	22.0	35.7	(15.0)	(26.7)
X = F (**5d**)	−512.934 23	21.8	35.8	(14.8)	(26.7)
X = CF_3 (**5e**)	−746.432 98	22.6	35.3	(15.6)	(26.3)
X = NO_2 (**5f**)	−616.151 85	23.4	35.0	(16.4)	(26.0)

[a] All values in kilocalories mole. Projected HF/6-31G* values are given in parentheses.

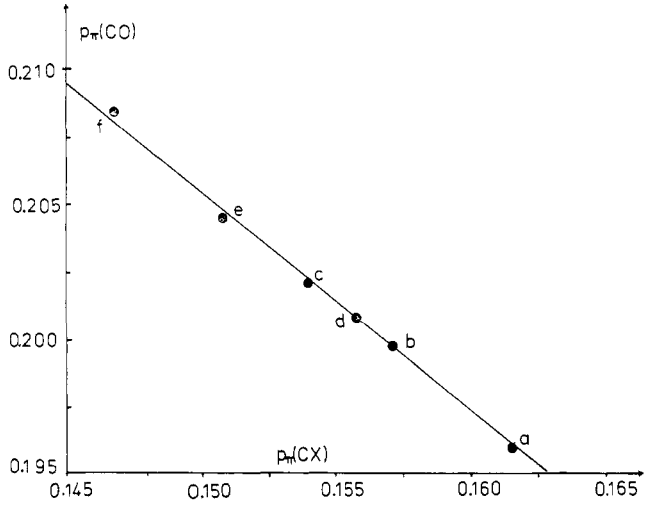


Figure 2. Correlation of calculated overlap populations of pπ(CO) and pπ(CX) of **5**.

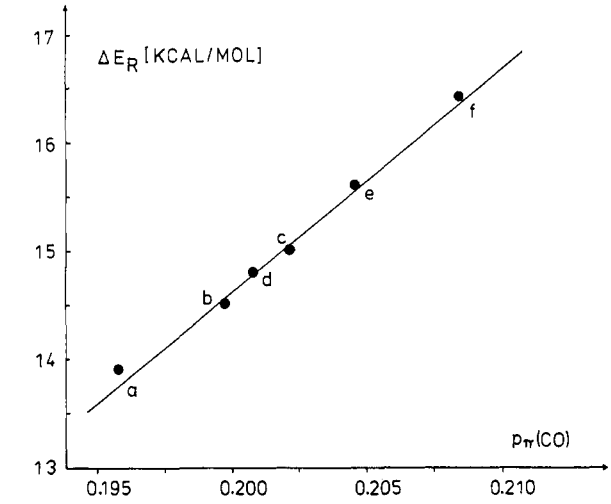


Figure 3. Calculated barriers to rotation ΔE_R plotted against pπ(CO) overlap population.

As pointed out in part 1, HF/STO-3G stabilization energies provide a realistic account of the electronic effect of a substituent attached to a hydroxycarbenium or hydroxyallyl cation.[3] Therefore, we determined the electronic effect of the substituent of the aryl group of **5** from HF/STO-3G energies of the formal reaction 1 in which **5c** has been used as the reference cation. The

$$XC_6H_4—CH=CHCHOH^+ + C_6H_6 \rightarrow C_6H_5—CH=CHCHOH^+ + XC_6H_5 \quad (1)$$

stabilization energies obtained in this way are shown in Table III.

The absolute stabilization energies shown in Table III are the largest for the rotational transition state (TS) and the least for the inversion TS. This means that the rotational TS is more sensitive to π-donor or π-acceptor substituents than the starting minimum energy form (ME) which in turn is more sensitive than the inversion TS. This finding is in accord with the results given in the preceeding paper in this issue.[3]

The HF/STO-3G values for the barriers to stereomutation by rotation and inversion of **5a–f** are given in Table IV. As can be seen by comparing HF/6-31G* and HF/STO-3G values for the stereomutation barriers of the 1-hydroxyallyl cation **6** (first entry in Table IV), the values obtained with the minimal basis set are too large by 7–9 kcal/mol. By assuming similar discrepancies for the HF/STO-3G barriers of compounds **5**, projected HF/6-31G* barriers can be derived (see Table IV). The rotational barrier for **5c** so obtained (15.0 kcal/mol) compares favorably with the stereomutation barrier of **2c**/**3c** (Table II), while the inversion barrier is too large by about 12 kcal/mol. Similar observations can be made when extending the comparison to the other substituted cations (see Tables II and IV). It is quite clear from these results that the rotation mechanism has a substantially lower barrier than inversion. In the gas phase, ions **2**/**3** and **5** would be expected to stereomutate by rotation.

