CH bond on the $\bar{2}$ $^2B_1$ surface is not supported by the resonance Raman intensities or theoretical results. The direct photodissociation would yield strong intensity in ν_2, the CH stretch. The Raman bands at 2917 and 3020 cm^{-1} in Figure 3 are due to the methane buffer gas. No strong Raman bands in the CH stretch region are observed when argon is used as a buffer gas. The terminal CH$_2$ groups would rotate to the perpendicular geometry of allene corresponding to motion in the ν_9 coordinate of the allyl radical, giving rise to $2\nu_9$ in the Raman spectrum. Neither of these features appears in the Raman spectrum resonantly enhanced by the $\bar{2}$ $^2B_1$ state.

Conclusions

Examination of the allyl radical by resonance Raman spectroscopy has shown that the literature infrared frequencies should be reassigned and that the ab initio theoretical frequencies are essentially correct. Qualitative analysis of the observed resonance Raman intensities indicates that the photoisomerization on the $\bar{2}$ $^2B_1$ surface of the allyl radical proceeds by a disrotary process, in agreement with theoretical predictions. The Raman spectra indicate that the central CH bond does not directly photodissociate on the $\bar{2}$ $^2B_1$ excited-state surface. Work is in progress on the perdeutero allyl-d_5 radical to confirm the assignments of the ν_6 and $2\nu_{12}$ features.

# Hemiacetal Anions: A Model for Tetrahedral Reaction Intermediates

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Abstract: A deprotonated hemiacetal ion is used as a model intermediate for nucleophilic addition reactions at a carbonyl group. The acidity of the cyclic hemiacetal 2-hydroxytetrahydropyran has been estimated to be $\Delta G^\circ_{acid} \geq 351 \pm 2$ kcal/mol. The basicity of the deprotonated ion was found to be 347 ± 2 kcal/mol, different from the acidity by 4 kcal/mol. This difference is ascribed to an isomerization reaction in the ion. The electron affinity of the neutral radical corresponding to removal of an electron from the ion was measured with use of electron photodetachment spectroscopy and was found to be 49.6 ± 2.5 kcal/mol. The structure of the isomerized ion is assigned as a hydrogen bond stabilized enolate ion. The implications of the strong acidity of the hemiacetal for the stability of tetrahedral reaction intermediates are discussed. Thermochemical arguments suggest that tetrahedral adducts of this type are often global minima on the reaction potential surface. The addition reactions of different alkoxide–alcohol complexes with benzaldehyde are discussed in terms of the stability of the corresponding tetrahedral addition product.

I. Introduction

Nucleophilic carbonyl addition reactions play a critical role in a variety of chemical and biochemical processes, including enzyme-catalyzed hydrolysis of carboxylic acid derivatives. Due to their biological relevance, as well as their synthetic utility, carbonyl addition reactions have been extensively studied.[1] Studies of the reaction mechanism in solution suggest that the reaction proceeds through an intermediate tetrahedral structure where the oxygen carries the negative charge, as shown in eq 1.[2-6]

$$\text{(1)}$$
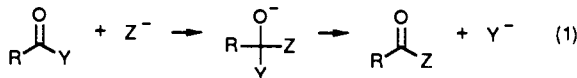
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Scheme I
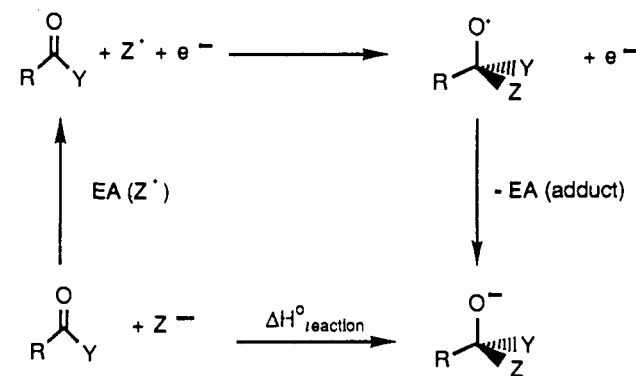
Nucleophiles	EA
CH_3^-	2 kcal/mol
CH_3O^-	37 kcal/mol
Cl^-	83 kcal/mol

This intermediate has been implicated in kinetic and isotope exchange experiments.[2a,3,4] In certain cases, direct spectroscopic evidence for its existence has been found.[5]

(6) (a) Fodor, G.; Letourneau, F.; Mandova, N. *Can. J. Chem.* **1970**, *48*, 1465. (b) Zaugg, H. E.; Popendick, V.; Michaels, R. J. *J. Am. Chem. Soc.* **1964**, *86*, 1339. (c) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49.

In the gas phase, however, where solvent effects are absent, the existence of such a tetrahedral intermediate is less certain.[7] The enthalpy of addition to form the tetrahedral species will depend on a variety of factors, including, most importantly, the stabilities of the attacking nucleophile and the tetrahedral adduct. This relationship is illustrated in the thermochemical cycle shown in Scheme I for three different nucleophiles. If we make the rough approximation that the difference in energy between the neutral carbonyl + Z[*] and the neutral adduct is relatively small compared to the difference between their ionic counterparts, the heat of reaction to form the tetrahedral adduct reduces to the difference in the electron affinities of the relevant nucleophile and the adduct.
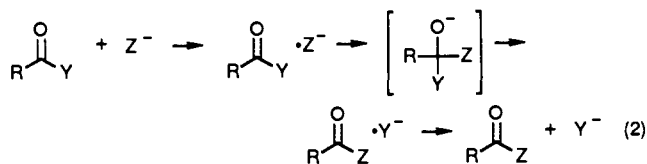
Although the electron affinity of the tetrahedral adduct is unknown, predictions about its stability can be made for certain limiting cases. When the attacking nucleophile is a very strong base with a correspondingly low electron affinity, such as CH_3^-, the tetrahedral species is expected to be quite stable. In the case of addition of CH_3^- to acetone, for example, the relevant electron affinities are $EA(CH_3^{\cdot}) = 1.845$ kcal/mol and $EA(t\text{-}BuO^{\cdot}) = 44.04$ kcal/mol; formation of the addition product is therefore strongly exothermic, and these reactions are expected to result in tetrahedral intermediates.[8] Hydride ion has been observed to add to formaldehyde in the presence of a bath gas forming methoxide ion;[9] the tetrahedral structure in this reaction has been confirmed by calculations.[10]

Conversely, for reactions involving very stable anions such as Cl^- with large electron affinities, formation of the tetrahedral species is expected to be relatively unfavorable. Since chloride exchange has been observed in reactions of Cl^- with acetyl chlorides, however, the tetrahedral adduct must be reasonably stable.[11] Even if the tetravalent species is a transition state rather than a stable intermediate, this result implies that the EA of the adduct must be enormous, indeed greater than that of Cl^-. This enhanced stability of the tetrahedral adduct anion relative to a "normal" alkoxide ion is presumably due to the presence of two electron-withdrawing groups. The magnitude of this effect, however, is remarkable.

The stability of the tetrahedral adduct in addition reactions involving nucleophiles with intermediate electron affinities is less clear. For reactions involving alkoxide ions, for example, the electron affinity of the tetrahedral adduct might be expected to be similar to that of the attacking nucleophile, RO^-. The addition process is then close to thermoneutral and may not occur due to unfavorable entropic factors. If, however, the electron affinity of the adduct is unusually large, analogous to the chlorine-containing adduct discussed previously, the formation of the tetrahedral species may be favorable. Thus, without an experimental or theoretical measure of the stability of the tetrahedral anion, no simple prediction for the structure of the reaction intermediate is available.

