# Conformations of Cyclohexyl Rings after Electron Impact

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**Abstract:** The stereochemistries of the electron impact induced McLafferty rearrangement of a series of cyclohexyl acetates and diethyl cyclohexylmalonates are studied using deuterium-labeling techniques. A calculation of the fraction of $\gamma$-hydrogen abstraction occurring from each chair conformer of six cyclohexyl derivatives is accomplished, based on the behavior of the conformationally homogeneous 4-*tert*-butylcyclohexyl derivatives. The results demonstrate a good correlation between the conformer distribution from which fragmentation occurs and the conformer distribution calculated for the precursor neutral molecules before ionization. This result is consistent with the proposal that $\gamma$-hydrogen abstraction is faster than chair–chair interconversion. For these compounds an alternative explanation, that little conformational excitation is produced by electron impact, cannot be excluded by these data. In either case, these results provide additional support for the concept that these cyclohexyl derivatives fragment predominantly from chair conformers, and should assist in the interpretation of stereochemical effects in the mass spectra of cyclohexyl derivatives.

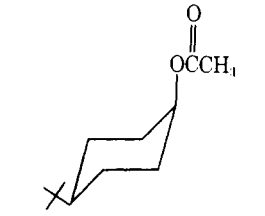
The extreme sensitivity of the mass spectrometric technique and the wealth of structural information present in a typical spectrum make mass spectrometry uniquely useful for determining the gross structures of organic molecules. It is particularly unfortunate, then, that mass spectroscopy has generally proven ineffective at determining molecular stereochemistry; stereochemical assignments on the basis of the electron impact induced behavior of a single stereoisomer are hazardous and rarely attempted.[1,2] One prerequisite for such determinations is detailed knowledge of the stereochemical requirements of appropriate electron impact induced fragmentation reactions involving hydrogen transfer.[3] However, before this information can find extensive application to the determination of molecular stereochemistry, a second prerequisite must be fulfilled; some information about the conformations of ions undergoing fragmentation must be available. If, for example, a fragmentation occurs predominantly from high-energy conformers, observation and interpretation of stereospecific behavior will be difficult. Conversely, if little conformational excitation is imparted by electron impact, and a fragmentation occurs predominantly from a single low-energy conformer with a well-defined and predictable geometry, interpretation of any observed effect will be simplified.

Little attention has been devoted toward estimating the conformational excitation imparted by electron impact. Perhaps the most relevant experiments demonstrated an Arrhenius dependency in the stereoselectivity of the electron impact induced elimination of acetic acid from diastereotopically labeled 2-butyl acetates.[4] This observation has been interpreted as evidence that molecular ions that fragment in rearrangement reactions maintain a close or exact correspondence to the thermal energy (temperature) of the precursor neutrals.[4] This result suggests that the conformer population of electron impact produced ions which will undergo fragmentation with hydrogen transfer should be similar to the conformer population before ionization.

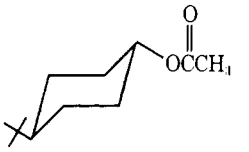
The elegant implication of boat-like conformers in the dehydration of certain cyclohexanols[5] appears at first glance to suggest a contrary conclusion. However, analysis of internuclear distances in a chair-like cyclohexanol suggests that this result is foreordained by the geometric requirements for hydrogen abstraction. Since an axial or equatorial hydroxyl group cannot approach any ring hydrogen atom within the requisite[6,7] 2.5 Å for hydrogen abstraction if the ring remains in a chair conformation, dehydration must occur from a high-energy boat conformation, regardless of the conformational population at any instant. Thus, this result merely demonstrates that, under certain circumstances, high-energy conformers can be reached; it tells little about the actual instantaneous conformer distribution of ions prior to fragmentation.

Cyclohexyl derivatives nevertheless seem particularly appropriate compounds for an investigation into the conformation of ions after electron impact. Acyclic structures characteristically exist in many conformations, some with similar geometries and energies. In contrast, most cyclohexyl rings prefer a single stable chair conformation separated by significant and predictable energy differences from an alternative chair and boat and twist-boat conformations.[8] Since the geometry of the most stable chair conformer is well defined from solution chemistry data, and since there is excellent evidence that ionization does not produce gross alterations of molecular geometry,[9] interpretation of results will be simplified.

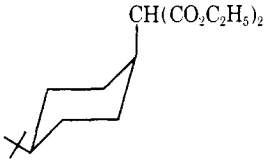
Studies on conformationally constrained cyclohexyl derivatives such as the *cis*- and *trans*-4-*tert*-butylcyclohexyl acetates I and II and the corresponding diethyl malonates III and IV have established the stereoselectivity characteristic of the



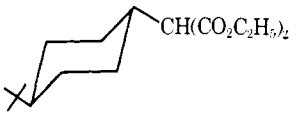

I




II




III




IV

McLafferty rearrangement of these functional groups. Deuterium-labeling experiments have demonstrated that the axial acetates and malonates fragment with very predominant cis-equatorial hydrogen abstraction, while the equatorial acetates and malonates exhibit very predominant trans-equatorial hydrogen abstraction.[10] These results argue that fragmentation is occurring predominantly from ions with a chair-like cyclohexyl ring. For example, the very predominant trans-equatorial hydrogen abstraction exhibited by the equatorial malonate IV is readily rationalized if hydrogen abstraction occurs from the indicated chair conformer. However, the cis hydrogen is more readily accessible to the carbonyl oxygen in most boat conformers. The near absence of any observed cis hydrogen ab-

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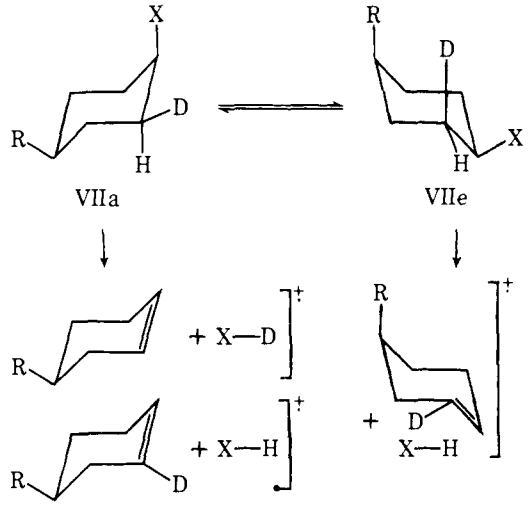
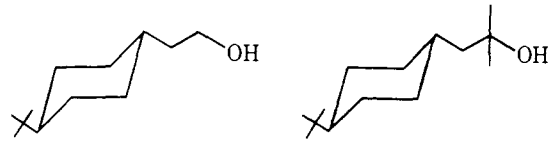
**Scheme I**