As we have shown for the hydroxyallyl cations,[3] the trend in the ab initio rotation barriers is linked to the calculated values of pπ(CX) and pπ(CO) overlap populations, i.e., the higher the π-donor (acceptor) ability of X, the higher (lower) is the π-bond

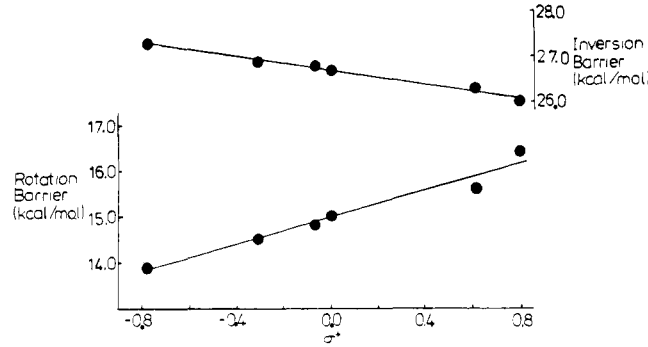


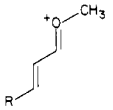
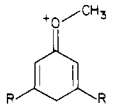
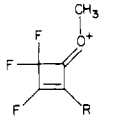
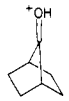
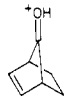
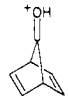
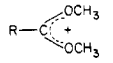
Figure 4. Calculated barriers to stereomutation of **5** by rotation and inversion plotted against σ^+.

character of the XC and CC$^+$ bond. As the π-bond character of the CO bond is decreased (increased), a lower (higher) rotational barrier results. This interplay between the electronic nature of the p-substituent X and the magnitude of the rotational barriers are illustrated by Figures 2 and 3.

A further striking feature of the ab initio results becomes clear when the calculated barriers are plotted against σ^+, Figure 4. A reasonably good correlation is obtained for both the inversion and rotation barriers, but *the slopes of the lines are opposite*. As was shown above, π-donor substituents facilitate rotation at the CO bond of **5**. The reverse is true for the inversion process: π-donor substituents raise the barrier to inversion. The conclusion reached earlier based on the experimental results that the stereomutation of the related OMe cations **2**/**3a–f** in solutions proceeds by rotation is fully substantiated by these calculations.

Crossover from a Rotation to an Inversion Mechanism. The experimentally observed dependence of the magnitudes of the stereomutation barriers on the nature of the ring substituent, measured with the methoxy-substituted systems, is larger than the one suggested by HF/STO-3G calculations for the hydroxy cations. However, this is not surprising since the STO-3G basis

Table V. Experimental Stereomutation Barriers for Some Methoxycarbenium Ions

compound		$\Delta G^{\ddagger}$, kcal/mol	solvent	mechanism[a] gas	mechanism[a] solution	ref
$CH_2OCH_3^+$	7	12.8	SbF_5/SO_2ClF	I	R	12
		14.0	FSO_3H/SbF_5	I	R	3
		9.6	FSO_3H/SbF_5	I	R	3
	8; R = H	19.9	FSO_3H/SbF_5	I	R	13
	9; R = CH_3	18.6	FSO_3H/SbF_5	I	R	13
	2/3c; R = C_6H_5	15.0	FSO_3H/SbF_5	R	R	this work
	2/3g; R = $C_6H_3(CF_3)_2$	17.1	FSO_3H/SbF_5	I	I	this work
	10; R = H	12.7	HF/BF_3	R	R	14
	11; R = CH_3	11.4	HF/BF_3	R	R	14
	12; R = F	16.4	SbF_5/SO_2	R	R	15
	13; R = Cl	15.9	SbF_5/SO_2	R	R	15
	14; R = OCH_3	15.7	SbF_5/SO_2	R	R	15
	15	18.4	FSO_3H	R	R	16
	16	14.7	FSO_3H	R	R	16
	17	11.7	FSO_3H	R	R	16
	18; R = H	>15	CF_3COOH	R	R	17
	19; R = CH_3	15	CF_3COOH	R	R	17