An additional consideration in gas-phase acyl-transfer reactions is the possible existence of stable ion–dipole clusters bound simply by electrostatic interactions. This type of cluster is typically bound by 10–12 kcal/mol.[12] Thus, for the reaction to proceed through a stable tetrahedral intermediate, its formation must be exothermic

by more than 10–12 kcal/mol. If adduct formation is endothermic or only slightly exothermic, the reaction may proceed through two ion–dipole minima separated by a tetravalent transition state, eq 2. Since the cluster and the adduct have the same mass, they

$$R \overset{O}{\underset{}{\overset{\|}{C}}} Y + Z^- \longrightarrow R \overset{O}{\underset{}{\overset{\|}{C}}} Y \cdot Z^- \longrightarrow \left[R \overset{O^-}{\underset{Y}{\overset{|}{C}}} Z \right]^- \longrightarrow$$

$$R \overset{O}{\underset{Z}{\overset{\|}{C}}} \cdot Y^- \longrightarrow R \overset{O}{\underset{Z}{\overset{\|}{C}}} + Y^- \quad (2)$$

cannot be differentiated by their mass to charge ratio. Many attempts have focused on whether the tetrahedral adduct is a stable intermediate or a transition state by use of indirect structural probes.[7,11,13-19] The ion–dipole structure of the acetyl chloride–chloride reaction intermediate has been supported theoretically by Blake and Jorgensen[7c,20a] and Yamabe and Minato.[20b] Cooks and co-workers have studied a series of addition products formed by attack of Cl^- on carbonyl-containing compounds. On the basis of measurements of kinetic isotope effects, they report that some addition products are covalently bound tetrahedral species, whereas others are ion–dipole complexes.[13] Other experiments have focused on the binding energies of the addition products. McMahon and co-workers found that fluoride ion forms much stronger bonds with simple aldehydes and esters than does chloride ion.[14]

In the case of alkoxide addition to carbonyl compounds, where the heat of formation of the tetrahedral species is unknown, the structure of the intermediate has been the subject of considerable research.[17-19] Bartmess has observed formation of an addition product from solvated methoxide and acetaldehyde.[17h] Bowie and co-workers report that addition of solvated methoxide to simple ketones and aldehydes results in formation of an addition product that, on the basis of calculations, they describe as a solvated enolate ion.[18] An extensive survey of methoxide + aldehyde and methoxide + ester reactions has been reported by Nibbering and van der Wel.[19] On the basis of chemical probes of the intermediate's reactivity, they conclude that the cluster and the adduct coexist and therefore must be extremely close in energy.

Nucleophilic attack by hydroxide is better understood.[21-24] Bohme and co-workers observed an addition product in the re-

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(17) (a) Klass, G.; Sheldon, J. C.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1337. (b) Sheldon, J. C.; Currie, G. J.; Lahnstein, J.; Hayes, R. N.; Bowie, J. H. *Nouv. J. Chim.* **1985**, *9*, 205. (c) Sheldon, J. C.; Bowie, J. H. *Aust. J. Chem.* **1983**, *36*, 289. (d) Sheldon, J. C.; Bowie, J. H.; Hayes, R. N. *Nouv. J. Chim.* **1984**, *8*, 79. (e) Fukuda, E. K.; McIver, R. T. *J. Am. Chem. Soc.* **1979**, *101*, 1979. (f) Kleingeld, J. C.; Nibbering, N. M. M.; Grabowski, J. J.; DePuy, C. H.; Fukuda, E. K.; McIver, R. T. *Tetrahedron Lett.* **1982**, *23*, 4755. (g) McDonald, R. N.; Chowdhury, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 901. (h) Bartmess, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 2483.

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Model for Tetrahedral Reaction Intermediates

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action of hydroxide with formaldehyde in the presence of a bath gas.[21] The tetrahedral species has been calculated to be an energetic minimum for this reaction by both Jorgensen et al.[22] and Yamabe.[23] These calculations are supported by van der Wel and Nibbering,[19] who studied the same reaction experimentally using isotope labeling. They observed proton transfer within the adduct, suggesting that it is a long-lived stable intermediate and must therefore be a covalent tetrahedral species.

In order to determine the relative stabilities of the ion–dipole cluster versus the tetrahedral adduct in alkoxide addition reactions, a direct measurement of adduct stability is clearly desirable. It was recognized by Bartmess, Hays, and Caldwell that deprotonated hemiacetals should be good models for intermediates in alkoxide + aldehyde reactions.[16] Measurements of the acidities and electron affinities of these anions can provide vital information about the intrinsic stability of tetrahedral reaction intermediates. Bartmess studied the cyclic hemiacetal 2-hydroxytetrahydropyran (**1**) formed by intramolecular rearrangement from 5-hydroxy-valeraldehyde, eq 3. In solution, the hemiacetal is favored by

$$O\!\!\diagdown\!\!\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\!\!OH \rightleftharpoons \overset{OH}{\bigcirc_{O}} \qquad (3)$$

$$\mathbf{3} \qquad\qquad \mathbf{1}$$
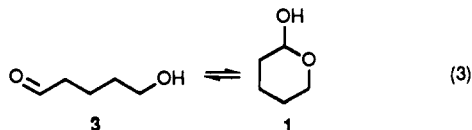
~2 kcal/mol over the open-chain form, and thus, the reaction equilibrium lies substantially to the right.[25] (Most acyclic hemiacetals are only slightly thermodynamically favored and therefore are difficult to isolate.[26]) Bartmess reported an acidity of 361 kcal/mol for the 2-hydroxytetrahydropyran based on a bracketing experiment and found that the ion had probably rearranged subsequent to its formation.

We embarked on the present study to gain more detailed information about the stability of deprotonated hemiacetal anions and thus tetrahedral reaction intermediates. In particular, we desired a definitive structural determination of the methoxide–aldehyde addition products observed by Nibbering.[19] To this end, the electron affinity of the anion produced by deprotonation of 2-hydroxytetrahydropyran was measured with electron photodetachment spectroscopy. The acidity of the hemiacetal was also remeasured and its precision significantly increased. In addition, the reactions of ethoxide–ethanol and ethoxide–methanol with benzaldehyde were studied and compared with the reactions of methoxide–methanol, as reported by Nibbering.[19]

In this paper, we report the acidity of 2-hydroxytetrahydropyran and the basicity of the anion produced by its deprotonation, as well as the electron affinity of the neutral radical corresponding to this anion. Deuterium-exchange reactions of this anion help to confirm a suggested structure. The strong acidity of the hemiacetal suggests that, for reactions of alkoxides with aldehydes, tetrahedral intermediates are significantly more stable than ion–dipole complexes. The different reactivities of the alcohol–alkoxide complexes with benzaldehyde are discussed in terms of the stabilities of the corresponding tetrahedral addition products.
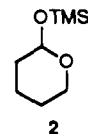
II. Experimental Section

A. Chemicals. All chemicals were purchased from Aldrich and used as received with the exception of the compounds specifically mentioned in the following text. Samples were degassed by three freeze-pump–thaw cycles prior to introduction into the high-vacuum system. 3-Fluorobenzyl alcohol was deuterated by mixing the alcohol with deuterated water (MSD Isotopes) and then drying over sodium sulfate. The synthesis of 2-(trimethylsiloxy)tetrahydropyran (**2**) was adapted from a literature preparation of tetrahydropyranyl ethers[27] with use of dihydropyran and trimethylsilanol, prepared by the method of Fukukawa and Kohoma.[28]

$$\overset{OTMS}{\underset{\mathbf{2}}{\bigcirc_{O}}}$$

The trimethylsilyl ether was isolated by preparative gas chromatography.