VIIa VIIe

1, R = $(CH_3)_3C$; X = $OCOCH_3$
2, R = $(CH_3)_2CH$; X = $OCOCH_3$
3, R = H; X = $OCOCH_3$
4, R = $(CH_3)_3C$; X = $CH(CO_2C_2H_5)_2$
5, R = $(CH_3)_2CH$; X = $CH(CO_2C_2H_5)_2$
6, R = H; X = $CH(CO_2C_2H_5)_2$

straction is inconsistent with extensive fragmentation from boat conformer. The stereoselectivity of the lead tetraacetate induced cyclization of alcohols such as V and VI confirms that



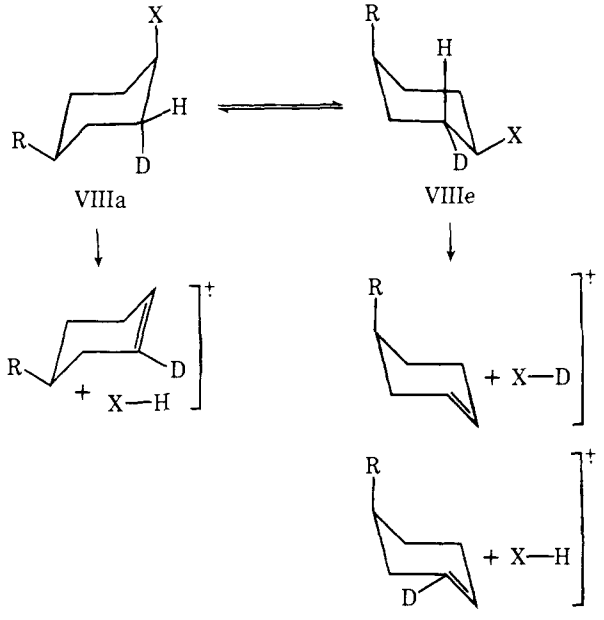
V VI

the observed trans elimination is steric in origin and is characteristic of hydrogen abstraction proceeding through a chair conformer of the cyclohexyl ring.[11]

The conclusion that cyclohexyl derivatives I–IV fragment predominantly from the chair conformation and the observed stereoselectivities permit a direct probe into the conformer populations of fragmenting ions. A structure such as VII (Scheme I), where R is a hydrogen or an alkyl group less bulky than a *tert*-butyl group and X is an acetate or diethyl malonate group, can exist in two chair conformations. The relative stability of the two conformations will depend on the nature of the R and X groups, but should be readily estimated from solution chemistry data. If the McLafferty rearrangement occurs from the axial conformer VIIa, the resulting stereoselectivity should be quantitatively similar to that of the conformationally constrained *cis*-4-*tert*-butylcyclohexyl derivative I or III; considerable deuterium abstraction should occur. Conversely, if fragmentation occurs from the equatorial conformer VIIe, the resulting stereoselectivity should be similar to that of the conformationally constrained *trans*-4-*tert*-butylcyclohexyl derivatives II or IV; little deuterium loss should be observed.

In contrast, if the mass spectral behavior of the trans-deuterated derivative VIII is examined, an opposite result is predicted (Scheme II). Fragmentation from the axial conformer VIIIa should result in negligible deuterium abstraction, while fragmentation from the equatorial conformer VIIIe should result in extensive deuterium loss. In each case, then, a relationship should exist between the extent of deuterium abstraction observed and the fractions of fragmentation occurring from each chair conformation. In an effort to examine the influence of different R and X groups on these fractions, a series of stereospecifically deuterated cyclohexyl acetates and

**Scheme II**



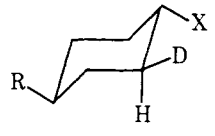
VIIIa VIIIe

1, R = $(CH_3)_3C$; X = $OCOCH_3$
2, R = $(CH_3)_2CH$; X = $OCOCH_3$
3, R = H; X = $OCOCH_3$
4, R = $(CH_3)_3C$; X = $CH(CO_2C_2H_5)_2$
5, R = $(CH_3)_2CH$; X = $CH(CO_2C_2H_5)_2$
6, R = H; X = $CH(CO_2C_2H_5)_2$

malonates with cis or trans oriented substituents at C-4 was prepared and their mass spectra were examined. The results of these experiments are described below.

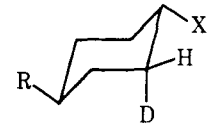
## Results

The McLafferty rearrangement of cyclohexyl acetates results in the extrusion of neutral acetic acid and the detection of an ion corresponding formally to ionized cycloalkene.[10] Thus, the stereoselectivity of the fragmentation can be assessed from the relative intensities of the peaks corresponding to ionized cycloalkene and cycloalkene-$d_1$ in the mass spectra of stereospecifically labeled compounds of the general formula VII, VIII, IX, and X. The data presented in Table I were obtained at an ionizing voltage of 70 eV and a source temperature of 100–120 °C. The indicated peak intensity ratios are cor-



IX

1, R = $(CH_3)_3C$; X = $OCOCH_3$
2, R = $(CH_3)_2CH$; X = $OCOCH_3$
3, R = $(CH_3)_3C$; X = $CH(CO_2C_2H_5)_2$
4, R = $(CH_3)_2CH$; X = $CH(CO_2C_2H_5)_2$



X

1, R = $(CH_3)_3C$; X = $OCOCH_3$
2, R = $(CH_3)_2CH$; X = $OCOCH_3$
3, R = $(CH_3)_3C$; X = $CH(CO_2C_2H_5)_2$
4, R = $(CH_3)_2CH$; X = $CH(CO_2C_2H_5)_2$

rected for the presence of small amounts of unlabeled acetate, the natural abundance of $^{13}C$, and the occurrence of a small amount of non-site-specific hydrogen abstraction.[12] The extent