[a] Predicted stereomutation mechanism, I, inversion; R, rotation.

set is known to severely underestimate the extent of charge delocalization and, as a result, the electronic effect of a π-donor (acceptor) substituent on the barriers. For example, the STO-3G $p\pi(CC^+)$ overlap value for **6** changes from 0.129 (ME) to 0.150 (rotational TS) while the 6-31G* overlap populations suggest a change almost twice as large (ME, 0.170; rotational TS, 0.211). The use of standard geometries also cushions electronic effects of the benzene ring substituent.

When compared with the observed barrier dependence on σ^+ ($\Delta G^{\ddagger} = 3.44\sigma^+ + 14.68$; $r = 0.996$), the calculated slopes of the lines for inversion and rotation shown in Figure 4 are too small by a factor of about 2. Taking this into consideration, two adjusted lines are obtained which suggest in principle that as sufficiently strong electron-withdrawing groups are put upon the aryl ring of **5**, there should be a crossover in the preferred pathway for stereomutation from rotation to inversion.

In order to make a more specific assessment as to the type and number of substituents necessary to induce a change in the stereomutation mechanism of the methoxy cations **2/3**, the lines shown in Figure 4 have to be corrected for the changes in the barriers when going from a hydroxy- to a methoxycarbenium ion. According to the ab initio barriers presented in the preceeding paper in this issue, these changes are relatively small in the case of the rotational barriers ($\leq$1 kcal/mol) but range from −5 to −7 kcal/mol for the inversion process. If the inversion barrier of **2c/3c** is set to 19–20 kcal/mol and the rotational barrier kept at 15 kcal/mol, a substituent with a σ^+ constant of 1 should lower the inversion barrier to 17–18 kcal/mol while the rotation barrier is increased to 18 kcal/mol. Since these predictions are based on the experimental stereomutation barriers of Table II, solvent effects are already included in this approach. *For substituents with a $\sigma^+ > 1$, the mechanism for stereomutation of cations* **2/3** *would be expected to change from rotation to inversion in solution.*

The above estimates, while approximate, point out that a switch in mechanism from rotation to inversion is expected as the aryl substituents become increasingly electron withdrawing. As was pointed out earlier, experimentally the $(CF_3)_2$-substituted systems, **2g/3g**, exhibit a large deviation from the σ^+ correlation relating the other ions. The direction of this deviation is such that cations **2g/3g** undergo stereomutation with a significantly lower activation energy than the 18.3 kcal/mol that would have been expected for a rotation process using a σ^+ value of 1.04.[9] It would seem very likely that the electron-withdrawing effect of two CF_3 groups on the aryl ring of these methoxy cations is sufficient to induce a change in the mechanism of stereomutation from rotation to inversion in solution.

Stereomutation Mechanisms of Related Methoxycarbenium Ions. The mechanistic investigations of the stereomutation of hydroxy- and methoxycarbenium ions presented here and in the preceeding paper in this issue[3] provide a basis to reconsider previously published stereomutation barriers. These data are collected in Table V.

In only a few of these cases has the stereomutation mechanism been discussed. For ions **7**,[12] **8**, and **9**,[13] stereomutation by inversion has been suggested, while for ions **10**, **11**,[14] **13**,[15] **18**, and **19**,[17] a rotation mechanism has been considered. On the basis of the results of this and the preceeding paper in this issue, we predict that all the ions of Table V, with the exception of **2g/3g**, stereomutate by rotation rather than inversion in solution. In the gas phase, however, the stereomutation mechanism will probably change to inversion in the case of **7–9** and possibly **15** (see below).

(12) Fărcaşiu, D.; O'Donnell, J.; Wiberg, K.; Matturro, M. *J. Chem. Soc., Chem. Commun.* **1979**, 1124–1125.
(13) Childs, R. F.; Hagar, M. *Can. J. Chem.* **1980**, *58*, 1788–1794.
(14) Brouwer, D. M.; Mackor, E. L.; MacLean, D. *Recl. Trav. Chim. Pays-Bas* **1965**, *85*, 114–116.
(15) Smart, B. E.; Reddy, G. S. *J. Am. Chem. Soc.* **1976**, *98*, 5593–5597.
(16) Lustgarten, R. K.; Brookhart, M.; Winstein, S. *Tetrahedron Lett.* **1971**, 141–144.
(17) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058–3063.