B. Acidity Bracketing. Acidity values were measured by use of ion cyclotron resonance spectroscopy (ICR), with Fourier transform mass spectrometry (FTMS) used for data collection. Acidity-bracketing experiments monitored proton-transfer reactions between the compound of interest (HA), reference acids (HB), and their conjugate bases (A⁻ and B⁻, respectively). Both the forward and reverse reactions, shown in eqs 4 and 5, respectively, were monitored. If a reference acid is found for

$$B^- + HA \rightarrow HB + A^- \qquad (4)$$

$$A^- + HB \rightarrow HA + B^- \qquad (5)$$
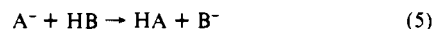
which both the forward and reverse pathways are accessible, an equilibrium constant may be measured and ΔG°_{acid} determined. No acids were found that set up an equilibrium with 2-hydroxytetrahydropyran, so the acidity could only be estimated. The acids used and the reactions observed are described in the Results.

FTMS, described in detail elsewhere,[29] was carried out with use of an IonSpec FTMS-2000 data collection system. Experiments were performed in a 1-in. cubic ICR cell placed between the poles of an electromagnet, which was operated at 1.0–1.2 T. Typical background pressures were $(0.5–2) \times 10^{-8}$ Torr. Standard notched ejection techniques were used to isolate the ions of interest.

The deprotonated hemiacetal was generated by proton abstraction from the neutral hemiacetal or nucleophilic displacement of the trimethylsiloxy hemiacetal. The primary ion for both methods, fluoride, was generated by dissociative electron capture from nitrogen trifluoride (Ozark-Mahoning). Fluoride can deprotonate 2-hydroxytetrahydropyran (**1**) or react with **2** to generate the deprotonated hemiacetal.[30] Both methods of anion generation were used for the acidity bracketing. Results were independent of the method of generation, suggesting that the anions were not vibrationally excited. Typical neutral pressures used were nitrogen trifluoride, $(2–3) \times 10^{-7}$ Torr; 2-(trimethylsiloxy)tetrahydropyran or 2-hydroxytetrahydropyran, $(1–3) \times 10^{-6}$ Torr; and the reference acid, $(1–3) \times 10^{-6}$ Torr. Uncorrected pressures were measured with use of a Varian 844 vacuum ionization gauge.

C. Electron Photodetachment Spectroscopy. The deprotonated hemiacetal was also studied by electron photodetachment spectroscopy with use of an ICR spectrometer operating in the drift mode, described in detail elsewhere.[31] The better signal to noise ratio obtained with continuous generation, irradiation, and detection of ions allows the measurement of small changes in signal amplitude.

Electron photodetachment spectroscopy consists of monitoring an anion population as a function of wavelength to determine a relative cross section for the loss of an electron, eq 6. These are bound to continuum

$$A^- \xrightarrow{h\nu} A^\cdot + e^- \qquad (6)$$

transitions, and the spectrum is integral in nature. Onsets in the spectrum are assigned from slope changes in the plot of relative cross section versus wavelength.[31b] The adiabatic electron affinity of the neutral will be determined if this is a transition between the ground rovibrational state of the anion and the ground rovibrational state of the neutral. If the anion population is vibrationally excited, an onset will be seen at energies lower than the adiabatic electron affinity.

The deprotonated hemiacetal was generated from 2-(trimethylsiloxy)tetrahydropyran (**2**) $(1 \times 10^{-6}$ Torr) plus fluoride ion (nitrogen trifluoride pressure, 2×10^{-7} Torr), as described in Acidity Bracketing; uncorrected pressures were measured with a Varian UHV-24 ionization gauge. The anion concentration was measured with use of capacitance bridge detection with a frequency lock,[31c] which ensures that the detection frequency corresponds to the resonant cyclotron frequency of the anions. Data collection and analysis were performed with an IBM-XT. A typical

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(25) (a) Equilibrium for neat 2-hydroxytetrahydropyran: Hurd, C. D.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 5324. (b) Equilibrium for 2-hydroxytetrahydropyran in various solvents: Wolfenden. R.; Liang, Y.-L. *J. Biol. Chem.* **1988**, *263*, 8022.

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(28) Fukukawa, S.; Kohoma, S. *Sci. Ind. (Japan)* **1955**, *29*, 70.

(29) Freiser, B. S. In *Techniques for the Study of Ion–Molecule Reactions*; Farrar, J. M., Saunders, W. H., Jr., Eds.; John Wiley and Sons: New York, 1988; Chapter 3.

(30) Generally, fluoride would be expected to attack at silicon to generate the alkoxide. In this case, fluoride reacts with **2**, generating trimethylsiloxide anion, which subsequently reacts with another neutral via an S_N2 displacement, yielding the deprotonated hemiacetal.

(31) (a) Wetzel, D. M.; Brauman, J. I. *Chem. Rev.* **1987**, *87*, 607. (b) Wetzel, D. M.; Salomon, K. E.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 3835. (c) Marks, J.; Drzaic, P. S.; Foster, R. F.; Wetzel, D. M.; Brauman, J. I.; Uppal, J. S.; Staley, R. S. *Rev. Sci. Instrum.* **1987**, *58*, 1460.

data scan consisted of measuring base-line anion signal (no light) at the start and at the end of a scan and collecting signal measurements at 10–30 consecutive wavelengths; a signal measurement generally consisted of 10 000 readings collected over a period of 3.3 s. The entire photodetachment spectrum consisted of scans of several small overlapping wavelength regions; each wavelength region was averaged from at least four scans. The fractional decreases at each wavelength were corrected for the photon intensity to yield relative electron detachment cross sections.

Low-resolution data were obtained with use of a 1000-W xenon arc lamp (Canrad-Hanovia) with a 0.25-m high-intensity monochromator (Kratos Analytical) and a visible grating (200–800 nm). A slit width of 4.4 mm was used, resulting in a wavelength spread of 14.5 nm, full width at half-maximum (fwhm). The grating was calibrated by directing an expanded beam from a He–Ne laser into the monochromator. The lamp power was measured from the amplified response of a thermopile (Eppley Laboratory, Inc.). Due to experimental constraints, power measurements could not be taken during a data scan and were therefore obtained after a scan.

High-resolution data were obtained by use of a dye laser (Coherent 590) that was pumped by an argon ion laser (Coherent Innova 200). Two wavelength regions were examined by use of Exiton dyes Rhodamine 560 (540–590 nm) and Rhodamine 590 (575–650 nm). Wavelengths were selected with a three-plate birefringent filter; spectral bandwidth was 0.1 nm. The wavelength calibration was obtained separately from the data scans by using the optogalvanic effect.[32a,b] The laser beam was directed into a Ca/Ne hollow cathode lamp; scans of the laser wavelengths resulted in voltage changes in the lamp whenever the wavelength was tuned to an electronic transition of an atomic species present in the lamp. From known electronic transitions for these atoms,[32c] a calibration was assigned. Dye-laser power scans were obtained simultaneously with data collection by using a beam splitter to send a small portion of the beam into a thermopile (Eppley Laboratories, Inc.).