**Table I.** Electron Impact Induced Acetic Acid Loss from Stereospecifically Labeled Cyclohexyl Acetates

| compd | $(M^{+\cdot} - DOAc)/(M^{+\cdot} - DOAc + M^{+\cdot} - HOAc)$[a,b] | $(M^{+\cdot} - DOAc/M^{+\cdot} - DOAc + M^{+\cdot} - HOAc)$*cis-d*/$(M^{+\cdot} - DCAc/M^{+\cdot} - DOAc + M^{+\cdot} - HOAc)$*trans-d* |
|---|---|---|
| *cis*-4-*tert*-butylcyclohexyl-*cis*-2-*d* acetate (VII-1) | 0.34 ± 0.03 | 8.5 |
| *cis*-4-*tert*-butylcyclohexyl-*trans*-2-*d* acetate (VIII-1) | 0.04 ± 0.01 | |
| *cis*-4-isopropylcyclohexyl-*cis*-2-*d* acetate (VII-2) | 0.36 ± 0.02 | 7.2 |
| *cis*-4-isopropylcyclohexyl-*trans*-2-*d* acetate (VIII-2) | 0.05 ± 0.01 | |
| cyclohexyl-*cis*-2-*d* acetate (VII-3) | 0.14 ± 0.01 | 0.5 |
| cyclohexyl-*trans*-2-*d* acetate (VIII-3) | 0.26 ± 0.01 | |
| *trans*-4-isopropylcyclohexyl-*cis*-2-*d* acetate (X-2) | 0.06 ± 0.02 | 0.2 |
| *trans*-4-isopropylcyclohexyl-*trans*-2-*d* acetate (IX-2) | 0.29 ± 0.02 | |
| *trans*-4-*tert*-butylcyclohexyl-*cis*-2-*d* acetate (X-1) | 0.07 ± 0.01 | 0.2 |
| *trans*-4-*tert*-butylcyclohexyl-*trans*-2-*d* acetate (IX-1) | 0.30 ± 0.02 | |

[a] Results are the average of at least four determinations at 110 ± 10 °C, and are corrected for unlabeled acetate, $^{13}C$ effects, and hydrogen abstraction from other than C-2 and C-6. [b] Error limits are statistically derived and represent 95% confidence limits.

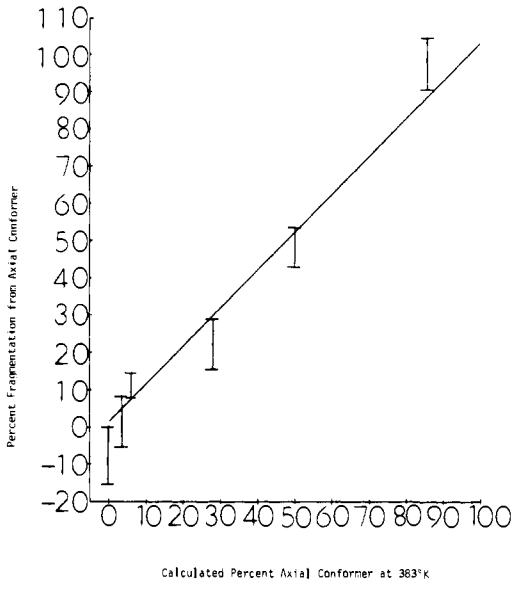



**Figure 1.** Plot of the percent fragmentation from the chair conformer with an axial functional group (calculated from mass spectral data) vs. the percent concentration of that conformer among neutral molecules at 383 K.

of the latter process was, in every case, calculated from the mass spectra of the corresponding *2,2,6,6-d*$_4$ derivative. Error limits are statistically derived from the results of at least four separate sample introductions and correspond to 95% confidence limits. No statistically significant variation in the indicated ratio could be detected as the ionizing voltage was varied from 70 eV to threshold (13 eV nominal). First and (occasionally) second field-free region metastables were detectable, but too weak for accurate measurement of their intensities. Although no significant variation of the peak intensity ratios was observed as the source temperature was varied over 100–120 °C, modest variation was observed when the source temperature was altered more drastically.

Peaks corresponding to ionized cycloalkene can also be generated by electron impact on pyrolytically generated alkene. The relatively cool source and inlet system temperatures used in these experiments were chosen to minimize these processes. Several lines of evidence suggest that the ions studied here do, in fact, arise by electron impact on the cycloalkyl acetate. First, these acetates survive gas chromatography with no detectable decomposition at temperatures 100 °C higher than those utilized in the mass spectrometer. More tellingly, the electron impact induced loss of acetic acid from equatorial acetates is largely trans;[10] the pyrolytic process exhibits clean cis stereochemistry.[10] The stereochemistries observed in these studies, particularly the systematic variations with the nature and orientation of the 4-alkyl group, are inconsistent with significant occurrence of pyrolytic processes.

The McLafferty rearrangements of the diethyl cyclohexylmalonates studied here result in the elimination of cycloalkene and formation of a charged species corresponding formally to the enol of diethyl malonate.[10] The stereoselectivity of the elimination can be assessed from the relative intensities of the $C_7H_{12}O_4$ and $C_7H_{11}DO_4$ peaks in the mass spectra of stereospecifically labeled compounds of general formulas VII, VIII, IX, and X. The data in Table II, obtained at 70 eV and a source temperature of 100–120 °C, are corrected for isotopic impurities, the natural abundance of $^{13}C$, and the presence of a modest "McLafferty + 1".[13] Since inspection of the mass spectra of the *2′,2′,6′,6′-d*$_4$ analogues provided no evidence for non-site-specific hydrogen abstraction, no correction for such processes was necessary. Again, no significant variation in the corrected relative intensities of these peaks was apparent as the ionization voltage was varied from 70 eV to the threshold for accurate measurement. However, since the relative intensity of the "McLafferty + 1" peak increases markedly at low ionizing voltage,[13] the magnitude of the correction required, and thus the error limit, increases substantially. Study of the stereochemistry of the elimination among metastable ions was precluded by the weak metastable peaks observed for the McLafferty rearrangement, and by the confounding effect of the more intense metastable peaks corresponding to the "McLafferty + 1" process.

