JOC The Journal of Organic Chemistry

Perspective

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The Logic behind a Physical–Organic Chemist's Research Topics

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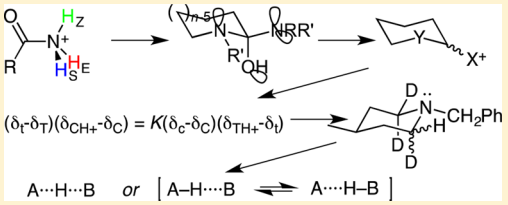
ABSTRACT: Although my research has no common theme or defining area, a coherence connects the diverse topics insofar as one project leads logically to another. Thus, studies on mechanisms of hydrogen exchange in amides and amidines led to the influence of hydrogen bonding and to NMR methods for chemical kinetics, including 2D-EXSY spectroscopy. Another connection was the OH^--catalyzed NH exchange in amines that had supported the hypothesis of stereoelectronic control. We therefore analyzed that hypothesis critically, tested it, found counterexamples, and proposed an alternative hypothesis. We next addressed one-bond NMR coupling constants in ethers and the reverse anomeric effect. The latter studies required a highly accurate NMR titration method that we developed to measure the additional steric bulk resulting from protonation of a substituent. This method is also applicable to measuring secondary isotope effects on acidity, and we could demonstrate that they arise from n-σ^* delocalization, not from an inductive effect. Other studies included kinetic isotope effects for both dissociation and H exchange of aqueous NH_4^+, for C−N rotation in amides, and for a hydride transfer. The role of hydrogen bonding led us to the rotation of NH_4^+ within its solvent cage and then to the symmetry of hydrogen bonds.



This Perspective is based on an address presented at the 249th National Meeting of the American Chemical Society in Denver, CO, on the occasion of the James Flack Norris Award in Physical-Organic Chemistry.[1] It demonstrates the ways whereby one physical-organic chemist, and physical-organic chemists in general, have investigated how molecular structure affects chemical reactivity. It also seeks to confirm my claim that "In my opinion, physical organic chemistry represents the intellectual basis of organic chemistry. It asks (and answers!) fundamental questions about how chemical substances behave, and it rationalizes that behavior."[2]

The reason that I won the James Flack Norris Award was for my "insight, rigorous analysis, and understanding of mechanisms and reactive intermediates", rather than any distinctive area of research with which I am associated. Instead of choosing one area to review here, I have tried to describe the path of my research for the past 40 years, as an expansion of an earlier article on this topic.[3] Each area seems to have engendered additional questions, leading to additional areas. Often those questions are marked by an intense skepticism, and the answers to those questions are supported by a logical analysis that I am proud of. I hope that this article will be as interesting, informative, and enjoyable to the reader as the research described here has been for me.

A BEGINNER'S RESEARCH

My Ph.D. thesis research was on mercuration of benzene, an electrophilic aromatic substitution that is accelerated by strong acid, and where we measured the H/D kinetic isotope effect.[4] To understand the origin of the acceleration it was necessary to consider acidity functions, including a new one, Hg_0, that we devised.[5] This led us to measure partial rate factors, including the effect of a substituent for activating or deactivating the position to which it was attached, which we dubbed an ipso factor.[6] Since then, ipso has become a standard designation, like ortho, meta, and para.

My wife Marilyn and I collaborated on her Ph.D. project on vibronic borrowing,[7] which led to the first explanation of negative A terms in magnetic circular dichroism. When I presented this as part of a pretenure seminar, the front row included Joe Mayer, Harold Urey, and Linus Pauling. I survived that, but soon felt that I was floundering at developing new research projects.

So I embarked on a sabbatical in 1972 to learn neurobiology, specifically to try to understand the molecular mechanisms of memory. The research did lead to a few publications,[8] but I admit that I did not learn enough, and a subsequent proposal for new funding from NIH was rejected.

PROTON EXCHANGE IN AMIDES

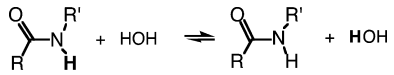
Shortly after that, I was fortunate to recover from what might have become a permanent lack of grant funding. Erno Daniel was a graduate student of my colleague Robert L. Vold, and I was a member of his Ph.D. exam committee. They were using NMR to measure rates of hydrogen exchange in aqueous urea, H_2NCONH_2.[9] This is an important reaction of amides that is even now used to probe the dynamics of protein motion and the accessibility of peptide NH groups to solvent. The rate can be measured by ^1H NMR by following the rate at which peptide NH protons wash into D_2O or by measuring the broadening of the NH signal or else by monitoring the collapse of the R′ doublet of RCONHR′, which is split by the adjacent NH (Scheme 1).

The reaction is both base- and acid-catalyzed. There is no question about the base-catalyzed mechanism. Base removes the NH, which is then replaced by a new H from solvent (Scheme 2a). What though is the mechanism of the acid-catalyzed reaction? At the time it was thought that the mechanism is simply protonation of the nitrogen, which is analogous to the base-catalyzed

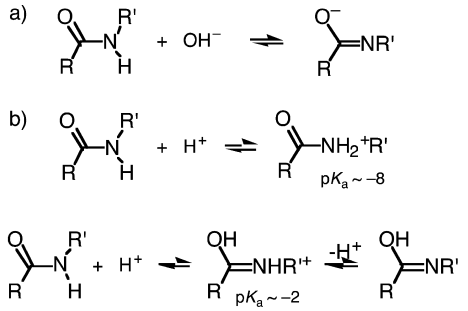
Received: September 30, 2016
Published: November 14, 2016

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

Scheme 1. NH Exchange in Amides



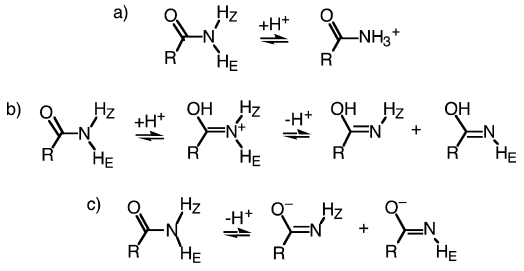
Scheme 2. Mechanisms of Proton Exchange of Amides: (a) Base-Catalyzed; (b) Acid-Catalyzed via *N*-Protonaton; (c) Acid-Catalyzed via Imidic Acid



mechanism (Scheme 2b), but with the order of deprotonation and protonation reversed. However, the nitrogen is hardly basic, because its lone pair is delocalized into the carbonyl, so it is not readily protonated. I thought that it was more likely that the mechanism involves protonation on the oxygen, which is considerably more basic. The proton on the nitrogen is thereby acidified, so that it can be removed, to form the imidic acid, RC(OH)=NH, as an intermediate (Scheme 2c). Reversal of those two steps then achieves proton exchange without requiring formation of the strongly acidic and therefore high-energy $RCONH_3^+$.

It occurred to me that it ought to be possible to distinguish between the two mechanisms with primary amides, $RCONH_2$. Because of the C−N partial double-bond character, the two NH are in different environments. One is H_Z, and the other is H_E. If the *N*-protonation mechanism is operative, the NH protons become equivalent in $RCONH_3^+$, and the two protons of $RCONH_2$ must exchange at the same rate (Scheme 3a). If reaction proceeds via the imidic acid, the two protons must exchange at different rates (Scheme 3b). How different those

Scheme 3. Stereochemistry in Proton Exchange of Primary Amides: (a) Acid-Catalyzed via *N*-Protonation; (b) Acid-Catalyzed via *O*-Protonation and Imidic Acids; (c) Base-Catalyzed via Imidate Anions



rates might be can be assessed by comparison with the base-catalyzed exchange, where the two protons in the two different environments again ought to exchange at different rates (Scheme 3c).

We even knew what to expect for the relative reactivities in both base and acid. By analogy to carboxylic acids, which are more stable as the *Z* conformer, the more stable conformer of an imidate anion, $RCONH^-$, should also be *Z*. Then the more acidic H of $RCONH_2$ ought to be H_E, so, to the extent that product-development control is operative, H_E ought to exchange faster in base. By analogy to imidate esters, RC(OR′) = NR′, which are more stable as the *E* configuration, the more acidic H of the *O*-protonated amide $RC(OH) = NH_2^+$ ought to be H_Z, which ought to exchange faster in acid. Notice that the faster H differs between base- and acid-catalyzed.

The rate of NH exchange cannot be so easily measured by NMR. Because of rapid spin relaxation of the ^{14}N quadrupole, those NH signals are very broad. However, the lab of my friend Jean Rivier at the Salk Institute had a JEOL spectrometer with the capability of decoupling ^{14}N and sharpening the NH signals. Figure 1 shows the ^1H NMR spectrum of acetamide in aqueous

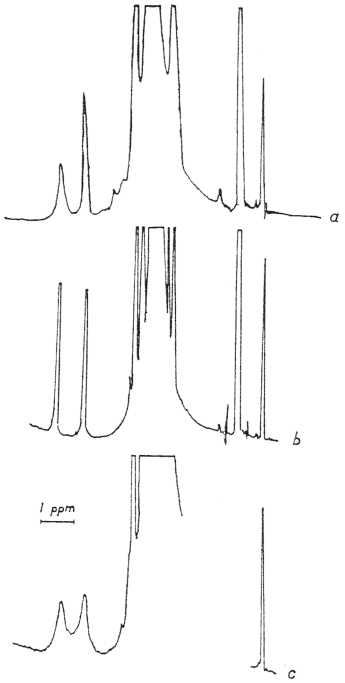


Figure 1. ^1H NMR spectrum of acetamide at (a) pH 7.94, (b) pH 5.95, (c) pH 1.94. Reproduced from ref 10. Copyright 1974 American Chemical Society.

solutions.[10] The broadening of the NH signals, more deshielded than the intense water signal, is due to NH exchange. It is clear that the signal for H_E is broader in base, as expected for the faster exchange. It is less clear that the widths of the two NH signals in acid are different, but because the two NH signals must have the same area and because the H_E signal is shorter, H_E must be broader. These results are general, not only for acetamide but also for acrylamide, methacrylamide, pivalamide, and benzamide.