D. Reactivity of Alkoxide–Alcohol Complexes. Reactions of methoxide–methanol, ethoxide–methanol, and ethoxide–ethanol complexes with benzaldehyde were monitored by FTMS (see previous text). Alcohol–alkoxide complexes were generated by reaction of the alkoxide ion with the relevant alkyl formate,[33] eqs 7–9. Methoxide and ethoxide were

$$MeO^- + HCOOMe \rightarrow MeOHOMe^-   (7)$$

$$MeO^- + HCOOEt \rightarrow MeOHOEt^-   (8)$$

$$EtO^- + HCOOEt \rightarrow EtOHOEt^-   (9)$$

generated by electron impact on methyl nitrite and ethyl nitrite, respectively. These alkyl nitrites were synthesized in situ, following the method of Caldwell and Bartmess.[34] Once the relevant alcohol–alkoxide complex was generated, it was isolated by standard notched-ejection techniques, and its reactivity with benzaldehyde was studied. Typical neutral pressures used were as follows: alkyl nitrites, $(1.0–2.0) \times 10^{-7}$ Torr; alkyl formates, $\sim 1.0 \times 10^{-6}$ Torr; benzaldehyde, $(0.5–2.0) \times 10^{-6}$ Torr.

III. Results

A. Acidity of 2-Hydroxytetrahydropyran. The reactions used to bracket the acidity of 2-hydroxytetrahydropyran are shown in Table I in order of increasing acidity. Reactions 1–4 are relatively fast and thus presumably exothermic. Methyl mercaptide ion reacts very slowly with the hemiacetal, even at pressures up to 5×10^{-6} Torr of the neutral. This slow reaction rate implies that the reaction is thermoneutral or slightly endothermic. The reverse reaction, deprotonation of methyl mercaptan by the anion produced by reaction 5, however, was not observed. Furthermore, neither ethyl mercaptan nor crotonaldehyde, both stronger acids than methyl mercaptan, displayed any reactivity with the deprotonated hemiacetal, reactions 6 and 7. A stronger acid still, 4-(trifluoromethyl)aniline, was required to reprotonate the anion, reaction 8. This proton transfer was relatively fast, as was reaction 9, abstraction of a proton from phenol. Thus, the apparent basicity of the deprotonated hemiacetal anion ($\Delta G^\circ_{base} \equiv -\Delta G^\circ$ for protonation of the anion) does not equal the acidity of the neutral

(32) (a) King, D. S.; Schenck, P. K. *Laser Focus* 1978, *3*, 50. (b) King, D. S.; Schenck, P. K.; Smyth, K. C.; Travis, J. C. *Appl. Optics* 1977, *16*, 2617. (c) *M.I.T. Wavelength Tables—Wavelengths by Element*; M.I.T. Press: Cambridge, 1982; Vol. 2.

(33) Blair, L. K.; Isolani, P. C.; Riveros, J. M. *J. Am. Chem. Soc.* 1973, *95*, 1057.

(34) Caldwell, G.; Bartmess, J. E. *Org. Mass. Spec.* 1982, *17*, 19.

Table I. Acidity Bracketing[a]

					$\Delta G^\circ_{acid},$[b] (kcal/mol)
(1)	$CF_3CH_2O^-$	$+ 1$	$\longrightarrow$	$X^{\cdot} + CF_3CH_2OH$	354.1
(2)	Et_3SiO^-	$+ 1$	$\longrightarrow$	$X^{\cdot} + Et_3SiOH$	353.6
(3)	(structure) $-CH_2^{\cdot}$	$+ 1$	$\longrightarrow$	$X^- + $ (structure) $-CH_3$	352.6
(4)	(structure)	$+ 1$	$\longrightarrow$	$X^{\cdot} + $ (structure)	351.4
(5)	MeS^-	$+ 1$	very slow $\nrightarrow$	$X^- + MeSH$	351.0
(6)	EtS^-	$+ XH$	$\nrightarrow$	$X^{\cdot} + EtSH$	349.2
(7)	$CH_2CHCHCHO^-$	$+ XH$	$\nrightarrow$	$X^- + CH_3CHCHCHO$	348.1
(8)	F_3C-(structure)$-NH^-$	$+ XH$	$\longleftarrow$	$X^{\cdot} + F_3C$-(structure)$-NH_2$	346.0
(9)	$PhO^{\cdot}$	$+ XH$	$\longleftarrow$	$X^- + PhOH$	342.9

[a] $1 = $ (structure with OH, O), $XH = C_5H_{10}O_2$, $X^- = C_5H_9O_2^-$. [b] 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*.
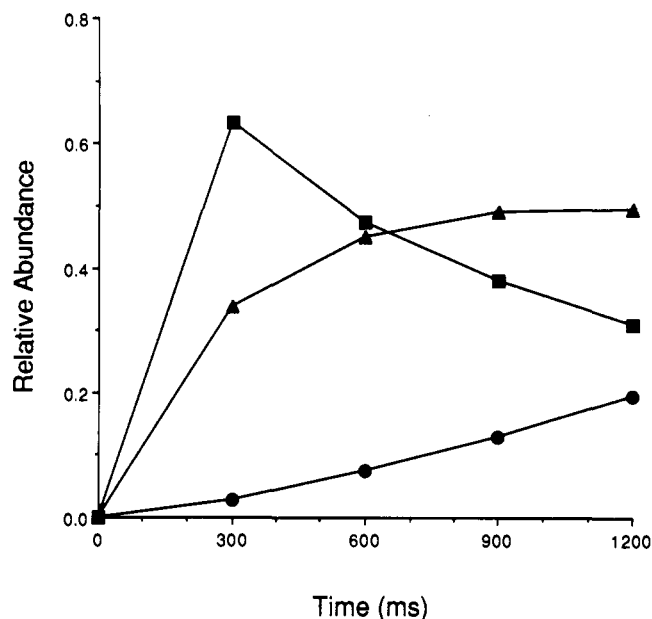

Figure 1. Incorporation of deuteriums into deprotonated 2-hydroxytetrahydropyran in the presence of *m*-fluorobenzyl alcohol-*d* as a function of time: square, m/z 101 (no D); triangle, m/z 102 (1 D); circle, m/z 103 (2 D).

hemiacetal ($\Delta G^\circ_{acid} \equiv \Delta G^\circ$ for deprotonation of the hemiacetal). The bracketed acidity, ΔG°_{acid}, is taken to be 351 ± 2 kcal/mol and the bracketed basicity, ΔG°_{base}, is taken to be 347 ± 2 kcal/mol.

B. Proton-Exchange Reactions. Additional information about the deprotonated hemiacetal anion was gained by monitoring the exchange reactions of the ion with a deuterium source. This technique was first applied to negative ions by DePuy and co-workers[35] and has been shown to provide important structural information about the anion.[35,36] Reaction of the deprotonated

(35) Stewart, J. H.; Shapiro, R. H.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* 1977, *99*, 7650.
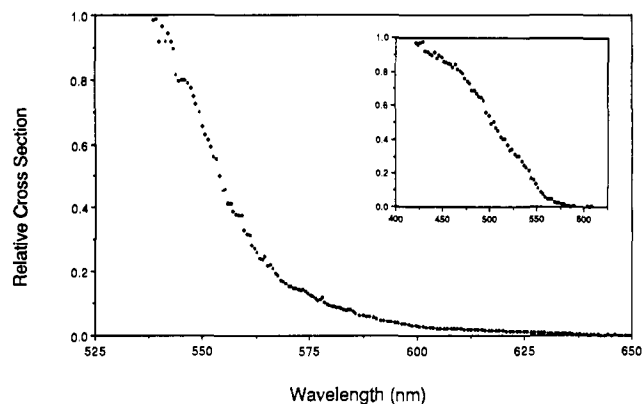
Figure 2. High-resolution electron photodetachment of deprotonated 2-hydroxytetrahydropyran. Tunable dye laser data. Inset: Low-resolution electron photodetachment of deprotonated 2-hydroxytetrahydropyran. Arc lamp/monochromator data with use of 4.4-mm slits; fwhm = 14.5 nm.

hemiacetal with *m*-fluorobenzyl alcohol-*d* yielded two products: the M + 1 and M + 2 anions. As can be seen in Figure 1, the deuteriums are sequentially incorporated, with the M + 2 anion observed only at long times. The anion formed by deprotonation of the hemiacetal must therefore possess two exchangeable protons, and its conjugate acid must have three exchangeable protons.