Preparation of Table III and Figure 1 requires calculation of the relative concentrations of the two chair conformers possible for each neutral molecule. There is ample precedent

**Table II.** Electron Impact Induced Cycloalkene Loss from Stereospecifically Labeled Diethyl Cyclohexylmalonates

| compd | $[C_7H_{11}DO_4^{+\cdot}]/[C_7H_{12}O_4]^{+\cdot} + [C_7H_{11}DO_4]^{+\cdot}$ [a,b] | $([C_7H_{11}DO_4^{+\cdot}]/[C_7H_{12}O_4^{+\cdot} + C_7H_{11}DO_4^{+\cdot}]cis\text{-}d)/([C_7H_{11}DO_4^{+\cdot}]/[C_7H_{12}O_4^{+\cdot} + C_7H_{11}DO_4^{+\cdot}]trans\text{-}d)$ |
|---|---|---|
| diethyl *cis*-4′-*tert*-butylcyclohexyl-*cis*-2′-*d*-malonate (VII-4) | 0.45 ± 0.02 | 22 |
| diethyl *cis*-4′-*tert*-butylcyclohexyl-*trans*-2′-*d*-malonate (VIII-4) | 0.02 ± 0.02 | |
| diethyl *cis*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (VII-5) | 0.25 ± 0.01 | 1.5 |
| diethyl *cis*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate (VIII-5) | 0.17 ± 0.02 | |
| diethyl cyclohexyl-*cis*-2′-*d*-malonate (VII-6) | 0.09 ± 0.005 | 0.24 |
| diethyl cyclohexyl-*trans*-2′-*d*-malonate (VIII-6) | 0.38 ± 0.01 | |
| diethyl *trans*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (X-4) | 0.03 ± 0.02 | 0.07 |
| diethyl *trans*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate (IX-4) | 0.43 ± 0.02 | |
| diethyl *trans*-4′-*tert*-butylcyclohexyl-*cis*-2′-*d*-malonate (X-3) | 0.06 ± 0.01 | |
| diethyl *trans*-4′-*tert*-butylcyclohexyl-*trans*-2′-*d*-malonate (IX-3) | 0.45 ± 0.02 | 0.13 |

[a] Results are the average of at least four determinations at 110 ± 10 °C, and are corrected for unlabeled compound and $^{13}C$ effects. [b] Error limits are statistically derived and represent 95% confidence limits.

**Table III.** Percent of McLafferty Rearrangement of Cyclohexyl Acetates and Malonates Proceeding through a Conformation with an Axial Functional Group

| compd | % axial before ionization[a] | % fragmentation through axial conformer: individual derivative[b] | % fragmentation through axial conformer: best value[c] |
|---|---|---|---|
| *cis*-4-isopropylcyclohexyl-*cis*-2-*d* acetate (VII-2) | 86 | 110 ± 20 | 98 ± 7 |
| *cis*-4-isopropylcyclohexyl-*trans*-2-*d* acetate (VIII-2) | | 96 ± 8 | |
| cyclohexyl-*cis*-2-*d* acetate (VII-3) | 28 | 26 ± 9 | 22 ± 7 |
| cyclohexyl-*trans*-2-*d* acetate (VIII-3) | | 15 ± 11 | |
| *trans*-4-isopropylcyclohexyl-*cis*-2-*d* acetate (X-2) | 3 | 0 ± 8 | 1 ± 7 |
| *trans*-4-isopropylcyclohexyl-*trans*-2-*d* acetate (IX-2) | | 4 ± 14 | |
| diethyl *cis*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (VII-5) | 50 | 49 ± 6 | 53 ± 5 |
| diethyl *cis*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate (VIII-5) | | 65 ± 10 | |
| diethyl cyclohexyl-*cis*-2′-*d*-malonate (VII-6) | 6 | 8 ± 4 | 11 ± 3 |
| diethyl cyclohexyl-*trans*-2′-*d*-malonate (VIII-6) | | ± 7 | |
| diethyl *trans*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (X-4) | 0 | −10 ± 10 | −8 ± 8 |
| diethyl *trans*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate (IX-4) | | −5 ± 5 | |

[a] Calculated composition before electron impact assuming $-\Delta G$ = 0.7 kcal/mol for $OCOCH_3$, 2.1 kcal/mol for $i$-$C_3H_7$, and 2.1 kcal/mol for $CH(CO_2C_2H_5)_2$ and a source temperature of 110 °C. [b] Calculated for each labeled compound using data and error limits in Tables I and II and using eq 2. [c] Value corresponds to least-squared error in combining each pair of data points.

to justify the assumption that the neutral molecules are thermally equilibrated with the source walls.[14] Therefore, conformer populations were calculated assuming a temperature of 110 °C, and using tabulated values for the free-energy differences between axial and equatorial groups.[8] Since the free-energy difference between axial and equatorial diethyl malonate groups has not been reported, an estimate was obtained by an NMR method. The conformer population of diethyl *cis*-4′-isopropylcyclohexyl malonate was determined by comparison of the chemical shift of the C-2 methine proton in the spectrum of that compound with the corresponding chemical shifts in the spectra of the conformationally homogeneous diethyl-2-decalyl malonates.[15] Since these experiments led to the conclusion that, within experimental error, equal concentrations of the two chair conformers were present, the $\Delta G$ values of a diethyl malonate and an isopropyl group must be similar; a value of 2.1 kcal/mol was used in these calculations.

The data in Tables I and II can be used to calculate the extent to which a particular compound undergoes McLafferty rearrangement from each chair conformer if several reasonable assumptions are made. First, it must be assumed that the stereoselectivity of the fragmentation of the conformationally homogeneous *cis*- and *trans*-4-*tert*-butylcyclohexyl acetates and malonates is quantitatively identical with respectively the stereoselectivity of fragmentation of the conformer with an axial functional group and the conformer with an equatorial functional group in the less constrained molecules studied here. Essentially the same assumption is commonly made in evaluating the results of solution-chemistry experiments on cyclohexyl derivatives, and has usually been found to be a valid approximation.[16] Since the error limits reported in Tables I and II are not negligible, it seems likely that the accuracy of this approximation is sufficient for this investigation. Second, it must be assumed that the extent of second-generation fragmentation from the McLafferty rearrangement ions is independent of their origins. If, for example, the McLafferty ion formed from an axial conformer undergoes further fragmentation more extensively than the corresponding ion formed from an equatorial conformer, the decreased intensity of the axial conformer's ion would lead to an underestimation of the fraction of reaction proceeding through that conformer. Fortunately, there is good reason to believe that this assumption is valid. As already mentioned, the relative intensities of the peaks corresponding to cis elimination and trans elimination do not change significantly as the ionizing voltage is varied from 70 eV to threshold. Since second-generation ions are markedly suppressed at low ionizing voltages, this result is inconsistent with differential fragmentation of the McLafferty ions at 70 eV. This result also seems plausible on an a priori basis. The McLafferty ions and neutrals formed by reaction from the two chair conformers are reasonably formulated as the same structures, and are expected to have comparable internal energies. Thus, the second-generation fragmentations of these ions should occur to a similar extent.