The observed barriers will depend on electronic, steric, and solvation effects. Stabilization by solvation of the rotational TS will play the major role in those cases where charge delocalization is not possible, e.g., **7** or **15**. The available data confirm increased solvation in the rotational TS of **7**.[3] For **15**, however, specific solvation of the positive C atom is sterically hindered by the CH_2–CH_2 units of the norbornane framework and should be less important.

Steric hindrance will directly influence the rotational barriers of ions **10**, **11**, and **15** by destabilizing either the ME (**10**, **11**: repulsion between OCH_3 and α-CH) or the rotational TS (**15**: repulsion between OCH_3 and CH_2CH_2). For example, the rotational barriers of **10** and **11** are significantly lower than would be expected from the combined electronic effects of two vinyl groups at the carbenium ion center.

The considerable decrease of the stereomutation barrier in the series **15**–**17** reveals that the electronic stabilization of the rotational TS via homoaromatic 2π delocalization, typical for norbornenyl cations, strongly influences rotation at the CO bond in **16** and **17**.[16] If the barrier for **16** (14.7 kcal/mol) is taken as a reference value for this kind of electronic stabilization, the observed $\Delta G^{\ddagger}$ values for stereomutation of **12**–**14** seem to indicate that homoaromatic stabilization[18] is less significant in these cyclobutenyl cations. This is in line with published NMR data of **12**–**14** which suggest planarity for the four-membered ring.[15]

As has been shown above, the relative electronic effects of a substituent on the carbenium ion stability are similar in the ME and the rotational TS (see Table III). Provided a measured stereomutation process has been identified to occur by rotation and provided steric and solvation effects play only a minor role, then the observed barrier can directly be used as a measure for the cation stability. Thus, the following increase of cation stabilities can be predicted: **8 < 9 < 2c/3c; 10 < 11; 12 < 13 < 14; 15 < 16 < 17; 18 < 19.**

Conclusion

The majority of methoxy- and hydroxycarbenium ions considered here and in the preceding paper in this issue[3] undergo stereomutation about the C–O bond by a rotation mechanism both in the gas phase and strong acid solution. The only exception to this generalization occurs when the ions have very strong electron-withdrawing groups conjugated with the carbenium carbon. The magnitude of the rotation barriers depends on electronic, steric, and solvent effects. If the first effect dominates, the barrier height can be used as a simple method of probing cation stability.

Experimental Section

^{1}H NMR spectra were recorded on Varian EM390, Bruker WH 250, and Bruker WH 400 spectrometers. FSO_3H was distilled from anhydrous NaF under N_2.

4-(Trifluoromethyl)-*trans*-cinnamaldehyde was prepared by an identical procedure with that used for 4-methylcinnamaldehyde.[19] The crude product was chromatographed on silica gel, eluting with CH_2Cl_2, and the oil obtained from the major slow moving band was distilled (140 °C: 4 mm) to give the title compound as white crystals (55%): mp 53–54 °C; ^{1}H NMR ($CDCl_3$) δ 7.0 (dd, J = 16.5, 7 Hz, H-2), 7.77 (d, J = 16.5 Hz, H-3), 7.9 (s, Ar H), 10.04 (d, J = 7 Hz, H-1); IR ($CHCl_3$) 2830, 2750, 1685, 2630, 2420, 2320, 2270, 2230, 1065, 1010, 980, 820 cm^{-1}; MS, m/e (M^+) calcd for $C_{10}H_7F_3O$ 200.0449, found 200.0497.