C. Electron Photodetachment Spectroscopy. The deprotonated hemiacetal anion was studied by use of electron photodetachment spectroscopy. The threshold region, 650–540 nm, taken with the laser is shown in Figure 2. A more extended spectrum, 610–420 nm, taken at lower resolution with the arc lamp/monochromator is shown as an inset to the figure. A long exponential-like tail from ~640–580 nm was observed with the laser, but not with the arc lamp. We tentatively ascribe this slowly increasing, featureless region to hot bands, i.e., a small population of vibrationally excited anions. The threshold for the deprotonated hemiacetal is assigned as 576 nm, with the large error bars of ± 30 nm corresponding to the uncertainty in the nature of the long tail. The electron affinity of the radical corresponding to the anion produced by deprotonation of 2-hydroxytetrahydropyran is thus assigned to 49.6 ± 2.5 kcal/mol.
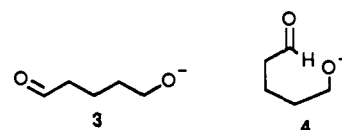
D. Reactivity of Alkoxide–Alcohol Complexes. The reactions of methoxide–methanol, ethoxide–ethanol, and ethoxide–methanol with benzaldehyde were studied. As observed by Nibbering,[19] reaction of methoxide–methanol with benzaldehyde was found to yield the methoxide–benzaldehyde addition product plus methanol. Ethoxide–methanol was also found to react with benzaldehyde, yielding both an ethoxide–benzaldehyde and a methoxide–benzaldehyde addition product. Despite the differing acidities of methoxide and ethoxide, these products were formed in approximately equal amounts.[37] The reaction of ethoxide–ethanol with benzaldehyde did not yield the corresponding addition product.

IV. Discussion

A. Chemistry of the Hemiacetal Anion. A possible explanation for the failure to establish an equilibrium between the deprotonated 2-hydroxytetrahydropyran and a reference acid is the existence of simple kinetic barriers along the proton-transfer reaction coordinate. If sufficiently large, these barriers could slow the thermoneutral reaction so as to be unobservable. Since the observed difference in ΔG°_{acid} and ΔG°_{base} is only 4 kcal/mol, this kinetic explanation cannot be immediately dismissed. In order to prevent the thermoneutral reaction, however, barriers would

have to be quite large, on the order of the hydrogen-bonded ion–molecule complex well depths, ~20–30 kcal/mol. A barrier this large for a simple proton-transfer reaction would be unprecedented. In addition, barriers this large would also slow the exothermic reactions, as predicted by Marcus theory.[38] Since we observe that these proton-transfer reactions either proceed rapidly or not at all, we do not believe that simple kinetic barriers are responsible for the failure to observe an equilibrium. In addition, the ability of the deprotonated hemiacetal anion to exchange two protons for deuteriums in the collision complex with a deuterium source argues strongly that some chemical transformation in the anion has occurred, since 2-hydroxytetrahydropyran has only one acidic proton. Finally, these deuterium-exchange reactions suggest that the proton-transfer barriers are accessible, even for endothermic reactions.

A more plausible explanation for the difference in the measured acidity and basicity is that the deprotonated hemiacetal isomerizes to a more stable form, X⁻, as suggested by Bartmess.[16] This more stable anion is a weaker base and therefore requires a stronger acid to reprotonate it. Thus, the observed acidity is a measure of the stability of the hemiacetal anion, and the basicity reflects the stability of some other isomerized anion. Since the neutral molecule exists partially as an open-chain hydroxy aldehyde as well as a hemiacetal, a possible structure for the isomerized anion is the corresponding alkoxide ion, **3**. Depending on its confor-

mation, this anion might also be stabilized through interaction with the aldehydic proton, **4**. These structures can be discounted, however, by considering the basicity of the isomerized anion, $\Delta G^\circ_{base}(X^-) = 347$ kcal/mol. Structure **3** is expected to be a much stronger base; its basicity can be approximated by that of a large alkoxide, for example $\Delta G^\circ_{base}(t\text{-BuO}^-) = 368$ kcal/mol.[8] Structure **4** may be more stable than structure **3** by 6–8 kcal/mol because of the internal ion–dipole interaction (the ion–dipole interaction provides an enthalpy stabilization of 10–12 kcal/mol, which yields a free energy stabilization of 6–8 kcal/mol after allowing for entropy losses).[12] Its expected basicity—$\Delta G^\circ_{base}(4) = 368 - 7$ kcal/mol = 361 kcal/mol—however, is still 14 kcal/mol stronger than the measured basicity.

Another possible structure is the enolate anion, **5**, which is formed by a ring opening and subsequent proton transfer. The
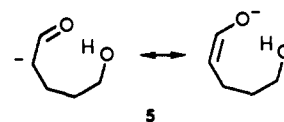
ring opening and proton transfer would almost certainly involve kinetic barriers, but these may be surmountable in the collision complex. Enolate anions are quite stable, and this enolate anion is expected to be even more so due to the hydrogen-bonding stabilization by the O–H group. The basicity of a typical enolate ion is $\Delta G^\circ_{base} = 359$ kcal/mol, and the hydrogen-bonded interaction would be expected to stabilize the anion by at least 10 kcal/mol, including the loss of entropy incurred by ring closure.[8] This stabilized enolate anion, **5**, is therefore a good candidate for the structure of the isomerized hemiacetal anion. Reprotonation of the enolate anion would presumably occur at the α-position to generate the hydroxy aldehyde rather than at the oxygen, which would generate the less stable hydroxy enol. This enolate ion, **5**, is the intramolecular equivalent of the solvated enolate ion formed by addition of methoxide to acetone, suggested by Bowie.[18]

Further confirmation of the structure of X⁻ is gained from the isotope-exchange experiments described in section III. The ex-

(36) (a) Hunt, D. F.; Sethi, S. K. *J. Am. Chem. Soc.* **1980**, *102*, 6953. (b) DePuy, C. H.; Bierbaum, V. M.; King, G. K.; Shapiro, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 2921. (c) Squires, R. R.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1981**, *103*, 4256. (d) Squires, R. R.; Bierbaum, V. M.; Grabowski, J. J.; DePuy, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 5185.

(37) Baer, S.; Stoutland, P. O.; Brauman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 4097.

(38) (a) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249. (b) Dodd, J. A.; Brauman, J. I. *J. Phys. Chem.* **1986**, *90*, 3559. (c) Dodd, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1984**, *106*, 5356.

Scheme II
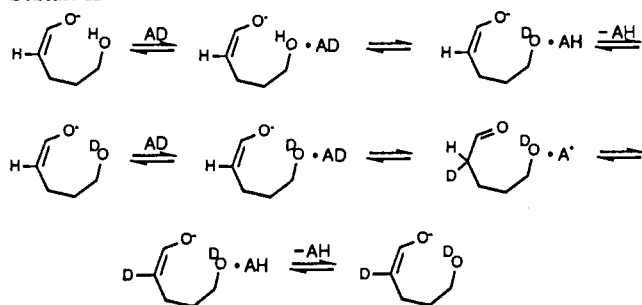
perimentally observed anion exchanges two protons with an external deuterium source. This is consistent with the enolate anion that would be expected to have two exchangeable protons, Scheme II.