If these assumptions are valid, a simple algebraic procedure permits determination of the fraction of fragmentation occurring from each conformer. For example, for cis-substituted cis-deuterated compounds of general structure VII

$$F_r = F_{ax}(Ax) + F_{eq}(Eq) \quad (1)$$

where $F_{ax}$ is the fraction of McLafferty peak intensity corresponding to cis deuterium abstraction in the cis-deuterated *cis*-4-*tert*-butyl compound VII-1 or VII-4, $F_{eq}$ is the fraction of McLafferty peak intensity corresponding to cis deuterium abstraction in the cis-deuterated *trans*-4-*tert*-butyl compound X-1 or X-3, and $F_r$ is the fraction of peak intensity corresponding to deuterium abstraction in the cis deuterated cis-4-substituted compound VII. The quantities (Ax) and (Eq) are the fractions of McLafferty fragmentation proceeding through respectively conformers VIIa and VIIe. Since (Ax) + (Eq) = 1, eq 1 can be solved for the fraction of McLafferty fragmentation proceeding through the conformer with the functional group axial (VIIa):

$$(Ax) = \frac{F_r - F_{eq}}{F_{ax} - F_{eq}} \quad (2)$$

The same relationship applies to the spectra of cis-substituted trans-deuterated compounds of general structure VIII, if $F_{ax}$ is redefined as the fraction of McLafferty peak intensity corresponding to trans deuterium abstraction in the trans-deuterated *cis*-4-*tert*-butyl compound VIII-1 or VIII-4, $F_{eq}$ is the fraction of McLafferty peak intensity corresponding to trans deuterium abstraction in the trans-deuterated *trans*-4-*tert*-butyl compound IX-1 or IX-3, and $F_r$ is the corresponding peak intensity in the spectrum of the trans-deuterated 4-alkyl compound. The quantities (Ax) and (Eq) now are the fractions of McLafferty fragmentation proceeding through respectively conformers VIIIa and VIIIe. Similar relationships can be derived and used to calculate the fraction of reaction proceeding through a particular chair conformer in the trans-4-substituted cyclohexyl derivatives. The results of these calculations appear in Table III. It is notable that the error limits for the fraction of fragmentation proceeding through the axial conformer are appreciable. However, the indicated limits generally correspond to an uncertainty of 1–2% in the relative intensities of the peaks corresponding to deuterium abstraction and protium abstraction. It therefore seems unlikely that further experimentation in these laboratories would produce dramatically more precise results. It seems likely that, to a first approximation, the fraction of fragmentation proceeding through a particular conformer will not depend on the stereochemistry of the deuterium.[17] Therefore, the data for each pair of deuterated compounds have been combined using the principle of least-squared error to generate a single best value.[18] The results of these calculations also appear in Table III.

## Discussion

Consideration of the results in Tables I–III leads to an immediate conclusion: even a modest energy difference between two conformers is sufficient to produce very predominant fragmentation from the more stable conformer. For example, *cis*-4-isopropylcyclohexyl acetate can exist in two chair conformers (cf. VIIa-2 and VIIe-2); the conformation with an axial acetate group (VIIa-2) is more stable by about 1.2 kcal/mol. The results in Table III indicate that the McLafferty rearrangement occurs from this conformer more than 90% of the time. Similarly, the two chair conformers of diethyl cyclohexyl malonate differ in stability by about 2.1 kcal/mol. The more stable conformer (equatorial malonate group) accounts for about 90% of the McLafferty rearrangement. The observation that stability differences of 2 kcal/mol or even less are sufficient to control the conformation from which reaction occurs is an important one. It suggests that, for many conformationally mobile systems and fragmentation reactions, stereochemically dependent differences in mass spectral behavior can be interpreted on the basis of the geometry of the most stable conformer, even if the stability difference between conformers is not large. This observation is significant if mass spectral behavior is to find eventual application to the solution of stereochemical problems.

A number of explanations could account for these results, depending on the relative rates of chair–chair interconversion and $\gamma$-hydrogen transfer. If the former process is the more rapid, these data require that little conformational excitation is imparted by electron impact to those ions eventually undergoing the McLafferty rearrangement. It is notable that Green has reached a similar conclusion using a very different approach.[4] However, an alternative explanation for these results postulates that $\gamma$-hydrogen transfer is faster than chair–chair interconversion. If so, $\gamma$-hydrogen abstraction will occur from whatever chair conformation a particular molecule is in at the instant of ionization. This will lead to a correlation between the fraction of $\gamma$-hydrogen abstraction from a particular conformer and the relative concentration of that conformer before ionization. Figure 1 is a plot of the fraction of $\gamma$-hydrogen abstraction proceeding through the axial conformer vs the calculated concentration of that conformer at the source temperature. The two variables are well correlated ($R = 0.98$); the best least-squared line has a $y$ intercept of 0.01 and a slope of 1.08. The near-unit slope then indicates that the "yield" of McLafferty ion from the two conformers is about equal; the high correlation confirms that the "yield" from a particular conformer is insensitive to the steric environment of the C-4 alkyl group. Since the relative stabilities of the two

chair conformers can be accurately estimated from solution-chemistry data, the data in Table III can be used to calculate the temperature of the neutrals in the mass spectrometer's source. These data best fit a temperature of 353 ± 75 K (error limit statistically derived) in good agreement with the actual source temperature (383 ± 10 K). This result raises the possibility that extensions of these experiments could permit study of the conformations of molecules in the gas phase.