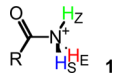
I was delighted. I had "proved" the mechanism that I considered more likely. The NH protons exchange at different rates. That was my criterion for the imidic-acid mechanism. I was ready to publish, but there was an annoying discrepancy. It is H_E that is broader, not only in base, where that was expected, but also in acid, where it was contrary to expectation. How can H_E exchange faster in acid, when that is the less acidic proton?

Such a contradiction forced me to question the assumptions that I had made. In particular, I had assumed that if the *N*-protonation mechanism is operative, the NH protons in $RCONH_3^+$ must become equivalent, and the two protons of $RCONH_2$ must exchange at the same rate. But is it true that *N*-protonation must make H_E and H_Z equivalent? All that is required to make them

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

equivalent is rotation about the C−N bond, which has become single. In $RCOCH_3$, which is isoelectronic to $RCONH_3^+$, that rotation has a barrier of ∼1 kcal/mol, so that the rate of rotation is $\sim 10^{12}$ s^{-1}. But $RCONH_3^+$ is an exceedingly strong acid, with a pK_a estimated as −8. It is a much stronger acid than H_3O^+, so that proton transfer from $RCONH_3^+$ to H_2O is thermodynamically so favorable that is should be diffusion-controlled. Water does not even need to diffuse to $RCONH_3^+$, because it is the solvent, which surrounds the ion. But if we pretend that the reaction is diffusion-controlled, with a second-order rate constant of 10^{10} M^{-1} s^{-1}, then the rate constant for proton transfer to 55 M water is $\sim 10^{12}$ s^{-1}, which is the same as the rate of the C−N rotation. Therefore, the NH protons in $RCONH_3^+$ need not become equivalent, and the two protons of $RCONH_2$ need not exchange at the same rate.

To understand the details of the NH exchange, it is necessary to consider the conformers of $RCONH_3^+$. In the most stable conformation (**1**) an H eclipses the O. *N*-Protonation of $RCONH_2$



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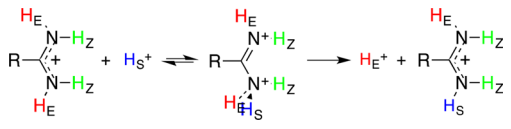
to form **1** cannot occur by 90 °C−N rotation and transfer of H^+ to the now basic nitrogen because the rate of C−N rotation in an amide is much too slow to account for the observed NH exchange. Instead, the H^+ is transferred perpendicular to the molecular plane, to produce the *N*-protonated amide in conformation **1** (or its enantiomer), with H_Z remaining in the molecular plane. That species can lose H_S back to solvent, or it can lose H_E. It cannot lose H_Z because, according to the principle of microscopic reversibility, if H^+ did not add to the rotated amide, it does not separate from the rotated amide. The only way to lose H_Z is for $RCONH_3^+$ to rotate. If that rotation is slow, only H_E will exchange. If that rotation is fast, H_Z and H_E will become equivalent, and they will exchange at the same rate, as was naively expected. If the rotation and the deprotonation are of nearly the same rate, then H_E will exchange faster than H_Z, just as observed. Therefore, the results in Figure 1 are consistent with exchange via *N*-protonation, but with the unusual feature that H_E exchanges faster than H_Z, owing to a competition between C−N rotation and deprotonation in the intermediate $RCONH_3^+$.

PROTON EXCHANGE IN AMIDINIUM IONS

The results in Figure 1 are no more than consistent with the *N*-protonation mechanism and do not necessarily exclude the alternative mechanism via the imidic acid. In contrast, amidinium ions, which had been found to undergo NH exchange in H_2SO_4,[11] can exchange only by the *N*-protonation mechanism via a dicationic intermediate (Scheme 4). Figure 2 shows ^{1}H NMR spectra of benzamidinium ion in H_2SO_4 solutions of increasing acidity.[12] Again, the NH signals show unequal broadening, and the one assigned as H_E is broader. These spectra are convincing evidence that an *N*-protonated intermediate is such a strong acid that its lifetime is too short to permit rotational equilibration about the C−NH_3^+ bond.

Scheme 4. Stereochemistry of Acid-Catalyzed NH Exchange in an Amidinium Ion



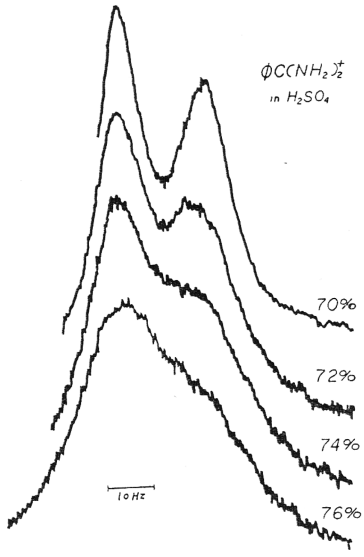


Figure 2. ^{1}H NMR spectrum of benzamidinium ion (Scheme 4, R = Ph) in H_2SO_4. Reproduced from ref 12. Copyright 1974 American Chemical Society.

These results were sufficient to justify funding from NSF to enable me to continue and extend such studies. Grant support from NSF has since then been continuous for 40 years.

Base-catalyzed proton exchange of amidinium ions is also interesting in that the NH assigned as H_Z exchanges detectably faster than H_E.[13] That was surprising because both of those protons are more acidic than the protons of H_2O. Each of them ought to undergo thermodynamically favorable and, consequently, encounter-controlled deprotonation by OH^-, with the same rate for both. This paradox was rationalized by the Swain−Grunwald mechanism, with breaking of an NH···OH_2 hydrogen bond in an amidine hydrate as the rate-limiting step.

In sulfuric acid, which is viscous, ^{14}N quadrupolar relaxation is so fast that the amidinium NH peaks in Figure 2 are sharp enough for NMR kinetics. That encouraged us to use ethylene glycol, which is also viscous, as a solvent for further ^{1}H NMR studies of NH exchange kinetics.

SITE-TO-SITE RATE CONSTANTS

There is another distinction between the two mechanisms for NH exchange in primary amides. The imidic-acid mechanism (Scheme 3b) is simple in that the two NH protons exchange only with solvent. In contrast, the *N*-protonation mechanism (Scheme 3a) allows for intramolecular exchange accompanying the intermolecular. If C−NH_3^+ rotation occurs following *N*-protonation, the H that started as H_Z may change position but remain on N. If k_{ij} designates the rate constant for exchange from site *i* to site *j* (*i*, *j* = H_E, H_Z, $H_{Solvent}$), then it can be shown that the *N*-protonation mechanism requires $k_{ES} > k_{ZS} = k_{ZE} = k_{EZ}$, whereas the imidic-acid mechanism requires $k_{ZE} = 0 = k_{EZ}$. Therefore, the distinction between the two mechanisms is that the *N*-protonation mechanism requires intramolecular exchange to be competitive with intermolecular, whereas there is no intramolecular exchange with the imidic-acid mechanism (although it is necessary to take account of any uncatalyzed intramolecular exchange from C−N rotation in the amide itself).

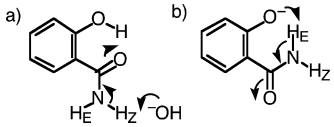
The familiar line-shape methods for NMR kinetics do not provide such site-to-site rate constants. Instead, we used saturation transfer, which we extended to multisite exchange.[14] The procedure requires irradiating site *i* (or two sites of three) so as to

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

equalize the populations of its α and β spins. It is only the excess of nuclei in the lower-energy spin state that is responsible for an NMR signal. If that excess is eliminated, signal i disappears. Also, if nuclei in site i are exchanging with nuclei in site j, the intensity at site j is also reduced, competitively with spin-lattice relaxation, which acts to restore that signal. From the extent of the reduction, and from the measurement of a spin-lattice relaxation time, it is possible to measure the site-to-site rate constant k_{ji}. The applicable pulse sequence is the same as for detecting the enhancement of signal intensity by a nuclear Overhauser effect.

To verify the method, rates of base-catalyzed proton exchange in a variety of primary amides were measured by line-shape analysis in aqueous solution and also by saturation transfer in ethylene glycol.[15] As with the five amides previously studied, H_E exchanges faster than H_Z. The site-to-site rate constants k_{ZE} and k_{EZ} are zero, or no larger than the rates due to uncatalyzed C−N rotation in the amide, as expected for exchange via the imidate anion (Scheme 3c). Salicylamide is an exception, in that H_E and H_Z exchange at the same rate, which is higher than for benzamide. This result answers the question posed about the reason for the higher rate observed for NH exchange in *N*-methylsalicylamide.[16] It must be due to specific-base intramolecular general-acid catalysis (Scheme 5a) rather than intramolecular general-base catalysis (Scheme 5b), which would accelerate only H_E.

Scheme 5. Two Mechanisms for Acceleration of Base-Catalyzed NH Exchange in Salicylamides



Similar studies on acid-catalyzed NH exchange of several primary amides in ethylene glycol found that intramolecular exchange occurs with acetamide and acrylamide, which therefore exchange via *N*-protonation (Scheme 3a).[17] In contrast, intramolecular exchange is considerably slower than intermolecular in cyanocetamide and ethyl oxamate, which therefore exchange via the imidic acid (Scheme 3b). Therefore, the answer to the mechanistic question is not simple; both mechanisms are possible.