3,5-Bis(trifluoromethyl)cinnamaldehyde. A solution of 3,5-bis(trifluoromethyl)benzoic acid (5.16 g) in anhydrous ether (40 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (4.2 g) in ether (40 mL) under an atmosphere of dry nitrogen. The reaction mixture was heated under reflux for 3 h and then cooled in ice. The residual $LiAlH_4$ was decomposed by dropwise addition of water, and the resultant suspension was poured onto a 5% solution of sulfuric acid whilst cooling in ice. The ether layer was separated, and the aqueous layer was extracted with ether (3 × 40 mL). The combined ether extracts were washed with water and dried ($MgSO_4$). The oil obtained after removal of the solvent was distilled on a Kugelrohr oven (150 °C: 4 mm) to give **3,5-bis(trifluoromethyl)benzyl alcohol** (4.41 g, 90%): mp 53–54 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, OH, exchangeable with D_2O), 4.98 (s, CH_2), 8.05 (s, ArH). IR ($CHCl_3$) 3620, 3430 (br), 2920, 2880, 2625, 2365, 2370 (br), 1130 (br), 900, 875 cm^{-1}; MS, m/e (M^+) calcd for $C_9H_6F_6O$ 244, found 244.

A solution of the above alcohol (4.38 g) in dichloromethane (15 mL) was added to a stirred suspension of pyridinium dichromate[20] (8.02 g) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with ether (100 mL), and the inorganic residue was removed by filtration over a short column of silica gel. The solvent was removed under reduced pressure and the residual oil was distilled (50 °C: 3 mm) to give **3,5-bis(trifluoromethyl)benzaldehyde** (3.13 g, 72%): ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1 H, ArH), 8.40 (s, 2 H, ArH), 10.20 (s, CHO); IR (thin film) 2820, 2715, 1715, 1620, 1365, 1280, 1170, 1130, 890, 840, 690, 670 cm^{-1}; MS, m/e (M^+) calcd for $C_6H_4F_6O$ 242.0166, found 242.0166.

The above aldehyde (2.26 g) was converted to 3,5-bis(trifluoromethyl)-*trans*-cinnamaldehyde, **20**, by using the procedure of Scholtz and Wiedemann.[19] The crude product was digested with pentane containing 30% dichloromethane, and the solution was kept at −20 °C for several days to give **20** as pale yellow crystals (0.8 g, 32%). Preparative GLC of the mother liquor (10% Carbowax on Chromosorb W) afforded further **20** as white crystals: mp 80–82 °C (from petroleum ether); ^{1}H NMR ($CDCl_3$) δ 6.87 (dd, J = 16.5, 7.5 Hz, H-2), 7.62 (d, J = 16.5 Hz, H-3), 8.0 (s, 1 H, ArH), 8.07 (s, 2 H, ArH), 9.87 (d, J = 7.5 Hz, H-1); IR ($CHCl_3$) 2830, 2740, 1690, 1635, 1370, 1270 (br), 1130 (br), 970, 895 cm^{-1}; MS, m/e (M^+) calcd for $C_{11}H_6F_6O$ 268.0323, found 268.0311.

Ketals. A modification of the method of Van Allen[21] was used in each case; the following procedure is typical. A solution of *trans*-cinnamaldehyde (3.3 g) in a mixture of trimethyl-*o*-formate (4 mL) and anhydrous methanol (2 mL) was treated with ammonium nitrate (0.10 g), and the mixture was boiled under reflux in a nitrogen atmosphere for 1.5 h. The reaction mixture was allowed to cool and was treated with an excess of anhydrous sodium carbonate. After stirring for 1 h the inorganic material was removed by filtration, and the residue obtained after removal of the solvent was distilled on a Kugelrohr oven (120 °C: 3 mm) to give *trans*-cinnamaldehyde dimethyl ketal **1c** (3.25 g, 73%) (lit.[22] bp 130–132 °C/15 mm); ^{1}H NMR (CCl_4) δ 3.27 (s, $(OCH_3)_2$), 4.92 (d, J = 4.5 Hz, H-1), 6.0 (dd, J = 16.5, 4.5 Hz, H-2), 6.67 (d, J = 14.5 Hz, H-3), 7.28 (m, 5 H, ArH); IR (thin film) 3060, 3015, 2990, 2940, 2830, 1660, 1495, 1450, 1350, 1180, 1125, 1045, 960, 745, 690 cm^{-1}.