The preceding analysis assumes that γ-hydrogen abstraction is fast compared to chair–chair interconversion. The evidence supporting this assumption is not strong. The energy barrier for chair–chair interconversion is well-known from solution-chemistry data ($\Delta H^{\ddagger}$ = 8.3 kcal/mol, $\Delta S^{\ddagger}$ = −11 eu for a typical monosubstituted cycloalkane[19]). However, the corresponding parameters for the hydrogen-abstraction step of the McLafferty rearrangement of even very simple molecules have not been determined.[20] Theory predicts a $\Delta S^{\ddagger}$ of −8 to −10 eu for γ-hydrogen abstraction in these derivatives, since two rotational degrees of freedom are lost in the transition state.[21] Estimation of $\Delta H^{\ddagger}$ for γ-hydrogen abstraction is more difficult, although the very low isotope effects characteristic of these reactions are clearly consistent with a small $\Delta H^{\ddagger}$.[10,22] Another fact that may be relevant to the problem is that γ-hydrogen transfer occurs within $10^{-12}$ s for many carbonyl compounds,[23] even at the low internal energies characteristic of field ionization.[24] In contrast, the rate of chair–chair interconversion of neutral cyclohexyl compounds at 110 °C is about six orders of magnitude slower. However, since the excitation imparted to these derivatives by electron impact is unknown, ring interconversion of ions could conceivably be much faster than for neutrals. Further, the molecules studied here are more sterically constrained than the subjects of the field ionization studies; attainment of the optimal transition-state geometry for γ-hydrogen transfer may be slowed by the bulk of the cyclohexyl ring. Thus, although it seems plausible to propose that γ-hydrogen transfer is faster than ring interconversion, additional studies will be required before the relative rates of these processes can be rigorously evaluated. Attempts to study these fragmentations among longer lived, less energetic ions have been frustrated by the very weak first field-free region metastables observed for these processes and the more intense metastable corresponding to the "McLafferty + 1" process.[10]

Whatever the relative rates of γ-hydrogen abstraction and ring interconversion, several additional observations are worthy of note. The close correlation observed between the fraction of axial conformer present at ionization and the fraction of reaction from that conformer lends strong support to the conclusion[10] that hydrogen abstraction is, in each case, occurring predominantly from chair conformers. It is unlikely that this correlation would be observed if fragmentation occurred from boat conformers to a significant extent.

Finally, it should be noted that inspection of Figure 1 indicates that the data points for acetates and malonates lie, within experimental error, on the same line. Acetate and malonate groups differ considerably in their steric and electronic characteristics. The McLafferty rearrangement of these compounds results in very different products (cycloalkene and enolic diethyl malonate). The remarkably similar behavior exhibited by the groups suggests that the observed stereochemical effects may eventually prove characteristic of many different McLafferty-type rearrangements.[10]

## Conclusions

The results of these experiments are consistent with the proposal that electron impact imparts little additional conformational excitation to molecules that will eventually fragment in rearrangement reactions; these data are consistent with a "conformational temperature" after ionization equal to or near that of the precursor neutral molecules. An alternative explanation for the observed stereoselectivities seems more likely; it postulates that γ-hydrogen abstraction is much faster than chair–chair interconversion. Perhaps the most important results obtained here are empirical. There is a good correlation between the conformer distribution of the neutral molecules and the fraction of McLafferty rearrangement observed from a particular conformer. Even in cases where the stability difference between two chair conformers was modest (ca. 2 kcal/mol), more than 90% of the McLafferty rearrangement involved the reaction of the more stable conformer. If this result proves to be fairly general for other molecular structures and other fragmentation reactions, interpretations of stereospecific mass spectral behavior will be simplified.

## Experimental Section[25,26]

***cis*-4-Isopropylcyclohexyl-*trans*-2-*d* acetate (VIII-2)** was prepared by a procedure analogous to that utilized for the generation of the corresponding 4-*tert*-butyl derivative.[10] Epoxidation of 4-isopropylcyclohexene with *m*-chloroperbenzoic acid,[27] followed by ring opening with $LiAlD_4$–$AlCl_3$,[28,29] gave a mixture of *cis*-4-isopropylcyclohexanol-*trans*-2-*d* and *trans*-3-isopropylcyclohexanol-*trans*-4-*d*. The mixture was converted into the corresponding 3,5-dinitrobenzoates according to the procedure of Stork and White.[30] Repeated recrystallizations (hexane) gave pure *cis*-4-isopropylcyclohexyl-*trans*-2-*d* 3′,5′-dinitrobenzoate, mp 102–104 °C. A sample of authentic *cis*-4-isopropylcyclohexanol (isolated from the commercially available[31] mixture of cis and trans alcohols by column chromatography) converted to the 3,5-dinitrobenzoate exhibited an identical melting point and an undepressed mixture melting point with the dinitrobenzoate of the labeled alcohol; both dinitrobenzoates exhibited spectra consistent with their structures, and essentially identical with each other. NMR: δ 0.94 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 5.41 (1 H, m, >CHOCOPh), 9.19 (3 H, m, aromatic protons).

Hydrolysis of the ester generated *cis*-4-isopropylcyclohexanol-*trans*-2-*d* whose spectral characteristics agreed closely with those reported for the unlabeled compound,[30] and which possessed a gas chromatographic retention time identical with that of an authentic sample of unlabeled alcohol. Acetylation in the usual fashion[10] generated *cis*-4-isopropylcyclohexyl-*trans*-2-*d* acetate: NMR δ 0.82 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 1.98 (3 H, s, $-OCOCH_3$), 4.93 (1 H, m, >CHOCO); IR ($CHCl_3$) 1723 $cm^{-1}$ (ester C=O); mass spectrum no molecular ion, base peak at *m/e* 125 ($M^{+\cdot}$ − HOAc). Since no molecular ion was detected in the acetate mass spectrum, the alcohol was converted to the corresponding trimethylsilyl derivative. The trimethylsilyl ether exhibited $M^{+\cdot}$ at *m/e* 215 and $M^{+\cdot} - CH_3$ at *m/e* 200, and demonstrated an isotopic purity of 98% *d*.

***cis*-4-Isopropylcyclohexyl-*cis*-2-*d* acetate (VII-2) and *trans*-4-isopropylcyclohexyl-*cis*-2-*d* acetate (X-2)** were prepared by procedures analogous to those utilized for the generation of the corresponding 4-*tert*-butyl derivatives.[10] Deuterioboration of 4-isopropylcyclohexene followed by careful oxidation with cold alkaline $H_2O_2$[28] generated a mixture of four cyclohexanols. Careful column chromatography separated the axial alcohols (*cis*-4-isopropylcyclohexanol-*cis*-2-*d* and *trans*-3-isopropylcyclohexanol-*cis*-6-*d*) from the equatorial alcohols (*trans*-4-isopropylcyclohexanol-*cis*-2-*d* and *cis*-3-isopropylcyclohexanol-*cis*-6-*d*). Both mixtures were converted to the corresponding 3,5-dinitrobenzoates.[30] Isolation of pure *cis*-4-isopropylcyclohexanol-*cis*-2-*d* was by a procedure exactly analogous to that described above for the *trans*-2-*d* derivative. The pure dinitrobenzoate, alcohol, and acetate exhibited physical and spectral characteristics virtually identical with those reported for the *trans*-2-*d* derivative. The trimethylsilyl ether exhibited an isotopic composition of 98% *d*.