Rates of acid-catalyzed proton exchange were also measured by saturation transfer in a wider series of primary amides in ethylene glycol.[18] The intramolecular rate constant k_{ZE} is equal to the intermolecular k_{ZS}, whereas k_{ES} is larger. This is the evidence for the *N*-protonation mechanism, but where the intermediate $RCONH_3^+$ is so strong an acid that its lifetime is too short to allow rotational equilibration around the C−N bond. Figure 3 shows the ^{1}H NMR spectrum of benzamide-^{15}N in ethylene glycol at an apparent pH of 2.0: The lower spectrum is an ordinary spectrum with off-resonance decoupling, showing doublets for H_E and H_Z, split by $^1J_{NH}$. The upper spectrum is with the solvent OH saturated. There is a greater transfer of saturation to H_E, which therefore is exchanging faster. Similar experiments, with saturation of H_Z or H_E, lead to a reduction of the intensity of H_E or H_Z, respectively. Therefore, there is also intramolecular exchange. From those intensities the rate constants were evaluated, and k_{ZE} and k_{EZ} do equal k_{ZS}, as required for the *N*-protonation mechanism (Scheme 3a).

In contrast, for $RCONH_2$ (R = $NCCH_2$, H_2NCOCH_2, EtOCO, $ClCH_2$, Cl_2CH), all with electron-withdrawing substituents,

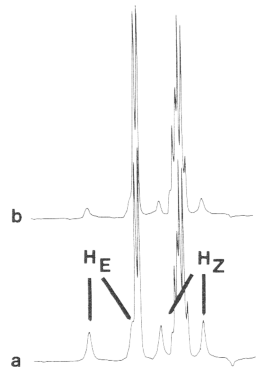


Figure 3. NH and aromatic CH region of ^{1}H NMR spectrum of benzamide-^{15}N in ethylene glycol at apparent pH 2.0: (a) with off-resonance saturation; (b) with solvent OH saturated. Reproduced from ref 18. Copyright 1981 American Chemical Society.

intramolecular exchange is slower than intermolecular, indicating a switch to the imidic-acid mechanism (Scheme 3b). We finally obtained evidence for this mechanism, which we had originally thought to be the more likely one, even though we were surprised to find that it is not always the dominant one.

A change of mechanism is also suggested by the change of slope of a plot of $\log_{10} k$ vs the pK_a of the corresponding RCOOH, from ca. 0.3 for amides with electron-withdrawing substituents to ca. 1 for other amides. The dependence of mechanism on substituents makes sense in terms of the structure of the transition states. According to Hammond's postulate,[19] the transition state of the *N*-protonation mechanism resembles the cationic $RCONH_3^+$ intermediate, whereas the transition state of the imidic-acid mechanism resembles the uncharged imidic-acid intermediate so that the former is more strongly destabilized by electron-withdrawing substituents.

Saturation-transfer studies of acid-catalyzed exchange of amidinium ions $ArC(NH_2)_2^+$ confirmed the observation, based on line-broadening (Figure 2), that H_E exchanges faster than H_Z.[20] There was a question regarding signal assignments, which seemed to undergo a solvent-induced shift on going from water to H_2SO_4, which could be confirmed with anionic lanthanide-shift reagents.[21]

An alternative to saturation transfer is 2D-EXSY (exchange spectroscopy) NMR, which has become a very powerful method for exchange kinetics.[22] An appropriate pulse sequence produces a two-dimensional NMR spectrum with diagonal peaks corresponding to a normal spectrum, plus off-diagonal peaks that correspond to site-to-site exchange. From the intensities it is possible, by matrix diagonalization, to evaluate the site-to-site rate constants. Figure 4 shows the 2D-EXSY spectrum of acrylamide undergoing acid-catalyzed NH exchange in ethylene glycol.[23] The diagonal peaks, from bottom left to top right, are H_E, H_Z, CH (vinylics), CH (vinylic), and H_S (OH of solvent), with CH_2 of solvent offscale. The rate constants (after the rate constant for spontaneous C−N rotation in the amide is subtracted) are k_{ES} = 4.9 s^{-1}, k_{ZS} = 2.5 s^{-1}, k_{ZE} = 2.2 s^{-1}, and k_{EZ} = 2.5 s^{-1}. The non-zero intramolecular exchange is evidence for the *N*-protonation mechanism (Scheme 3a), and the faster ES exchange is a consequence of a competition between deprotonation and C−N rotation in the $RCONH_3^+$ intermediate. In contrast, in thioacetamide, CH_3CSNH_2, there is no off-diagonal peak between H_E and H_Z, consistent with the imidic-acid mechanism (Scheme 3b).

Some interesting features of the influence of hydrogen bonding on exchange kinetics are shown by diamide **2**.[24] The base-catalyzed

DOI: 10.1021/acs.joc.6b02390
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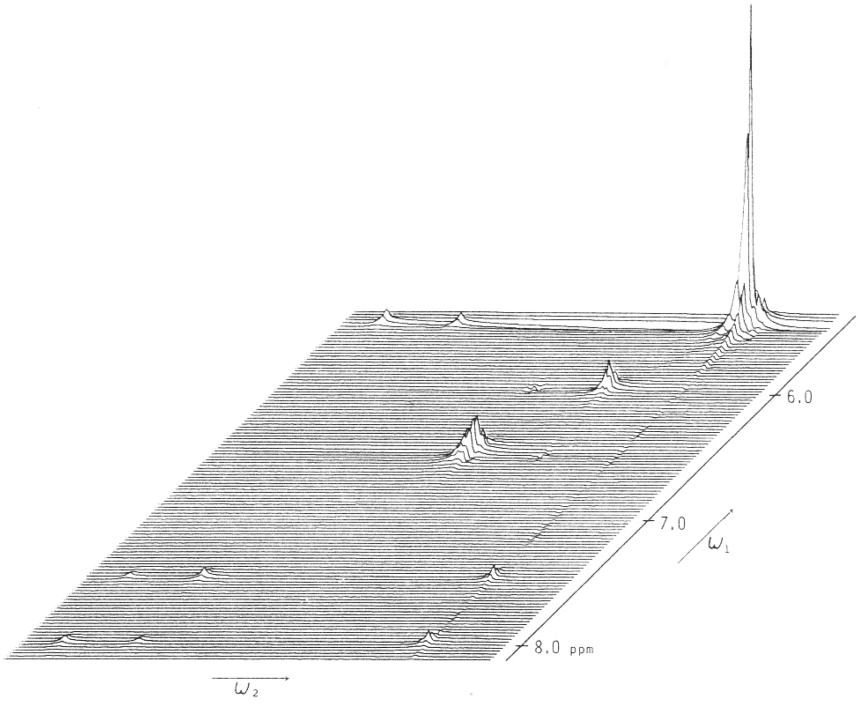
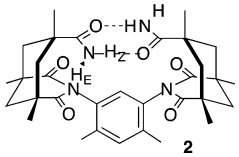


Figure 4. 2D EXSY ^{1}H NMR spectrum of acrylamide in ethylene glycol at apparent pH 1.75. Reproduced from ref 23. Copyright 1984 American Chemical Society.

exchange of H_Z is retarded ca. 30-fold. The exchange is considered to proceed by direct abstraction of the proton from within the hydrogen bond. The acid-catalyzed exchange shows $k_{ES} > k_{ZS} = k_{ZE} = k_{EZ}$. Therefore, this proceeds by the *N*-protonation mechanism, but apparently there is no retardation of C−N rotation in $RCONH_3^+$, despite the hydrogen bonding.



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N-ALKYLAMIDES

To further probe the effects of substituents on mechanism, we returned to *N*-alkylformamides and similar secondary amides,[25] which also permit comparison of intermolecular and intramolecular exchange, which in this context becomes cis/trans isomerization. Both *N*-methylformamide and *N*-*tert*-butylformamide show intramolecular exchange competitive with intermolecular, but *N*-formylglycine ($HCONHCH_2COOH$), formanilide ($HCONHPh$), and *N*-methylcyanoformamide ($NCCONHCH_3$) show only intermolecular. Again, these latter amides, with electron-withdrawing substituents, exchange via the imidic-acid mechanism (Scheme 2c). Further studies of *N*-methylformamide, as well as saturation-transfer studies on acetamide, in such nonpolar solvents as 90% THF and cyclohexanol, found that despite the electron-donating substituents these amides exchange predominantly via the imidic acid mechanism.[26] Again, these changes of mechanism are consistent with the Hammond postulate in that the transition state for the *N*-protonation mechanism (Scheme 2b), which resembles the *N*-protonated intermediate, is destabilized by electron-withdrawing substituents and by nonpolar solvents.

To further probe the imidic-acid mechanism, the proton-exchange kinetics of imidate esters $RC(OR') = NR''$ in strong acid was studied.[27] Also, to better model the base-catalyzed exchange (Scheme 2a), imidate anions were prepared by treating the amide with NaH or KH in THF or Me_2SO.[28] The *E* stereoisomer is generally more stable than the *Z*, contrary to the expectation above, but the equilibrium constant is strongly solvent dependent. The imidate anions could be protonated by rapid addition of trifluoroethanol, to regenerate the amide as a nonequilibrium *E*/*Z* mixture, which then returned to equilibrium at a measurable rate.

The barrier to *E*/*Z* interconversion in imidate anions was found to be 19−23 kcal/mol, as measured by saturation transfer. For a series of *N*-arylformimidate anions, $HC(O^-)=NAr$, the slope ρ of a Hammett plot of the rate constants is +2.3 ± 0.2, consistent with a mechanism involving sp^2 nitrogen inversion, not C=N rotation.[29]

To probe substituent effects further, we measured the rates of acid-catalyzed NH exchange of a series of *N*-methylacetamides $ZCH_2CONHCH_3$ and tried to correlate them with the pK_a of the corresponding carboxylic acid, ZCH_2COOH.[30] Figure 5 shows the results. There is a change of slope, from 0.43 for amides with electron-withdrawing substituents (dashed line), to ∼1.84 for amides with electron-donating substituents. This corresponds to a change of mechanism from the imidic-acid mechanism (Scheme 2c), which is less sensitive to substituent effects, to the *N*-protonation mechanism (Scheme 2b), which is more sensitive. Off the curve, at log *k* = 7, is *N*,*N*′-dimethylurea, which exchanges via the *N*-protonation mechanism, as had been concluded for so electron-rich a substrate.[9] The point at pK_a 3.67 is for Z = CH_3CONH (acetylglycine *N*-methylamide), which is the closest model for a peptide residue in a protein.