In order to ascertain other thermodynamic properties of deprotonated 2-hydroxytetrahydropyran, it is necessary to convert the measured free energy term, $\Delta G°_{base}$, into an enthalpic term, $\Delta H°_{base}$, by use of an estimate of $\Delta S°_{base}$ for eq 10. This entropy

$$\qquad\qquad\qquad (10)$$
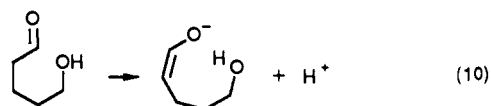
change can be divided into two parts: first, the entropy of cyclization of the hydrogen-bonded enolate and, second, the entropy of deprotonation for an aldehyde. The entropy of cyclization is estimated to be ~-13 eu from a simple analysis of the open-chain rotations.[39] Thus, the $T\Delta S°$ contribution from cyclization is ~-4.5 kcal/mol at $T = 350$ K. The entropy of deprotonation for an aldehyde is approximated by $\Delta S°_{acid}$ of propanal, which equals 22 eu.[8] At $T = 350$ K, the $T\Delta S°$ contribution for deprotonation is ca. 8 kcal/mol. Thus, the total entropy change for the reaction shown above, $\Delta S°_{base}$, is approximately 9 eu, which corresponds to a total $T\Delta S°$ contribution of 3 kcal/mol. Since $\Delta H°_{base} = \Delta G°_{base} + T\Delta S°_{base}$, the enthalpic acidity, $\Delta H°_{base}(X^-)$ $\equiv -\Delta H°$ for protonation of X^-, is calculated to be 350 kcal/mol at $T = 350$ K.

A similar analysis can be used to calculate $\Delta H°_{acid}$ of 2-hydroxytetrahydropyran by use of the measured acidity, $\Delta G°_{acid}$ = 351 kcal/mol. The entropy of deprotonation is approximated by that of a large alcohol: $\Delta S°_{acid}(t\text{-BuOH}) = 22$ eu.[8] Thus, at $T = 350$ K, $\Delta H°_{acid}$ of the hemiacetal equals 359 kcal/mol.

Additional information about the structure of X^- is gained from its electron affinity. The measured EA, 49.6 kcal/mol, is larger than that of a large alcohol $(EA(t\text{-BuO}^\bullet) = 44$ kcal/mol) or of an enolate radical $(EA(EtCHCHO^\bullet) = 38.5$ kcal/mol).[8] The electron affinity of X^- along with its basicity, $\Delta H°_{base}$, can be used to calculate the X–H bond strength. By use of eq 11, the X–H bond strength is calculated to be 86 kcal/mol, significantly less than the expected RO–H bond strength of 104 kcal/mol. This

$$BDE(X-H) = \Delta H°_{base} + EA(X^\bullet) - IP(H) \qquad (11)$$

calculated bond strength is consistent with the expected bond strength of an aldehyde α-hydrogen; for example, the bond strength of $MeCH_2CHO$ is 89 kcal/mol.[8] The 3 kcal/mol difference could be due in part to some cyclic stabilization of the neutral hydroxy aldehyde or possibly to an accumulation of small errors. This bond strength is not consistent with any other structure we can imagine.

The reaction hypersurface for the deprotonation and subsequent rearrangement of the 2-hydroxytetrahydropyran is complex. The rearrangement certainly involves energetic barriers, since it is not possible to observe an equilibrium between the hemiacetal and the hydrogen-bonded enolate ion. The ring opening requires passage through the relatively unstable solvated anion of the

hydroxy aldehyde 9. Since the unrearranged deprotonated hemiacetal anion is never observed, it must be at least slightly higher in energy than 9. The rearrangement product, the hydrogen-bonded enolate ion, on the other hand, must be lower in energy than 9 since reversible deprotonation is never observed.

For the weakest acid where reaction is barely observed (MeSH, $\Delta G°_{acid}$ = 351 kcal/mol), therefore, the energy at the entrance channel must be roughly comparable to that of 9, the solvated anion of the hydroxy aldehyde. This is reasonable since the typical basicity, $\Delta G°_{base}$, of a large alkoxide is ~368 kcal/mol and the stabilizing interaction afforded by the hydrogen-bonded solvent, MeSH, could be expected to lower the energy of the anion of the hydroxy aldehyde by an additional 15–20 kcal/mol.

The probable mechanism for the formation of the enolate ion involves initial formation of the ion–dipole complex of B^- and the hemiacetal 6, followed by proton-transfer forming 7, which could then ring open to form 9. (The hemiacetal could also undergo ring opening via a concerted mechanism to yield 9 directly; however, this pathway appears to be energetically prohibited.[40]) Proton transfer between the solvent and the anion of the hydroxy aldehyde, resulting in formation of 10, followed by proton abstraction at the α-position, would then lead to formation of the solvated enolate ion 11. The overall reaction $6 \rightarrow 10$ is slightly
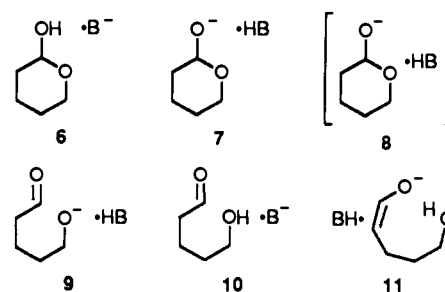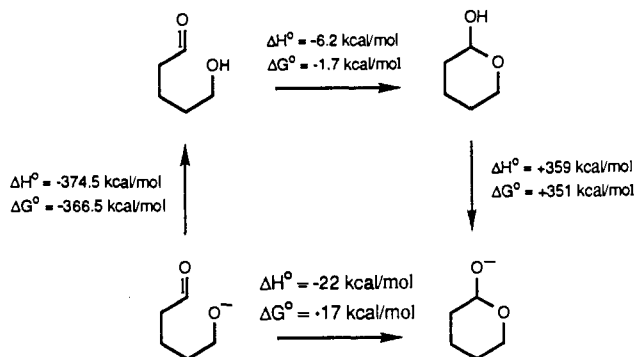
endothermic, owing to the cyclic stabilization of the hemiacetal (see later text). In order for the initial ring opening to occur forming 9, however, the solvent molecule must be transferred from the initial site of negative charge, on the deprotonated hemiacetal, to the developing charge on the hydroxy aldehyde. As illustrated by 8, this necessitates passage through a species where the solvent molecule is not optimally positioned, thereby incurring a loss in solvation energy up to 15 kcal/mol. If the hemiacetal were comparable in acidity to a typical alcohol, then 7 would just be accessible since the difference in acidity between MeSH and a typical alcohol is roughly equal to the solvation stabilization energy in the complex 7. The reaction to form 9 from 7 would then be somewhat endothermic (because of the cyclization energy, see later text), and there would be insufficient energy to form 9. Moreover, there would certainly be insufficient energy to form 8, which lacks the specific solvation of 9. That is, there would not be sufficient energy to desolvate the hemiacetal anion. Since the hemiacetal anion can be desolvated, however, 7 must lie well below the entrance channel so that 8 and 9 are accessible. Thus, the hemiacetal must be a significantly stronger acid than a typical alcohol. Because the reaction is fast, we assume the limiting factor to be the stability of 9 rather than that of 8, and we place the acidity of the hemiacetal as roughly comparable to that of MeSH. In the ensuing discussion, this value, $\Delta G°_{acid}$ = 351 kcal/mol, is taken to be the acidity of the hemiacetal; it is important to keep in mind, however, that the true acidity value could be higher. In fact, the value we have chosen is consistent with other experimental results discussed later.