4-Methoxy-*trans*-cinnamaldehyde dimethyl ketal, 1a, was prepared from 4-methoxy-*trans*-cinnamaldehyde[19] by using the procedure given above. The product was distilled (140 °C/3 mm): yield 50%; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, $(OCH_3)_2$), 3.77 (s, OCH_3), 4.88 (d, J = 5.6 Hz, H-1), 5.95 (dd, J = 16.5, 4.5 Hz, H-2), 6.63 (d, J = 16.5 Hz, H-3), 6.82 (d, J = 9 Hz, ArH), 7.32 (d, J = 9 Hz, ArH); IR (thin film) 2990, 1680, 1610, 1515, 1245, 1170, 1120, 1045, 960, 840 cm^{-1}; MS m/e M^+) calcd for $C_{12}H_{18}O_3$ 208.1099, found 208.1114.

4-Methyl-*trans*-cinnamaldehyde dimethyl ketal, 1b, was prepared from 4-methyl-*trans*-cinnamaldehyde[19] and purified by fractional distillation. The center cut (bp 120–123) °C, 4 mm) afforded **1b** (62%); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3 H, $ArCH_3$), 3.35 (s, $(OCH_3)_2$), 4.93 (d, J = 5 Hz, H-1), 6.07 (dd, J = 16.5, 5 Hz, H-2), 6.70 (d, J = 16.5 Hz, H-3), 7.13 (d, J = 9 Hz, ArH), 7.33 (d, J = 9 Hz, ArH); IR (thin film) 2990, 2935, 2830, 1660, 1515, 1445, 1350, 1185, 1125, 1045, 960, 905, 840, 790 cm^{-1}; MS, m/e (M^+) calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1135.

4-Chloro-*trans*-cinnamaldehyde dimethyl ketal, 1d, was prepared from 4-chloro-*trans*-cinnamaldehyde.[23] The product was distilled (130 °C: 3 mm) (45%): ^{1}H NMR ($CDCl_3$) δ 3.38 (s, $(OCH_3)_2$), 4.95 (d, J = 4.5 Hz, H-1), 6.10 (dd, J = 17, 4.5 Hz, H-2), 6.72 (d, J = 17 Hz, H-3), 7.35 (s, 4 H, ArH); IR (thin film) 2990, 2940, 2830, 1590, 1490, 1405, 1350, 1190, 1125, 1050, 960, 845, 800 cm^{-1}; MS, m/e (M^+) calcd for $C_{11}H_{13}ClO_2$ 212.0604, found 212.0604.

4-(Trifluoromethyl)-*trans*-cinnamaldehyde dimethyl ketal, 1e, was prepared from 4-(trifluoromethyl)-*trans*-cinnamaldehyde by using the procedure given above. The product was purified by distillation (oven temperature 150 °C: 4 mm), (yield 55%): ^{1}H NMR ($CDCl_3$) δ 3.42 ($(OCH_3)_2$), 5.0 (d, J = 4.5 Hz, H-1), 6.28 (dd, J = 16.5, 4.5 Hz), 6.83 (d, J = 16.5 Hz, H-3), 7.60 (m, ArH); IR (thin film) 2940, 2840, 1615, 1415, 1320, 1160, 1130, 1060, 1010, 960, 850, 810 cm^{-1}; MS, m/e (M^+) calcd for $C_{12}H_{13}F_3O_2$ 246.0868, found 246.0839.

3,5-Bis(trifluoromethyl)-*trans*-cinnamaldehyde dimethyl ketal, 1g, prepared from **20**, was purified by preparative TLC (Kieselgel, eluting

(18) The term homoaromaticity is used here in a qualitative sense. For an exact definition see: Cremer, D.; Kraka, E.; Slee, T. S.; Bader, R. F. W.; Lau, C. D. H.; Nguyen-Dang, T. T.; MacDougall, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 5069–5075.

(19) Scholtz, M.; Wiedemann, A. *Chem. Ber.* **1903**, *36*, 845–854.

(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(21) Van Allen, J. A. *Org. Synth.* **1963**, *4*, 21–22.

(22) Straus, von F.; Heinze, H. *Ann. Chem. (Paris)* **1932**, *493*, 191–217.