Also relevant are the above conclusions regarding *N*-formylglycine and acetylglycine *N*-methylamide. These are the closest models for peptide residues in proteins, and they imply

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

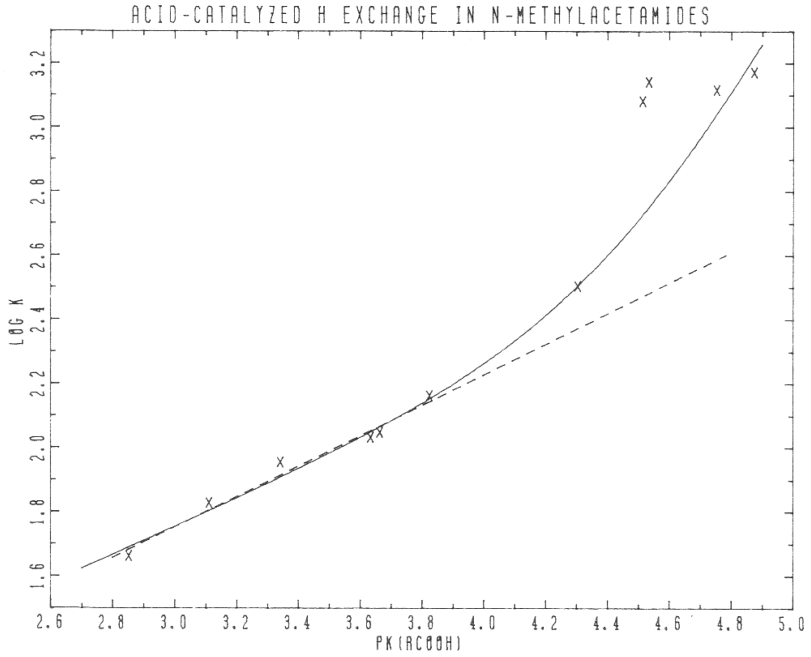

Figure 5. Correlation between log k_H for acid-catalyzed proton exchange in *N*-methylacetamides, $ZCH_2CONHCH_3$, and the pK_a of the corresponding ZCH_2COOH. Reproduced from ref 30. Copyright 1982 American Chemical Society.

Table 1. Average Micellar Charge Effects on Rates of Amide NH Exchange

micelle	$\log(k_H/k_H^0)$	$\log(k_H/k_H^0)$	$\log(k_{OH}/k_{OH}^0)$	ΔpH_{min}
anionic	2.0 ± 0.2	1.5[a]	−3.4 ± 0.2	2.71 ± 0.13
cationic	−0.75 ± 0.06	−1.5 ± 0.16[a]	−0.18 ± 0.25	−0.13 ± 0.14

[a]Urea NH.

that the NH groups of peptide backbones exchange predominantly via the imidic acid (but not the primary $CONH_2$ of glutamine and asparagine side chains, which exchange via *N*-protonation). Because the imidic-acid mechanism was the one I had originally expected, this conclusion was particularly gratifying, even if it is not general. Besides, it has important implications for solvent access to peptide residues because NH exchange via the imidic acid requires access to both O and N.

Another comparison of amide NH exchange is of long-chain *N*-methylamides or *N*-methylureas in micelles, relative to aqueous *N*-methylbutyramide or *N*,*N*′-dimethylurea. Because this was the first study to cover all four combinations of H^+- and OH^--catalyzed reactions in anionic and cationic micelles, it permitted a complete analysis of electrostatic contributions. Table 1 lists the average rate ratios k/k^0 for exchange in a micelle, relative to aqueous solution,[31] along with ΔpH_{min}, the change in pH_{min}, the pH at which the rate is minimum. The uncertainties are from the apparently random variations with counterion, headgroup, chain length, etc. The largest effects are for anionic micelles, a 100-fold increase for the acid-catalyzed exchange and a 2500-fold decrease for the base-catalyzed. The effects of cationic micelles are smaller, a 30-fold decrease in k_H for *N*-methylureas, or 6-fold for ordinary amides, but essentially no change in k_{OH}. These changes result in a shift of pH_{min} by 2.7 for the anionic micelles but no significant shift for the cationic micelles.

The results in anionic micelles are quite reasonable because the negatively charged environment stabilizes the cationic transition state in acid catalysis and destabilizes the anionic transition state in base catalysis, thereby increasing pH_{min}. The decreases of k_H in cationic micelles, although smaller, are also reasonable, because the positively charged environment destabilizes the cationic transition state, but the invariances of k_{OH} and pH_{min} in cationic micelles were unexpected because the positively charged environment ought to accelerate exchange.

It took ten years before we developed and published an explanation for the invariance of k_{OH} in cationic micelles. We rejected explanations based on a change of the local $[H^+]$ or $[OH^-]$ at the micelle surface or on the pseudophase model (competition between the counterions and $[H^+]$ or $[OH^-]$) because these explanations are only qualitatively consistent with the observation, not quantitatively. Instead, we invoked the Brønsted formulation of medium effects, which allows a focus on the stabilization of the transition state. Because the positive charge of a cationic micelle is buried within the $N(CH_3)_3^+$ headgroup while the negative charge of the transition state for k_{OH} is delocalized over N and O and therefore diffuse, the electrostatic stabilization is weak, so that k_{OH} is not accelerated in cationic micelles. Unfortunately, our rejection of the reigning pseudophase model led to a flawed analysis of our claims, with ad hoc assumptions.[32] Nevertheless, we affirm that the key to the asymmetry in Table 1 is that the interaction between $-NMe_3^+$ and imidate anion is quite different from that between $-SO_3^-$ and *N*-protonated amide or urea.

Some similar results were obtained recently from the NH exchange into D_2O of the 6:4 complex of secondary amide **3** with Ga^{3+}.[33] This carries a net negative charge of −12, which accelerates k_H by 10^5-fold and retards k_{OH} by 10^8-fold. Consequently, pD_{min} increases from 3 in an ordinary amide to 9. Further retardation occurs when the complex encapsulates Me_4N^+ or Et_4P^+, but both k_H and k_{OH} are retarded. In this case, the reduction not only

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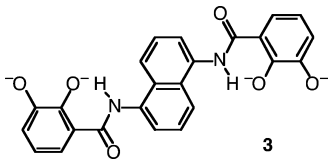
of k_H but also of k_{OH} by cationic guests was attributed to a steric effect, but how this operates is not clear.



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In summary, we conclude that amides with electron-withdrawing substituents exchange via the imidic acid, including the NH of peptides and protein backbones, whereas ordinary amides exchange by *N*-protonation, but the intermediate $RCONH_3^+$ or $RCONH_2R'^+$ is so acidic that its lifetime is too short to allow rotational equilibration about the C−N bond. Further details are available in a review.[34]

RATES OF C−NH_3^+ ROTATION, MODELED BY H−NH_3^+ ROTATION

Can C−NH_3^+ rotation really be competitive with deprotonation of $RCONH_3^+$, an acid of pK_a ∼−8? Although this is isoelectronic to $RCOCH_3$, whose rotation has a barrier of ∼1 kcal/mol and a rate of rotation ∼10^{12} s^{-1}, C−NH_3^+ rotation may be slower because it requires breaking $NH^{\delta+}\cdots OH_2$ hydrogen bonds. We modeled this rotation by the rotation of $^{15}NH_4^+$ within its solvent cage, as measured from the spin-lattice rotation time $T_1(^{15}N)$ (because it is the tumbling of NH_4^+ that relaxes the ^{15}N nucleus). The rotational correlation times τ_c are listed in Table 2.[35] The

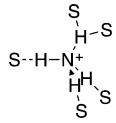
Table 2. ^{15}N Spin-Lattice Rotation Times and the Rotational Correlation Time of $^{15}NH_4^+$

solvent	T_1(s)	τ_c(ps)
96% HSO_4	57	0.46
H_2O	44	1.1
85% H_3PO_4	16.6	1.7
18-crown-6/acetone	16.4	2.8
50% aq ethanol	18	2.8
methanol	13.6_2	3.8
ethylene glycol	8.5	6
pyridine	4.97	10
glycerol	3.6	12
DMSO	3.96	13
ethanol	3.6	14
N-methylacetamide	2.6	20

value of 1.1 ps for τ_c in water is indeed very short, so that C−NH_3^+ rotation in $RCONH_3^+$ can be competitive with its deprotonation, as surmised.

What feature of the solvent is responsible for the variation in the rate of NH_4^+ rotation? There is no statistically significant variation of τ_c with solvent viscosity η, dielectric relaxation time τ_D, or molecular dipole moment μ. Indeed, ρ, the correlation coefficient between τ_c and μ is −0.005, perhaps a record opposite to "champion" correlation coefficients near 0.9999. The best correlation of the τ_c data in Table 2 is with the solvent's oxygen atom density, for which $\rho = -0.84$. This is consistent with a view of the solvation as involving multiple clustering of solvent molecules S around the ion, as suggested in Scheme 6. The solvents for which τ_c is short can place many oxygens near the hydrogens, so that as the ion rotates, it can make a new hydrogen bond as it breaks the old one, without losing much of the strength of the hydrogen bond.