Separation of the desired dinitrobenzoate of *trans*-4-isopropylcyclohexanol-*cis*-2-*d* was accomplished by repeated recrystallization of the dinitrobenzoate mixture (hexane). The pure dinitrobenzoate exhibited mp 122–123 °C (lit.[30] 123–123.7 °C). An authentic sample of unlabeled *trans*-4-isopropylcyclohexyl 3′,5′-dinitrobenzoate was prepared and observed to exhibit very similar physical and spectral characteristics and an undepressed mixture melting point with the labeled compound. NMR: δ 0.91 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 5.01 (1 H, m, >CHOCOPh), 9.18 (3 H, m, aromatic protons); IR ($CHCl_3$) 1722 $cm^{-1}$ (ester C=O).

Hydrolysis generated *trans*-4-isopropylcyclohexanol-*cis*-2-*d* whose

physical and spectral characteristics agreed closely with those reported for the unlabeled compound.[32] The corresponding acetate (X-2) exhibited NMR $\delta$ 0.79 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 1.93 (3 H, s, $-OCOCH_3$), 4.56 (1 H, br m, >CHOCO–); IR ($CHCl_3$) 1715 $cm^{-1}$ (ester C=O); mass spectrum no molecular ion, base peak at $m/e$ 125 ($M^+ \cdot - HOAc$). The trimethylsilyl ether was prepared from the labeled alcohol and exhibited $M^+$ at 215 and $M^+ - 15$ at $m/e$ 200; an isotopic purity of 98% $d$ was calculated.

***trans*-4-Isopropylcyclohexyl-*trans*-2-*d* acetate (IX-2)** was prepared by procedures analogous to those used for the generation of the corresponding 4-*tert*-butyl derivative.[10] A solution of 150 mg of *cis*-4-isopropylcyclohexanol-*cis*-2-*d* in 10 mL of reagent acetone was treated with Jones reagent at 0 °C; the ice bath was removed and the mixture stirred for 10 min. After removal of acetone sub vacuo, the mixture was diluted with 10 mL of $H_2O$, extracted into ether, washed with $H_2O$, and dried ($MgSO_4$). The ether solution was concentrated to about 5 mL under reduced pressure and immediately added to a slurry of $LiAlH_4$ (500 mg) in dry ether (25 mL). After overnight reflux, the excess hydride was decomposed and the alcohol mixture isolated by an extractive procedure. Gas chromatographic analysis indicated that the mixture was predominantly (ca. 80%) equatorial alcohol. Preparative TLC ($Al_2O_3$ plates, PhH (3)-$CH_2Cl_2$ (7) eluent) gave pure *trans*-4-isopropylcyclohexanol-*trans*-2-*d* (80 mg). The alcohol, acetate, and trimethylsilyl ether exhibited physical and spectral characteristics in good agreement with those reported for the corresponding *cis*-2-*d* compounds.[33] The mass spectrum of the trimethylsilyl derivative indicated an isotopic purity of 89% $d$.

**Diethyl *trans*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (X-4), diethyl *trans*-4′-isopropyl-*trans*-2′-*d*-malonate (1X-4), diethyl *cis*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate (VII-5), and diethyl *cis*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate (VIII-5)** were prepared by analogy to the procedures used for the corresponding 4′-*tert*-butyl compounds. Conversion of the appropriate labeled cyclohexanol to the corresponding tosylate,[34] followed by displacement with the sodium salt of diethyl malonate,[10,30] generated the desired diethyl malonates. The mass spectra of these compounds did not exhibit a significant molecular ion, but did exhibit a $M^+ - OC_2H_5$ peak at $m/e$ 240.

Diethyl *trans*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate and diethyl *trans*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate exhibited NMR $\delta$ 0.86 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 1.26 (6 H, t, $J$ = 7.0 Hz, $OCH_2CH_3$), 3.12 (1 H, d, $J$ = 8.5 Hz, $-CH(CO_2R)_2$), 4.12 (4 H, q, $J$ = 7.0 Hz, $OCH_2CH_3$); IR 1735 and 1755 $cm^{-1}$ (ester C=O).

Diethyl *cis*-4′-isopropylcyclohexyl-*cis*-2′-*d*-malonate and diethyl *cis*-4′-isopropylcyclohexyl-*trans*-2′-*d*-malonate exhibited NMR $\delta$ 0.88 (6 H, d, $J$ = 6.0 Hz, $-CH(CH_3)_2$), 1.25 (6 H, t, $J$ = 7.0 Hz, $OCH_2CH_3$), 3.32 (1 H, d, $J$ = 10.5 Hz, $-CH(CO_2R)_2$), 4.14 (4 H, q, $J$ = 7.0 Hz, $-OCH_2CH_3$); IR ($CHCl_3$) 1735 and 1755 $cm^{-1}$ (ester C=O).

**Cyclohexyl-*cis*-2-*d* acetate (VII-3)** was prepared by the deuterioboration–oxidation of cyclohexene,[10,28] followed by acetylation of the resulting alcohol. Both acetate and alcohol exhibited NMR and IR spectra and gas chromatographic behavior identical with those of the unlabeled compounds. The trimethylsilyl ether exhibited a molecular ion at $m/e$ 173 and a peak of $m/e$ 158 corresponding to loss of a methyl group. The $Me_3Si$ derivative exhibited an isotopic composition of 98% $d$.

**Cyclohexyl-*trans*-2-*d* acetate (VIII-3)** was prepared by $LiAlD_4$–$AlCl_3$-induced ring opening of cyclohexene oxide,[10,28] followed by acetylation of the resulting alcohol. Both acetate and alcohol exhibited NMR and IR spectra and gas chromatographic behavior identical with those of the unlabeled compounds. The corresponding trimethylsilyl ether indicated an isotopic purity of 98% $d$.

**Diethyl cyclohexyl-*cis*-2′-*d*-malonate (VII-6) and diethyl cyclohexyl-*trans*-2′-*d*-malonate (VIII-6)** were prepared from appropriately labeled cylohexanols by procedures analogous to those used in preparation of the corresponding 4-*tert*-butyl compounds. The labeled compounds exhibited boiling point (103–107 °C at 1.4 mm), gas chromatographic, and spectral behavior similar to those of diethyl cyclohexylmalonate:[35] NMR $\delta$ 1.27 (6 H, t, $J$ = 7.0 Hz, $-OCH_2CH_3$), 3.16 (1 H, d, $J$ = 9.0 Hz, $-CH(CO_2R)_2$), 4.20 (4 H, q, $J$ = 7.0 Hz, $-OCH_2CH_3$); IR ($CHCl_3$) 1730 and 1750 $cm^{-1}$ (ester C=O).