B. Stability of Cyclic Tetrahedral Adducts. This large acidity for 2-hydroxytetrahydropyran is striking: in enthalpic terms,

(39) Benson, S. W. *Thermochemical Kinetics*; John Wiley and Sons: New York, 1976.

(40) Concerted deprotonation of the hemiacetal yields the anion of the hydroxy aldehyde with the solvent molecule hydrogen-bonded to the carbonyl oxygen rather than to the alkoxide oxygen. This structure would be expected to be considerably higher in energy than the optimally solvated anion of the hydroxy aldehyde 9. Since the unsolvated anion of the hydroxy aldehyde is ~16 kcal/mol less stable than MeS$^-$, it is unlikely that the only slightly solvated anion of the hydroxy aldehyde is energetically attainable.

Model for Tetrahedral Reaction Intermediates

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Scheme III

ΔH° = -6.2 kcal/mol
ΔG° = -1.7 kcal/mol

ΔH° = -374.5 kcal/mol
ΔG° = -366.5 kcal/mol

ΔH° = +359 kcal/mol
ΔG° = +351 kcal/mol

ΔH° = -22 kcal/mol
ΔG° = -17 kcal/mol

Scheme IV

MeOH +

ΔH° = -11 kcal/mol
ΔG° = 0 kcal/mol
2

ΔH° = -381 kcal/mol
ΔG° = -373 kcal/mol
3

ΔH° = +359 kcal/mol
ΔG° = +351 kcal/mol
1

MeO$^-$ +

4

ΔH° = -33 kcal/mol
ΔG° = -22 kcal/mol

$\Delta H^\circ_{acid}(1) \approx 359$ kcal/mol. This is considerably more acidic than simple alcohols, ketones, or aldehydes. In fact, the acidity of its closest alcoholic analogue, cyclohexanol, is 374.5 kcal/mol, 16 kcal/mol less acidic than the hemiacetal.[41] Thus, substitution of an oxygen for a carbon in the β-position greatly increases the stability of the anion relative to the neutral. Since the neutrals are not expected to differ greatly in energy, this implies that the deprotonated hemiacetal anion is very stable.

An interesting consequence of the great stability of the cyclic hemiacetal anion is the large exothermicity of the ionic intramolecular cyclization reaction; i.e., formation of the deprotonated hemiacetal from the deprotonated hydroxy aldehyde is very exothermic. The cyclization energy of the neutral hemiacetal is also exothermic, but to a much smaller degree. Using an experimental measurement of the free energy change for eq 3 in solution[25] and an estimated entropic contribution ($T\Delta S^\circ$) of 4.5 kcal/mol for ring closure,[39] we estimate the enthalpy change for eq 3 to be $\Delta H^\circ_{cyclizn}$ = -6.2 kcal/mol. The cyclization energy for the hemiacetal anion will be equal to the energy difference for the neutrals plus the difference in acidities between the hydroxy aldehyde and the hemiacetal. This relationship is illustrated in Scheme III. The acidity of the hydroxy aldehyde is approximated by that of a large alcohol. The resulting cyclization energy for the deprotonated hemiacetal, shown in large type, is $\Delta H^\circ_{cyclizn}$ ($C_5H_9O_2^-$) = -22 kcal/mol and $\Delta G^\circ_{cyclizn}$($C_5H_9O_2^-$) = -17 kcal/mol. It is important to remember that the hydroxy aldehyde anion also has opportunity for ion–dipole stabilization that could lower the cyclization enthalpy by 10–12 kcal/mol and the cyclization free energy by 6–8 kcal/mol. Even including this stabilization, the tetrahedral hemiacetal anion is still 10 kcal/mol more stable than the hydroxy–aldehyde anion complex.

This large difference in energy between the hemiacetal anion and the alkoxide–aldehyde complex implies that, at least in the case of cyclic compounds, tetrahedral adducts of this type are more stable than their loosely bound ion–molecule counterparts. The relevance of this result to the formation of open-chain adducts in the reactions of alkoxides with aldehydes is discussed in the following text.

C. Open-Chain Tetrahedral Adducts. Although neutral hemiacetals formed by reaction of an alcohol with an aldehyde are enthalpically favored, the decrease in entropy incurred from the loss of three translational degrees of freedom makes the free energy change much less favorable. For example, using group additivity,[39] we find that addition of methanol to acetaldehyde has ΔH° = -11.3 kcal/mol but ΔG° is only -0.1 kcal/mol at T = 350 K. In the case of the cyclic hemiacetal discussed previously, the entropy loss is not as large since formation of the hemiacetal is intramolecular, and thus, no translational degrees of freedom are lost. For this reason, the cyclic hemiacetal can be isolated, whereas most open-chain hemiacetals are less accessible.[42]

As discussed previously, however, the hemiacetal anion is relatively much more stable than the hemiacetal neutral. Thus, even though the neutral open-chain hemiacetal may not be favored,
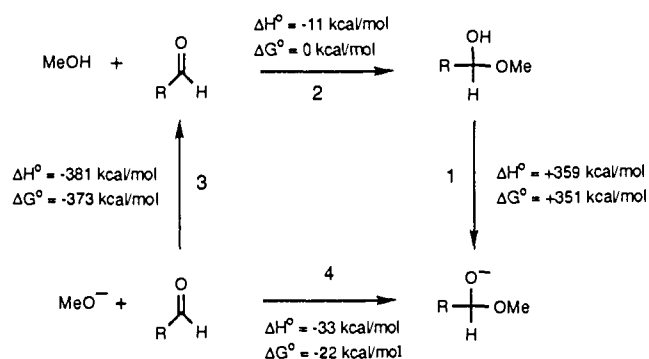
the deprotonated hemiacetal is greatly preferred. This situation is outlined in the thermochemical cycle in Scheme IV.

The acidity of the open-chain hemiacetal (both ΔH°_{acid} and ΔG°_{acid}), step 1 in Scheme IV, is approximated by the acidity of 2-hydroxytetrahydropyran. Since the cyclic hemiacetal is expected to be somewhat destabilized relative to its open-chain analogue due to geometric constraints imposed by the ring, the true acidity of the open-chain hemiacetal is likely to be slightly smaller. However, for the purposes of this discussion, the approximation is qualitatively accurate. As mentioned previously, ΔH° for step 2 is exothermic by 11 kcal/mol and ΔG° ~0 kcal/mol. Step 3 simply involves the deprotonation of methanol, and so the energy change equals the acidity of methanol.[8] The thermodynamic quantities for addition of methoxide to acetaldehyde, step 4, are thus calculated to be ΔH°_{addn} = -33 kcal/mol and ΔG°_{addn} = -22 kcal/mol. This enthalpy change is 11 kcal/mol greater than that calculated for the formation of the cyclic hemiacetal anion. This difference is accounted for in part by the smaller addition energy for the cyclic hemiacetal neutral and by the acidity difference between methanol, used in this example, and the model "large alcohol" used in the previous one. If t-BuO$^-$ were the attacking nucleophile, the enthalpy of addition would be reduced by 6 kcal/mol, the difference in acidity between MeOH and t-BuOH. Again, even taking into account the possibility of a 10–12 kcal/mol ion–dipole stabilization for the alkoxide + aldehyde complex, the tetrahedral species appears to be a stable minimum for these systems.