Scheme 6. Rotation of NH_4^+ within Its Solvent Cage via a Bifurcated H-Bond



SYMMETRY OF HYDROGEN BONDS

In connection with the influence of hydrogen bonds (H-bonds) on the rotation of NH_4^+ within its solvent cage, one often encounters a different question, namely about the symmetry of H-bonds.[36] Is the H-bond symmetric, with the H centered midway between the two donor atoms (**4**), or is it asymmetric (**5a** or **5b**), with the H closer to one donor but possibly jumping from one donor to the other? More precisely, is the potential-energy surface describing the H motion a single well (Figure 6a) or a double well (Figure 6b), which also encompasses an asymmetric double well (Figure 6c), where one tautomer is more stable than the other?

This question is well settled for the most familiar of H-bonds, in water, in proteins, and in DNA, where one of the donor atoms is much more basic than the other, so that the potential is as in Figure 6c. Less certain, and more controversial, are the H-bonds in "resonance-enhanced H-bonds", as in some enols, and in monoanions of dicarboxylic acids, which are "charge-assisted".[37] Some of these have centered H, in a single-well potential, and they are among the shortest and strongest of all H-bonds, especially that in FHF^-, for which the strength is 39 kcal/mol.[38] Certainly as the distance between the two heavy atoms decreases, and the potential-energy wells are forced closer to each other, the double-well potential of Figure 6b will be transformed into the single-well potential of Figure 6a.

This is an important and fundamental question about molecular structure. It has gained interest because of a proposal that short, strong H-bonds (SSHBs) or low-barrier H-bonds (LBHBs) stabilize intermediates and transition states in some enzyme-catalyzed reactions.[39] We attempted to answer this question. Regardless of the implications for enzyme catalysis, we ought to understand the conditions that favor single-well potentials if we are to claim that we understand H-bonds.

ISOTOPIC PERTURBATION

To address this question, we turned to the method of isotopic perturbation, which was developed by Saunders for the study of carbocations.[40] It succeeds even if rapid exchange coalesces signals. It depends on the measurement of the NMR isotope shift (isotope effect on chemical shift δ). This is defined in eq 1, where n is the number of bonds between the (heavy) isotope and the reporter nucleus.

$$^n\Delta = \delta_{heavy} - \delta_{light} \quad (1)$$

There are two contributions to the isotope shift, an intrinsic one, $^n\Delta_0$, due to the isotope itself, and an additional contribution, $^n\Delta_{eq}$, from the perturbation of an equilibrium between two tautomers (eq 2). This latter is best illustrated with 3-hydroxypropenal-*d* (Scheme 7, R = H), whose H, according to microwave spectroscopy, is in a double-well potential between the two oxygens.[41] The C−H stretching frequency of an aldehyde is unusually low, ca. 2770 cm^{-1}, whereas the C−H frequency of an enol is near 3020 cm^{-1}. Consequently, tautomer **6a** has a greater quantum-mechanical zero-point energy than does **6b**, so that the

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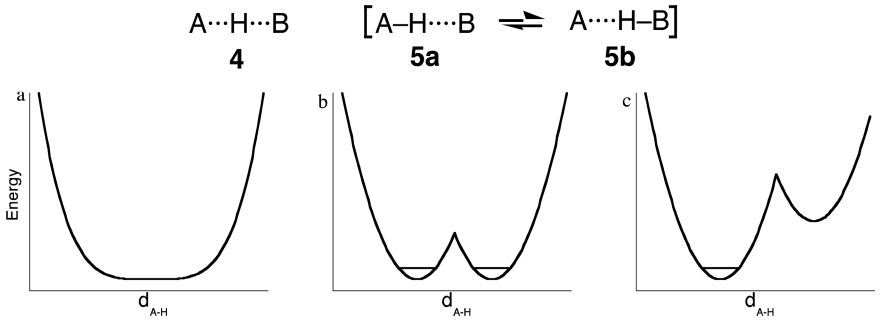
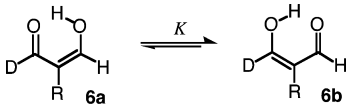


Figure 6. Potentials for H motion. (a) Single-well. (b) Double-well. (c) Asymmetric double-well.

Scheme 7. Tautomerism in 3-Hydroxypropenal-*d*



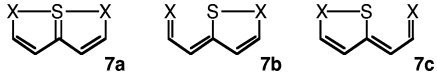
equilibrium favors **6b**, with an equilibrium constant K of 1.2 at 25 °C estimated from those frequencies. Moreover, the ^{13}C chemical shift of an aldehyde carbon is near 196 ppm, whereas that of an enol is near 173 ppm, with a difference D of 23 ppm. These considerations lead to an estimate of 1 ppm for the perturbation isotope shift of the H-bearing C, as given in eq 3.

$$ {}^{n}\Delta_{obs} = {}^{n}\Delta_{0} - {}^{n}\Delta_{eq} \quad (2) $$

$$ {}^{3}\Delta_{eq} = \delta_{CHD} - \delta_{CHH} = \frac{D(K-1)}{2(K+1)} \quad (3) $$

In practice, the substituted 3-hydroxypropenal **6**, R = Ph, is more convenient to study. It was prepared as a statistical mixture with 0, 1, and 2 deuteriums.[42] The measured separation between the signals of the HH and the HD isotopologues is 0.76 ppm (where isotopologues, or isotopic homologues, are isomers that differ in the number of isotopic substitutions). The separation is larger at lower temperature, where the equilibrium becomes more unbalanced. Similarly, a separation of 0.05 ppm is observed in the ^{1}H NMR spectrum because the same K is operative and because aldehyde CH is more deshielded than enol CH. Again, the separation is larger at lower temperature, which confirms that this is not an intrinsic shift, which is found to be temperature-independent. Thus, the isotope shifts are evidence for a mixture of two tautomers and an asymmetric structure.

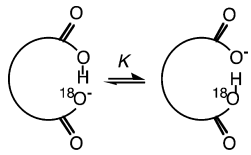
It might be thought that the isotope shifts and the asymmetry are a consequence of the introduction of an isotope. However, according to the Born-Oppenheimer approximation,[43] the potential-energy surface is determined only by the electronic wave function and not by the atomic masses. Indeed, α-deuterium-substituted 1,6-dioxa-6aλ^4-thiapentalene (**7a**, X = O) and 1,6,6aλ^4-trithiapentalene (**7a**, X = S) are symmetric, and not a mixture of tautomers (**7b** + **7c**).[44] In addition, the Li, Na, and K salts of **6**-*d* (R = Ph) show only a small negative D-induced isotope shift, and its Al, Pd, Rh, Si, Sn, Ge, and Sb complexes show only a small positive D-induced isotope shift.[45] Therefore, these are all intrinsic isotope shifts, as is characteristic for a symmetric species. Thus, the method of isotopic perturbation succeeds at distinguishing a single symmetric structure from a mixture of tautomers.



DICARBOXYLATE MONOANIONS

According to X-ray and (better) neutron diffraction studies,[46] the monoanions of some dicarboxylic acids have symmetric H-bonds, with their hydrogen centered between the two donor oxygens. This feature can be probed with mono-^{18}O substitution. If the monoanion is a mixture of two tautomers (Scheme 8),

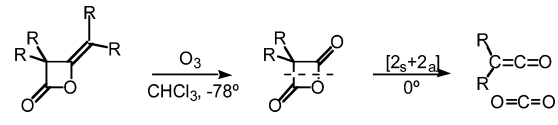
Scheme 8. Tautomerism in a Mono-^{18}O-substituted Dicarboxylate Monoanion



eqs 2 and 3 will apply to the ^{13}C NMR signals of the carboxyls, with $^{1}\Delta_0$ equal to 26 ppb, as measured in the dicarboxylic acid, and K equal to 1.01, based on the ^{18}O isotope effect on acidity.[47] These values lead to an predicted perturbation isotope shift $^{1}\Delta_{eq}$ of 20 ppb.

The synthesis of a dicarboxylic acid with exactly one ^{18}O is easy: just hydrolyze its anhydride in $H_2{}^{18}O$. This is the cue for discussing the synthesis of a special anhydride, malonic anhydride. This is a simple substance that had eluded synthesis since 1906 until we finally succeeded, by ozonolysis of a ketene dimer (Scheme 9).[48] The most convincing part of the structure proof

Scheme 9. Synthesis and Reactivity of Malonic Anhydrides (R = H, CH_3)



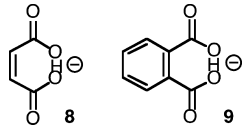
was a Raman signal at an exceptionally high 1947 cm^{-1}.[49] The anhydride is unstable, decomposing below room temperature to a ketene and CO_2. From the kinetics, $\Delta H^{\ddagger}$ is quite low, near 14 kcal/mol, and $\Delta S^{\ddagger}$ is near −20 cal/(mol K), negative because this is a $[2_s+2_a]$ cycloreversion, via a more organized transition state.[50]

We confirmed that succinic acid-^{18}O shows a separation between its two carboxyl ^{13}C signals of 26 ppb. On addition of small aliquots of OH^-, those signals move apart, reaching a maximum separation of 46 ppb at 1 equiv and then moving together with additional OH^- until with 2 equiv the separation returns to 26 ppb because the intrinsic $^{1}\Delta_0$ is the same in the dianion as in the diacid.[51] Again, the method of isotopic perturbation

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

recognizes a mixture of two tautomers, and the same behavior was seen in the titration of a mixture of ^{18}O isotopologues of formic acid, where the intermolecular comparison verifies the isotope effect on acidity.