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(26) The nomenclature used in the text of this paper is consistent with that used in previous work[10,11] but is not in strict accord with current *Chemical Abstracts* indexing nomenclature. For example, under the *Chemical Abstracts* system compounds VIII-1, VIII-2, and VIII-3 are (1$\alpha$,2$\beta$,4$\alpha$)-4-alkylcyclo-

hexan-2-*d*-ol acetates, while X-1, X-2, and X-3 are (1α,2α,4β)-4-alkylcyclohexan-2-*d*-ol acetates. According to the IUPAC rules of organic nomenclature, these compounds are respectively *c*-4-alkyl-*t*-2-[2-$^2H_1$]-*r*-1-cyclohexyl acetates and *t*-4-alkyl-*c*-2-[2-$^2H_1$]-*r*-1-cyclohexyl acetates. The authors thank K. L. Loening, Nomenclature Director, Chemical Abstracts Service, for his assistance.

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# Hydrogen Bonding of Water to Onium Ions. Hydration of Substituted Pyridinium Ions and Related Systems

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**Abstract:** The hydration energies of substituted pyridinium ions were measured in the gas phase by determining the equilibrium constants for the gas-phase equilibria $XpyH^+(OH_2)_{n-1} + OH_2 = XpyH^+(OH_2)_n$. It was found that the hydrogen-bonding energies $XpyH^+ \cdots (OH_2)_n$ decrease with increasing basicity of the substituted pyridines Xpy. This decrease of solvation energy of the ions is largely responsible for the attenuation of the substituent effect on the pyridine basicities in aqueous solution. The gas-phase hydration energies show that a rather large number of water molecules must be present in the gas-phase hydration of the pyridinium ions before the relative solvation effects in aqueous solution are approached. A similar result is found for the substituted phenols. A general relationship between the acidity of oxygen and nitrogen onium acids $BH^+$ and the hydrogen bond in $BH^+ \cdots OH_2$ is explored. The hydrogen-bond energy is found to increase with the acidity of $BH^+$. Largest hydrogen-bonding stabilization in $B_1HB_2^+$ is obtained when the basicities of $B_1$ and $B_2$ are equal. A qualitative molecular orbital model can explain these results.

## Introduction

Comparison of the substituent effects on the acidities of phenols and benzoic acids in the gas phase and in solution can be made by plotting the differences of the free energies of ionization in the gas phase $\delta\Delta G_i$(gas) vs. the corresponding quantities in aqueous solution. $\delta\Delta G_i$ is defined as the free-energy change for the proton-transfer reaction

$$AH + A_0^- = A^- + A_0H \quad (1)$$

$$BH^+ + B_0 = B + B_0H^+ \quad (2)$$

from AH, the substituted acid, to $A_0^-$, the unsubstituted conjugate base. The $\delta\Delta G_i$(gas) values are obtained from proton-transfer equilibria measured in the gas phase[1,2] while $\delta\Delta G_i$(aqua) can be calculated from the $pK_a$ values of the two acids in aqueous solution. Similar comparisons of the substituent effects in the gas phase and in solution can be made also for bases B and $B_0$ like substituted pyridines and pyridine.[3] It is found that the plots of $\delta\Delta G_i$(gas) vs. $\delta\Delta G_i$(aqua) lead to fairly good linear relationships. However, the slopes of the straight lines are considerably larger than unity. For benzoic acids[1] the slope is 10, for phenols[1] 7, and for substituted pyridines[3] about 3. This large attenuation of the substituent effect in solution must result from an effect of the substituent on solvation which partially cancels the effect of the substituent on the isolated molecule. It has been long recognized[4] that the major factor involved in the attenuation must be the substituent effect on the solvation of the ions. For example, an electron-withdrawing substituent like CN, which increases the intrinsic acidity of phenol, is expected to unfavorably affect the solvation of the cyanophenoxide ion and thus reduce the acidity increase of cyanophenol in aqueous solution. Since this cancellation effect may be as large as 90% (benzoic acids), a linear relationship between gas phase and solution requires a fairly accurate proportionality between the substituent effect in the gas phase and the opposing ion solvation effect.

Some time ago, we reported[5,6] a relationship between the basicity of $A^-$ and the hydrogen bond in the monohydrate $A^- \cdots HOH$ which showed that the strength of the hydrogen bond increases with the (gas phase) basicity of $A^-$. Similarly it was found[7,8] that the hydrogen bond in $BH^+ \cdots OH_2$ increases with the gas-phase acidity of $BH^+$. These results were obtained by measurements of the gas-phase equilibria

$$A^- + HOH = (AHOH)^- \quad (3)$$

$$BH^+ + OH_2 = (BHOH_2)^+ \quad (4)$$

As pointed out earlier,[1] the above relationships between the hydrogen bonding to a water molecule and the basicity of $A^-$ or the acidity of $BH^+$ provide the answer, on a one molecule solvation basis for the attenuation mechanism in solution. Thus a substituent that increases the acidity of AH decreases the basicity of $A^-$ and therefore decreases the hydrogen bonding in $A^- \cdots HOH$. The present work presents some new measurements of the hydration of substituted pyridinium ions in the gas phase and explores further the relationship between the acidity of $BH^+$ and the hydrogen bond in $BH^+ \cdots (OH_2)_n$. Some results relating to the analogous attenuation mechanism occurring in the phenols and hydrated phenoxide ions $A^- \cdots (HOH)_n$ are also included.

## Results and Discussion

**A. Hydrogen Bonding in $BH^+ \cdots OH_2$ and Related Systems.** The equilibrium constants $K_5$ of the hydration equilibria

$$XpyH^+ + OH_2 = XpyH^+ \cdots OH_2 \quad (5)$$

involving the substituted pyridinium ions $XpyH^+$ are shown in the van't Hoff plots in Figure 1. The $\Delta H_5°$ and $\Delta S_5°$ values obtained from these plots are given in Table I. As will be noticed from Table I, the entropy changes $\Delta S_5°$ are very similar and the small changes that are observed do not seem to fit a rational pattern. We assume that the observed $\Delta S$ differences

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