(23) Olsen, D. K.; Torien, B. E.; Morgan, C. D.; Braun, L. L. *J. Org. Chem.* **1980**, *45*, 4049–4052.

with hexanes containing 20% ether) and distillation (120 °C: 2.5 mm) (yield 43%): ^{1}H NMR ($CDCl_3$) δ 3.40 (s, $(OCH_3)_2$), 5.0 (d, J = 4.5 Hz, H-1), 6.30 (dd, J = 17, 4.5 Hz, H-2), 6.87 (d, J = 17 Hz, H-3), 7.85 (m, ArH); IR (thin film) 2940, 2835, 1785, 1640, 1470, 1455, 1380, 1275, 1175, 1125, 1105, 1050, 965, 890, 840, 690, 670 cm^{-1}; MS, m/e (M^+) calcd for $C_{13}H_{12}F_6O_2$ 314.0741, found 314.0719.

4-Nitro-*trans*-cinnamaldehyde dimethyl ketal, 1f, was prepared from 4-nitro-*trans*-cinnamaldehyde and was chromatographed over alumina, eluting with ether containing 40% hexanes. The main band afforded **1f** as colorless needles after recrystallization from hexanes (60%): mp 60–61 °C (lit.[24] 66–67 °C); ^{1}H NMR ($CDCl_3$) δ 3.39 (s, $(OCH_3)_2$), 4.99 (d, J = 4.5 Hz, H-1), 6.29 (dd, J = 16.5, 4.5 Hz, H-2), 6.84 (d, J = 16.5 Hz, H-3), 7.57 (d, J = 9 Hz, ArH), 8.22 (d, J = 9 Hz, ArH); MS, m/e (M^+) calcd for $C_{11}H_{13}NO_4$ 223.0884, found 223.0885.

Protonations. The ketal (15–20 mg) was weighed into an NMR tube, and the tube was cooled in dry ice/acetone. FSO_3H (0.3 mL) was added slowly down the wall of the tube and solution was effected by stirring with a thin glass rod.

Irradiations were carried out directly on FSO_3H solutions (**2c** and **2f**) in NMR tubes. The samples were placed in a partially silvered quartz Dewar with methanol as the heat-transfer medium and irradiated with light of wavelength 350 nm at ca. −70 °C.

NMR Spectral Simulations. Calculated spectra were obtained by using the program DNMR 3 by G. Binsch and D. A. Kleier, Quantum Chemistry Program Exchange.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. All calculations have been carried out at the Kölner Rechenzentrum.

Registry No. 1a, 63511-97-7; **1a** (aldehyde), 24680-50-0; **1b**, 95123-63-0; **1b** (aldehyde), 56578-35-9; **1c**, 63511-93-3; **1c** (aldehyde), 14371-10-9; **1d**, 95123-64-1; **1d** (aldehyde), 49678-02-6; **1e**, 95123-65-2; **1e** (aldehyde), 95123-61-8; **1f**, 95123-67-4; **1f** (aldehyde), 49678-08-2; **1g**, 95123-66-3; **2g**·FSO_3^-, 95123-69-6; **2b**·FSO_3^-, 95123-71-0; **2c**·FSO_3^-, 95123-73-2; **2d**·FSO_3^-, 95123-75-4; **2e**·FSO_3^-, 95123-77-6; **2f**·FSO_3^-, 95123-79-8; **2g**·FSO_3^-, 95123-81-2; **4c**, 95123-83-4; **5a**, 95123-84-5; **5b**, 95123-85-6; **5c**, 77406-43-0; **5d**, 95123-86-7; **5e**, 95123-87-8; **5f**, 95123-88-9; **6**, 57344-16-8; **20**, 95123-62-9; 3,5-bis(trifluoromethyl)benzoic acid, 725-89-3; 3,5-bis(trifluoromethyl)benzyl alcohol, 32707-89-4; 3,5-bis(trifluoromethyl)benzaldehyde, 401-95-6.

(24) Jenny, E. F.; Melzer, A. *Tetrahedron Lett.* **1966**, 3507–3512.