The astonishing result was that the same behavior, a maximum isotope shift in the monoanion, was seen for mono-^{18}O-substituted maleic and phthalic acid monoanions (**8**, **9**). We concluded that they are asymmetric, present as a mixture of tautomers, with double-well H-bonds in solution. It was not easy to publish this conclusion because it contradicted the well-established observation that these are symmetric, with a centered hydrogen. We therefore devised control experiments to test our conclusion: (1) The isotope shift is larger in D_2O, where K is larger. (2) The isotope shift is larger at lower temperature, where the equilibrium becomes more unbalanced, as with Scheme 7. This contrasts with the dianion, where the intrinsic $^1\Delta_0$ is independent of temperature. (3) In phthalic acid, the isotope shift is seen not only at the carboxyl carbon but also at ipso, ortho, and meta carbons. Those carbons are too distant from the ^{18}O for any intrinsic shift $^n\Delta_0$ (n = 2, 3, 4) to be resolvable. At ipso, the isotope shift is 50 ppb, a Δ_{eq} even larger than at carboxyl.



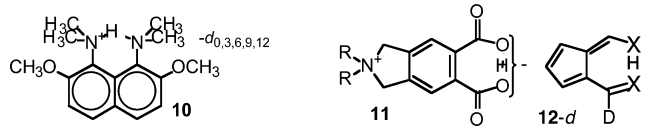
Therefore, we succeeded in publishing the conclusion that these monoanions are two tautomers, not a single symmetric species. However, we did not need to contradict 30 years of crystallography. Crystallographers are necessarily studying crystals, whereas our studies were the first in aqueous solution. Water is special because it is a polar solvent, which stabilizes the concentrated negative charge in a carboxylate anion more than the delocalized charge in a symmetric structure. Indeed, molecular orbital calculations support this interpretation.[52] It allowed proponents of SSHBs or LBHBs to distinguish the enzyme active site as being nonpolar, quite different from aqueous solution. In support, the isotope shifts of maleic and phthalate monoanions (**8**, **9**) are much smaller in organic solvents dimethyl sulfoxide, acetonitrile, and even tetrahydrofuran, which is nonpolar.[53]

We then performed one or more experiments too many. We went searching for symmetric H-bonds among carboxylic acid monoanions (Scheme 8) with a wide range of O−O distances. In organic solvents, the observed ^{18}O-induced isotope shifts at carboxyl carbons are much smaller than in aqueous solution, but they average 1.5 ppb and none is negative.[54] For aromatic diacids, the isotope shift is considerable at ipso carbons. Therefore, we concluded that all these monoanions exist as a pair of equilibrating tautomers not only in water but also in organic solvents. Even *dl*-2,3-di-*tert*-butylsuccinate monoanion, whose X-ray crystal structure shows a centered H, is a mixture of tautomers in solution,[55] despite its reputation for having the strongest H-bond, based on the record difference between its first and second pK_a.[56]

SOLVENT DISORDER AND SOLVATOMERS

What then is the difference between the crystalline phase, where these monoanions are symmetric, and solutions, where they are a mixture of tautomers? It is not the polarity of the solvent. We proposed that symmetry is not inherent in the monoanion but can depend on the environment. A crystal can guarantee that both carboxyl groups are in identical environments, whereas water and other solvents are disorganized. At any instant, one of the carboxyl groups is solvated better than the other, through H-bonding, ion pairing, or the orientation of solvent dipoles. The proton then attaches to the less solvated carboxyl, so that the H-bond is instantaneously asymmetric. This view, too, is supported by simulations.[57]

If the asymmetry arises from solvation of exposed carboxyls, might the solvation be less important if the charge is buried within the ion, or even if there is no charge, as in a zwitterion or a neutral species? Those possibilities were probed with **10**-d_n,[58] **11**-^{18}O,[59] and **12**-*d* (X = O, NAr).[60] For **10**, isotopic perturbation was provided by a statistical mixture of 0, 1, 2, 3, and 4 CD_3 groups, which increase the basicity of the N to which they are attached; yet each of these shows isotopic perturbation in its ^{13}C NMR spectrum and is a mixture of tautomers.



These results led to a reevaluation of the distinction posed in Figure 6. The observation of isotopic perturbation does not require a double-well potential-energy surface. It requires only that there be a mixture of tautomers, and not necessarily only two. Such tautomers can be called solvatomers, meaning isomers (or stereoisomers or tautomers) that differ in solvation. The mixture arises because of the disorder of solvation. At any instant one solvatomer happens to be solvated better than another. As the solvent reorganizes, the H in the H-bond shifts from one donor to the other, as suggested in Figure 7.

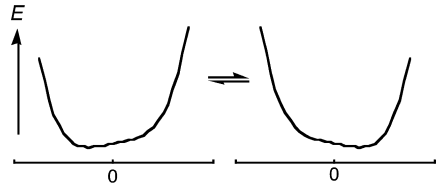


Figure 7. Equilibrating H-bond solvatomers, each with a single-well potential.

This view casts doubt on the ability of SSHBs or LBHBs to stabilize intermediates and transition states in enzyme-catalyzed reactions. If solvation is sufficient to distort the H-bond from its centered position, then there is little stabilization provided by that feature. Instead, we have suggested that proton transfer relieves the destabilization of an anionic Michaelis complex in an aprotic environment and thereby increases k_{cat}.[61] We admit that this is not a new idea.[62] Some of these results on H-bonds have been reviewed.[63]

Further evidence for the role of solvent disorder comes from a study of difluoromaleate monoanion (**13**).[64] Its X-ray crystal structure shows a centered H, but the ^{19}F NMR spectrum of its mono-^{18}O isotopologue shows an AB pattern in water, CD_2Cl_2, and CD_3CN. The dianion shows only a ^{19}F singlet, so ^{18}O substitution alone does not render the fluorines inequivalent. Therefore, the monoanion again is a mixture of tautomers. However, in the isotropic phase of the liquid crystal 4-cyanophenyl 4-heptylbenzoate the fluorines become equivalent because this phase is more ordered, with the two donor oxygens in the same environment.

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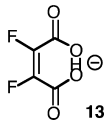

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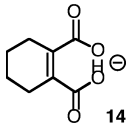
ANOTHER INTERPRETATION, AND A RESPONSE

Bogle and Singleton have simulated the trajectories of the anharmonic motion of the H in the H-bond of isotopically labeled phthalate monoanion (**9**) and calculated the resulting ^{13}C NMR isotope shifts at ipso carbons.[65] Their calculated values agree with our experimental ones in organic solvents. They therefore concluded that the ion is symmetric and that the chemical-shift separation arises from coupling between a desymmetrizing vibration and anharmonic isotope-dependent vibrations. They further concluded that there is no need to propose equilibrating tautomers in aprotic solvents, although they seem to accept them in water, where the ^{18}O-induced isotope shift at the ipso carbon of phthalate monoanion was found to be lower at higher temperature.[66]

We therefore measured the temperature dependence of the ^{18}O-induced isotope shift on the ^{13}C NMR spectrum of cyclohexene-1,2-dicarboxylic acid monoanion (**14**) in chloroform.[67] If Bogle and Singleton are correct, this ought to increase at higher temperatures, where the amplitudes of anharmonic motions are increased. Instead, we found that as the temperature decreases the isotope shift at the alkene carbons increases, to an extent consistent with an ^{18}O isotope effect on carboxylic acid acidity. Therefore, we reaffirmed that in both aqueous and organic solvents this monoanion is a mixture of tautomers in rapid equilibrium, rather than a single symmetric structure in which the chemical-shift separation arises from anharmonic isotope-dependent vibrations.



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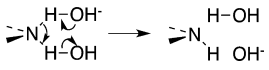
ANOTHER MECHANISM FOR NH EXCHANGE

As a counterpart to the amide NH exchange described above, we were interested in another mechanism for base-catalyzed NH exchange, but in amines, as shown in Scheme 10. Whereas base-catalyzed amide NH exchange proceeds via deprotonation to the imidate anion (Scheme 2a), this is a concerted process, where one OH^- removes a proton while another proton is donated to the lone pair from a water molecule. This is a reasonable mechanism because it avoids the creation of a nitrogen anion, which is a much stronger base than OH^-.

Scheme 10. Concerted Base-Catalyzed Proton Exchange in Amines

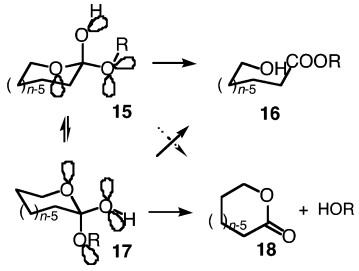


I discovered that this mechanism was proposed by Deslongchamps, Barlet, and Taillefer.[68] However, I also knew that there was no evidence for it, although we detected it in the reactions of some hydroxylamines, where it is fairly slow, with a second-order rate constant k_2 near 10^4 M^{-1} s^{-1}.[69] What puzzled me was the reason for postulating such a mechanism. I found that it was needed in order to support Deslongchanps' hypothesis of stereoelectronic control.[70] That led me to a critical examination of that hypothesis, which became a fascinating exercise in scientific logic.

STEREOELECTRONIC CONTROL IN HEMIORTHOESTER HYDROLYSIS

According to Deslongchanps' hypothesis of stereoelectronic control, preferential cleavage of tetrahedral intermediates occurs when two lone pairs are antiperiplanar to the leaving group. Scheme 11 shows the experimental evidence from hydrolysis of hemiorthoesters. In conformer **15** there are two lone pairs antiperiplanar to the OH, which can cleave. That does not lead to product but to precursor, so that by the principle of microscopic reversibility, the OH must enter antiperiplanar to those two lone pairs. Therefore, the hemiorthoester is formed initially in conformer **15**. There are also two lone pairs antiperiplanar to the ring oxygen, which can cleave to hydroxy ester **16**. But **15** cannot cleave the exocyclic OR (dashed arrow) because there is only one lone pair (on the OH, not shown) antiperiplanar to it, along with a C−O bond. To reach a conformation with two lone pairs antiperiplanar to the exocyclic OR, ring inversion is necessary, leading to **17**. Now this can cleave the exocyclic OR and produce **18**.