We can apply this result to a remarkable addition reaction reported by Nibbering and van der Wel.[19] These researchers observed that a methoxide–methanol complex reacts with benzaldehyde to form an aldehyde–methoxide addition product, eq 12. In order for this reaction to proceed, the stabilization gained

MeO$^-$ ·HOMe +

$\rightarrow$

$\left[\begin{array}{c} \end{array} \right]$ + MeOH (12)
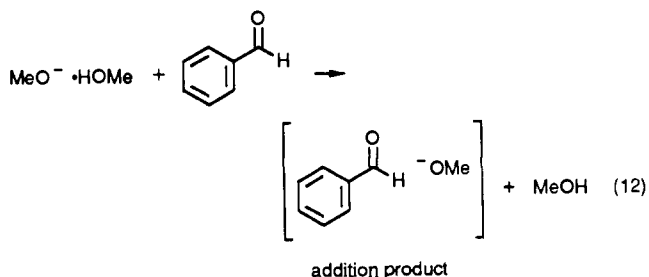
addition product

by forming the aldehyde–methoxide addition product must equal that of the hydrogen-bonded methanol–methoxide complex, measured to be 29.3 kcal/mol.[43] Simple complexation is expected to yield only 10–12 kcal/mol stabilization energy; the stabilization gained would not be expected to be comparable to that of the hydrogen-bonded methanol–methoxide complex. Formation of a tetrahedral adduct, however, *can* yield large amounts of stabilization energy, on the order of 30 kcal/mol. On the basis of

(41) Baer, S. Unpublished results.
(42) Streitwieser, A.; Heathcock, C. H. *Introduction to Organic Chemistry*, 3rd ed.; MacMillan Publishing: New York, 1985; Chapters 14, 27.

(43) (a) Paul, G. J. C.; Kebarle, P. *J. Phys. Chem.* **1990**, *94*, 5184. (b) Meot-Ner, M.; Sieck, L. W. *J. Phys. Chem.* **1986**, *90*, 6687. (c) Meot-Ner, M.; Sieck, L. W. *J. Am. Chem. Soc.* **1986**, *108*, 7525.

this analysis, we suggest that the addition product observed by Nibbering is a covalently bound tetrahedral anion.

The addition reaction of methoxide–methanol plus benzaldehyde proceeds easily, whereas the corresponding reaction of ethoxide–ethanol does not. This result can be understood in terms of Scheme I, the thermochemical cycle for formation of the tetrahedral adduct from the separated nucleophile and carbonyl compound. According to this model, the heat of reaction to form the addition product approximately equals the difference in the electron affinities between the attacking nucleophile and the tetrahedral adduct. The electron affinity of the alkoxide–benzaldehyde adduct would be expected to depend only slightly on the nature of the alkoxide due to its distance from the oxygen bearing the negative charge.[37] The difference in the heats of reaction to form methoxide–benzaldehyde and ethoxide–benzaldehyde from the free alkoxide then reduces to the difference in the electron affinities of methoxide and ethoxide.[8] The heat of reaction to form ethoxide–benzaldehyde is therefore ~3 kcal/mol less exothermic than the heat of reaction to give methoxide–benzaldehyde. This small difference is apparently enough to decrease the tetrahedral adduct formation energy just below the ethanol–ethoxide well depth, ~28 kcal/mol,[44] thereby making addition unfavorable.

The reaction of ethoxide–methanol with benzaldehyde results in formation of both methoxide–benzaldehyde and ethoxide–benzaldehyde. The energetics to give these two products are almost identical, since the methoxide and ethoxide adducts are so similar structurally. The slightly lower stability of ethoxide–methanol compared with ethoxide–ethanol[45] is apparently sufficient to make

the overall reaction exothermic.

These results suggest that the energy differences between the hydrogen-bonded alcohol–alkoxide complexes and the corresponding tetrahedral adducts are extremely small. Slight perturbations such as substitution of ethanol for methanol in the hydrogen-bonded complex are sufficient to make addition endothermic. This hypothesis is supported by equilibrium measurements by Nibbering and co-workers for the addition reaction of methoxide–methanol with benzaldehyde,[19] eq 12; these workers report $\Delta G°_{12} = -0.93$ kcal/mol.

V. Conclusions

Deprotonated 2-hydroxytetrahydropyran has been observed to rearrange to a more stable form. The isomerized structure is assigned as an enolate ion stabilized by an intramolecular hydrogen bond, on the basis of thermochemical arguments and proton-exchange experiments. This stabilized enolate ion is the intramolecular equivalent to the addition product of methoxide and acetaldehyde, observed by Bowie and co-workers.[18]

The large acidity of 2-hydroxytetrahydropyran indicates the stability of deprotonated hemiacetal anions. This acidity is used as a model for the stability of the tetrahedral reaction intermediate formed by addition of an alkoxide to an aldehyde with no enolizable protons. By use of thermochemical arguments to estimate the enthalpy of addition, the formation of the tetrahedral species was found to be exothermic by over 30 kcal/mol. This result suggests that the methoxide–benzaldehyde addition product observed by Nibbering[19] is a tetrahedral species rather than an ion–dipole complex.

(44) The EtOHOEt⁻ stabilization energy was extracted from the MeOHOMe⁻ stabilization energy and the difference in energy between MeOHOMe⁻ and EtOHOEt⁻, measured by Bartmess and co-workers.[45]
(45) Caldwell, G.; Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 4660.

Fragmentations of Gas-Phase Complexes between Alkali Metal Ions and Peptides: Metal Ion Binding to Carbonyl Oxygens and Other Neutral Functional Groups

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Abstract: Collision-induced fragmentations of gas-phase (M + Cat)⁺ complexes between 55 structurally diverse peptides and 5 alkali metal ions, Li⁺, Na⁺, K⁺, Rb⁺, and Cs⁺, are reported. Mechanisms for fragmentation indicate that neither N-terminal $(a_{n-m} + Cat - H)^+$ nor C-terminal $(y_{n-m} + Cat + H)^+$ fragment ions arise from complexes that contain the alkali metal ion bonded to a deprotonated (zwitterionic) carboxylate terminus. In cases in which there is no strongly interacting side chain, the metal ion is most likely bonded to an amide oxygen. Another reaction, which necessitates the metal ion being bonded toward the N terminus as opposed to being bonded to a carboxylate anion, differentiates C-terminal amino acids such as leucine and isoleucine. Decompositions of (M + Cat)⁺ complexes of C-terminal amides generally provide more extensive sequence information than C-terminal carboxylates. Fragmentation patterns, which change with increasing size of the alkali metal ion, are related to more favorable coordinative multisite binding between the larger metal ions and several amide oxygens, in analogy to known chemistry. The fragmentations thus do not reflect aqueous-phase bonding to a zwitterionic species but instead reflect the types of interactions that could occur between a metal ion and binding sites in less hydrophilic interiors of proteins.

Alkali metal ions, especially Na⁺ and K⁺, interact with a variety of biologically important peptides and proteins. Some macrocyclic antibiotic ionophores selectively bind and transport the ions through cell membranes.[1,2] Examples are the cyclic antibiotic

peptide valinomycin, which selectively binds K⁺, and monensin, which binds Na⁺. In contrast, dianemycin nonselectively binds any of the alkali metal ions.[1a] Linear peptides such as the pentadecapeptide gramicidin also bind alkali metal ions and transport them across cell membranes.[1a,c] Alkali metal ions activate some enzymes, and ATPase requires both Na⁺ and K⁺ in various steps

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