Anomerization of Furanose Sugars and Sugar Phosphates

John Pierce,[1a] Anthony S. Serianni,[1b] and Robert Barker*

Contribution from the Section of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, New York 14853. *Received August 16, 1984*

Abstract: Thermodynamic and kinetic parameters for the ring-opening and -closing reactions of several aldo- and ketofuranoses and their phosphate esters have been determined by NMR line-width and saturation-transfer methods. Cyclic forms interconvert via a single, acyclic carbonyl form under either acid or base catalysis. Ring-opening rates do not correlate with thermodynamic stability of the rings. For aldofuranose phosphates, α anomers open faster than β anomers; for ketofuranose phosphates the converse is observed. Intramolecular catalysis of anomerization by the phosphate group of sugar phosphates is documented. Biological and mechanistic implications of the observed kinetics are discussed.

Aqueous solutions of monosaccharides and their phosphate esters often contain several interconverting, tautomeric forms. Furanoses, pyranoses, septanoses, acyclic hydrates, aldehydes, ketones, and oligomers have been detected.[2] The chemistry of the monosaccharides is complicated by this structural diversity as the rates of their chemical and biochemical reactions may be determined by the concentration of a minor form and its rate of production from other forms, rather than by the total sugar concentration. Knowledge of the rates of interconversion of tautomeric forms is therefore required to interpret the observed chemical and biochemical reactivities of monosaccharides.

Studies of anomerization (the interconversion of cyclic anomers) of simple sugars began in the mid-19th century. Considerable kinetic data are available,[3] and overall rate constants for the interconversion of predominant forms have been determined for a variety of sugars. The reaction is subject to general acid and base catalysis, and the ring structure influences reaction rates.

The simplest mechanism for interconversion of tautomers (tautomerization)[4] involves the acyclic carbonyl form as the obligatory and sole intermediate (Scheme I). This mechanism has been proposed to interpret anomerization kinetic data,[3] including that which yields unimolecular ring-opening rate constants.[5] The role of the acyclic carbonyl form as the key intermediate, however, has been questioned, and pseudocyclic intermediates have been postulated.[3b,6] Recent kinetic experiments on sugars containing sulfur as the ring heteroatom have suggested that, in these compounds, interconversions of cyclic forms occur faster than formation of the acyclic carbonyl from cyclic forms.[7] Since the interpretation of most experiments on anomerization has depended on assumptions regarding the nature of the reaction intermediate, methods are needed to examine this intermediate and to test the validity of these assumptions.

Interest in the anomerization of sugar phosphates has been stimulated by the advancing studies of enzyme mechanisms and metabolic regulation. While the molecular dynamics of proteins have received considerable attention, the solution behavior of their substrates has often been neglected and investigators are confronted with the difficulties of studying the properties of sensitive and selective catalysts with reagents of undefined and changing nature. Unfortunately, measurements of the anomerization of

(1) (a) Central Research and Development Department, E. I. du Pont de Nemours & Co., Wilmington, DE 19898. (b) Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

(2) (a) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157. (b) Angyal, S. J.; Pickles, A. V. *Aust. J. Chem.* **1972**, *25*, 1695. (c) Blackmore, P. F.; Williams, J. F.; MacLeod, J. K. *FEBS Lett.* **1976**, *64*, 222. (d) Hayward, L. D.; Angyal, S. J. *Carbohydr. Res.* **1977**, *53*, 13. (e) Gray, G. R. *Acc. Chem Res.* **1976**, *9*, 418.

(3) (a) Pigman, W.; Isbell, H. S. *Adv. Carbohydr. Chem. Biochem.* **1968**, *23*, 11. (b) Isbell, H. S.; Pigman, W. *Ibid.* **1969**, *24*, 13. (c) Capon, B.; Walker, R. B. *J. Chem. Soc., Perkins Trans. 2* **1974**, *2*, 1600.

(4) Note that here we make a distinction between the general term, tautomerization, the interconversion of tautomers, and the term, anomerization, which specifically refers to interconversion of cyclic anomers.

(5) (a) Los, J. M.; Simpson, B.; Wiesner, K. J. *J. Am. Chem. Soc.* **1956**, *78*, 1564. (b) Wertz, P. W.; Garver, J. C.; Anderson, L. *Ibid.* **1981**, *103*, 3916.

(6) Maier, G. D.; Kusiak, J. W.; Bailey, J. M. *Carbohydr. Res.* **1977**, *53*, 1.

(7) Grimshaw, C. E.; Whistler, R. L.; Cleland, W. W. *J. Am. Chem. Soc.* **1979**, *101*, 1521.

0002-7863/85/1507-2448$01.50/0