Scheme 11. Stereoelectronic Control in Hemiorthoesters, Showing Two Lone Pairs Antiperiplanar to a Leaving Group



If ring inversion is slow relative to C−O cleavage, **17** and **18** are inaccessible. Experimentally, the kinetic product from **15** ($n = 6$) was entirely hydroxy ester **16**.[71] Therefore, ring inversion must be slow, which is reasonable for a six-membered oxacyclohexane ring. This then is the evidence for stereoelectronic control in hemiorthoester hydrolysis. Moreover, there are many similar results, and there are calculations that support a requirement for two lone pairs antiperiplanar to a leaving group.[72]

However, the kinetic product from **15** ($n = 5$) was also entirely **16**. In a five-membered oxacyclopentane ring, ring inversion becomes pseudorotation, with a rate constant near 10^{12} s^{-1}, faster than any possible C−O cleavage. According to the hypothesis of stereoelectronic control, **18** ($n = 5$) ought to have been formed. The fact that it was not formed means that its absence for $n = 6$ cannot be taken as evidence for stereoelectronic control.

There is a simple explanation for the exclusive formation of hydroxy ester **16** from **15** regardless of ring size, namely the destabilization of lactones, which is responsible for their greater reactivity toward hydrolysis.[73] Indeed, this explanation can account for all the evidence from hydrolysis of acetals, amides, and imidates adduced in support of stereoelectronic control.

STEREOELECTRONIC CONTROL IN AMIDINE HYDROLYSIS

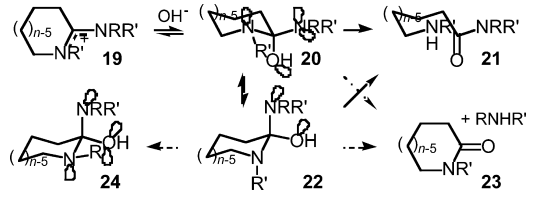
Because antiperiplanar lone pairs do provide better overlap with a leaving group, stereoelectronic control is a reasonable hypothesis. However, it must be probed without the bias of product

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

stabilities. A clue to how to avoid that bias comes from the comparison of esters with amides. Although lactones are destabilized relative to acyclic esters, there is no destabilization of lactams relative to acyclic amides. Therefore, amidine hydrolysis can provide a suitable test.

Scheme 12 shows the prediction of stereoelectronic control for the hydrolysis of cyclic amidines. Addition of OH^- to amidinium

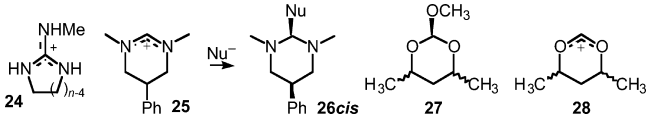
Scheme 12. Stereoelectronic Control in Hydrolysis of Amidines, Showing Two Lone Pairs Antiperiplanar to a Leaving Group



ion **19** must occur antiperiplanar to two lone pairs on the two nitrogens to produce hemiorthoamide **20** as initial intermediate. After rotation about the exocyclic C−N bond, which ought to be fast, there are lone pairs on the exocyclic NRR′ and the OH that are antiperiplanar to the endocyclic NR′, so that the C−NR′ bond can cleave, with protonation of the NR′, to form aminoamide **21**. It is not possible (dashed arrow) for **20** to cleave the exocyclic NRR′, which is antiperiplanar to only one lone pair, on the oxygen. Ring inversion converts **20** to **22**, which can also cleave the endocyclic NR′ to produce **21**. But **22** cannot cleave the exocyclic NRR′, to produce lactam **23**, because only one lone pair, on the OH, is antiperiplanar to that bond. That cleavage requires nitrogen inversion, to produce **24**, which now has two lone pairs antiperiplanar to the exocyclic NRR′. Regardless of whether ring inversion is fast, for n = 5 or 7, or slow, for n = 6, nitrogen inversion may be slow relative to cleavage to **21**. Therefore, if stereoelectronic control is operative, **21** is the only product, and not because of any thermodynamic preference for aminoamide over lactam.

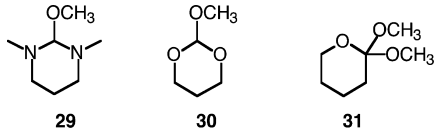
Our initial results supported stereoelectronic control, in that hydrolysis of **19** (n = 5, 6, R = H = R′) led only to aminoamide **21**, although this kinetic product is eventually converted to the thermodynamically more stable lactam **23**.[74] However, this test was flawed because of a mismatch of leaving abilities. For cleavage of a C−N bond to occur, the nitrogen must be protonated because a nitrogen anion is too poor a leaving group. From a study of unsymmetrical acyclic amidines it was found that the direction of cleavage is determined largely by the relative basicities of the two resulting amines.[75] Therefore, **21** (n = 5, 6, R = H = R′) was the only product simply because NH_3 is a poor leaving group. When the leaving abilities of RNH_2 and RR′NH are matched, hydrolysis of six-membered-ring amidines produces predominantly aminoamide **21** and only 3−9% lactam **23**, consistent with stereoelectronic control. However, hydrolysis of five- or seven-membered-ring amidines with matched leaving abilities produces substantial (ca. 50%) lactam **23**.[76] Similar results were obtained with R = CH_3 = R′, which eliminates the possibility of nitrogen inversion via proton exchange.[77] This selectivity is entirely parallel to E2 eliminations, which in six-membered rings show a strong preference for anti, but in five- and seven-membered rings can be syn.[78] Therefore, there is no general requirement for two lone pairs antiperiplanar to the leaving group. Moreover, stereoelectronic control, even in six-membered ring amidines, lowers the activation energy for cleavage by less than 2 kcal/mol.

Similar results were obtained in the hydrolysis of cyclic guanidines (**24**, n = 5, 6, 7).[79] In six-membered rings, antiperiplanar lone pairs are preferred, but in five- and seven-membered rings syn lone pairs are sufficient. Also, it was possible to isolate the stereochemical preference to the first step in amidine hydrolysis.[80] Above it was asserted that OH^- addition to **19** must occur antiperiplanar to two lone pairs, to produce **20** as an initial intermediate. In the addition of nucleophiles Nu^- to amidinium ion **25**, ***26cis*** is the kinetic product, even though it is less stable, because the nucleophile enters antiperiplanar to the developing lone pairs. However, the kinetic preference is generally only around 1 kcal/mol. Likewise, from the kinetics of the acid-catalyzed methoxy exchange in the stereoisomeric 2-methoxy-4,6-dimethyl-1,3-dioxanes (**27**) it was found that the stereoelectronic preference in nucleophilic addition to cation **28** (analogous to the formation of **15**) is worth no more than 2 kcal/mol.[81] More detailed evidence on the limitations of stereoelectronic control in reactions of tetrahedral intermediates is available in a review.[82]



■ ANOMERIC EFFECT

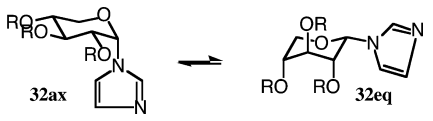
In connection with our studies of stereoelectronic control, we often encountered its thermodynamic counterpart, namely the anomeric effect.[83] This is the preference for an electronegative atom to be antiperiplanar to a lone pair. By comparing conformational equilibria in 2-methoxy-1,3-dimethylhexahydropyrimidine (**29**) and 2-methoxy-l,3-dioxane (**30**), we suggested that the anomeric effect here arises from dipole-dipole interactions.[84] Also, by comparing 2,2-dimethoxyoxane (**31**) with oxane itself or cyclohexane, we found that the anomeric effect lowers the barrier to ring inversion.[85]



■ REVERSE ANOMERIC EFFECT

We have devoted more attention to the so-called reverse anomeric effect. This is a claim that, in contrast to the above preference for an electronegative atom to be antiperiplanar to a lone pair, the preference of a positively charged substituent is to be syn to a lone pair. The strongest evidence for this effect was from conformational analysis of *N*-(tri-*O*-acetyl-α-D-xylopyranosy1)-imidazole (**32**) (Scheme 13).[86] In $CDCl_3$, the ring-inversion

Scheme 13. Reverse Anomeric Effect in Xylosylimidazoles



equilibrium favors **32ax** by 65:35 over **32eq**. On addition of acid, the equilibrium shifts to favor **32eq** by >95%. The protonated

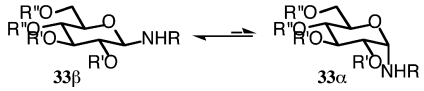
DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

imidazole is now equatorial, at the expense of three acetoxy groups, which must become axial. Because protonation of the distant nitrogen cannot change the size of the imidazolyl substituent, this result shows that the cationic substituent is more stable when syn to the lone pair on the ring oxygen.

Although we could rationalize this result on the basis of electrostatic interactions, we were skeptical because the experimental evidence depends on analysis of NMR coupling constants, not on direct measurement of the conformational equilibrium. We wanted to repeat this study with a group less exotic than imidazolyl, whose effective steric bulk might change unpredictably when protonated, owing to the need for ionic solvation.

We therefore investigated the anomeric equilibria of a series of glucosylamines (**33**, R = H, Me, Et, Bu; R′, R″ = combinations of H, CH_3CO, PhCH) and their protonated forms (Scheme 14).[87]

Scheme 14. Reverse Anomeric Effect in Glucosylamines



This equilibrium is not the ring inversion of the above study but anomerization, comparing α and β anomers, where only the NHR or NH_2R^+ changes position. The advantage is that the steric contribution from the bulk of an amino or ammonio substituent is known from the conformational equilibria of cyclohexylamine and cyclohexylammonium ion.

The steric bulk of a substituent X on a cyclohexane is expressed as its A value, as defined in eq 4. In particular, A_{NH_2} is 1.6 kcal/mol, which is less than $A_{NH_3^+}$, which is 1.9 kcal/mol. The 0.3 kcal/mol difference can be attributed to the extra H and to the need to solvate the positive charge. It ought to decrease the fraction of **33*α*** in acid by a factor of ∼1.6. Actually, the steric contribution to the equilibrium between **33*β*** and **33*α*** is slightly larger than 0.3 kcal/mol because C−O bond lengths are shorter than C−C, leading to larger steric effects. Then the fraction of **33*α*** in acid ought to decrease by >2-fold relative to the fraction for the free amine.

$$A_X = RT\ \ln([\text{equatorial X}]/[\text{axial X}]) \qquad (4)$$

We found by ^{1}H NMR integration that the effect of protonation on the equilibrium between **33*β*** and **33*α*** is small. For the amine, the average fraction of α anomer is 10%, but on protonation that fraction decreases to 3.5% in D_2O or 7.5% in organic media. If a reverse anomeric effect were operative, the fraction of **33*α*** in acid would be undetectable, diminished by both the increase of A and the reverse anomeric effect.

In terms of energies, the β anomer of the amines is favored by an average of 1.5 or 1.6 kcal/mol, whereas the β anomer of the ammonium ions is favored by an average of 2.0 kcal/mol in D_2O or 1.5 kcal/mol in organic solvents. Thus, the effect of protonation on this equilibrium is small. It is smaller even than what can be attributed simply to the greater steric bulk of a protonated amine. Therefore, the observed shift of the equilibrium toward **33*α*** must be attributed to a steric effect that is opposed by an enhanced anomeric effect of NH_2R^+, not a reverse one.

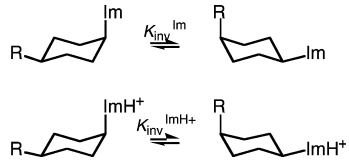
It should not be surprising that NH_2R^+ exerts an enhanced normal anomeric effect, greater than that of NHR. To the extent that the anomeric effect is the preference for an electronegative atom to be antiperiplanar to a lone pair, NH_2R^+ is more electronegative than NHR and exerts a greater anomeric effect.

STERIC HINDRANCE TO IONIC SOLVATION

We wanted to return to the equilibrium between **32ax** and **32eq**. Could the shift of equilibrium be due to an increased effective bulk of a protonated imidazolyl, which requires ionic solvation? How much larger *is* a protonated imidazolyl? That is the difference of A values, $A_{ImH^+} - A_{Im}$.

We can assess this with cis 4-substituted cyclohexylimidazoles, where there is no complicating anomeric or reverse anomeric effect. Scheme 15 poses the question and presents the method.

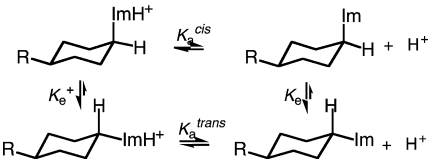
Scheme 15. Ring Inversion of Cis 4-Substituted Cyclohexylimidazoles and Their Protonated Forms



By low-temperature NMR integration the equilibrium constants for ring inversion were measured.[88] Also, it follows from eq 10 that $A_{Im} - A_R$ and $A_{ImH^+} - A_R$ are given by $2RT \ln K_{inv}^{Im}$ and $2RT \ln K_{inv}^{ImH^+}$. Then from the known A_{CH_3} and A_{Ph}, both A_{Im} and A_{ImH^+} were evaluated as 2.2 ± 0.1 kcal/mol, the same value regardless of whether the comparison was with methyl or phenyl and regardless of whether the substrate was protonated or not. Therefore, the difference $A_{ImH^+} - A_{Im}$ must be small, but its value cannot be measured with an accuracy better than ±0.1 kcal/mol.

We can also assess this with conformationally locked cyclohexylimidazoles. Scheme 16 poses the question and suggests an

Scheme 16. Thermodynamic Cycle Relating Cis and Trans 4-Substituted Cyclohexylimidazoles and Their Protonated Forms



improved method. According to eq 4, each A value is equal to $RT \ln([\text{equatorial Im}]/[\text{axial Im}])$, so the difference of A values is given by the first equality in eq 5, where K_e^+ and K_e are the equilibrium ratios for cis-to-trans conversion of a 4-substituted cyclohexylimidazolium ion and cyclohexylimidazole, respectively. The ratio K_e^+/K_e reflects the extra destabilization associated with having the ionic group axial, where its solvation is hindered. However, unlike the ring inversion in Scheme 15, interconversion of cis and trans does not occur, so K_e^+/K_e cannot be measured. We must focus instead on the ratio K_a^{cis}/K_a^{trans}. If we can measure this ratio of acidity constants, it must equal the desired ratio, K_e^+/K_e, because Scheme 16 is a thermodynamic cycle, leading to the complete form of eq 5.

$$A_{ImH^+} - A_{Im} = RT\ \ln(K_e^+/K_e) = RT\ \ln(K_a^{cis}/K_a^{trans}) \qquad (5)$$

The reason why K_a^{cis}/K_a^{trans} serves to evaluate the difference in A values is that the extra destabilization associated with having an ionic group axial also acidifies that group. The task then is to measure the relative acidities of cis and trans stereoisomers.

DOI: 10.1021/acs.joc.6b02390
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These could be separated, albeit incompletely, by HPLC, but the usual titration method is too inaccurate to compare K_a^{cis} with K_a^{trans}. Fortunately, there is a better method.

NMR TITRATION

To measure K_a^{cis}/K_a^{trans}, we developed a new NMR titration method and applied it to 4-phenylcyclohexylimidazole (Scheme 16, R = Ph). To a mixture of cis and trans stereoisomers small aliquots of acid are added, and the chemical shifts of H1 are measured after each addition. As the more basic stereoisomer is protonated, its chemical shift moves ahead of that of the less basic. The observed chemical shift of the cis stereoisomer, δ_c, is given in eq 6, where δ_C and δ_{CH^+} are limiting chemical shifts of unprotonated and protonated forms, respectively. A similar equation holds for δ_t. These equations then lead to eq 7, where $K = K_a^{cis}/K_a^{trans}$.

$$\delta_c = \frac{\delta_C[C] + \delta_{CH^+}[CH^+]}{[C] + [CH^+]} \quad (6)$$

$$\delta_c = \delta_C + \frac{(\delta_{CH^+} - \delta_C)(\delta_t - \delta_T)}{(1 - K)(\delta_t - \delta_T) + K(\delta_{TH^+} - \delta_T)} \quad (7)$$

Figure 8 shows such a plot for NMR titration of *N*-(4-phenylcyclohexyl)imidazole (Scheme 16, R = Ph) in aqueous acetone. The dashed horizontal and vertical lines display the limiting behaviors for the hypothetical case where the trans is very much more basic than the cis and is protonated first. The dashed diagonal line displays the limiting behavior for the hypothetical case where cis and trans have identical basicities. The + symbols are the experimental data, which deviate slightly but detectably from the diagonal, showing that the cis and trans stereoisomers have different basicities. The curve is the nonlinear least-squares fit to eq 7, from which it is possible to evaluate *K*.

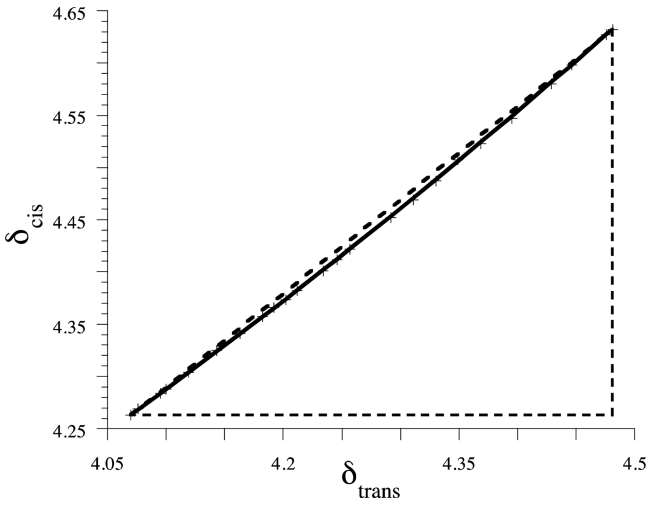

Figure 8. Plot of H1 chemical shifts of cis and trans *N*-(4-phenylcyclohexyl)imidazole (Scheme 16) on addition of small aliquots of acid. Reproduced from ref 88. Copyright 1994 American Chemical Society.

It is easier to convert these quantities to the linearized form in eq 8. Then a plot of the left-hand side against $(\delta_c - \delta_C)(\delta_{TH^+} - \delta_t)$ should be a straight line, with slope *K* and intercept 0.

$$(\delta_t - \delta_T)(\delta_{CH^+} - \delta_C) = K(\delta_c - \delta_C)(\delta_{TH^+} - \delta_t) \quad (8)$$

Figure 9 shows such a plot for NMR titration of *N*-(4-phenylcyclohexyl)imidazole stereoisomers in aqueous acetone. The correlation coefficient is 0.99965, the intercept is −0.0002 ± 0.0002, which is properly zero, and the slope is 1.114 ± 0.006. Then, from eq 5, the desired $A_{ImH^+} - A_{Im}$ is 0.089 ± 0.004 kcal/mol. This represents the extra repulsion energy of a protonated imidazole in the axial position of a cyclohexane, relative to unprotonated and relative to equatorial. This is not a simple size effect because protonation occurs on the distant nitrogen. But it does change the effective size because of the need for solvation of the positive charge. Moreover, although this effect is too small to have been measured from low-temperature NMR integration of the species in Scheme 15, whose error is ±0.1 kcal/mol, it is very accurately measurable by NMR titration.

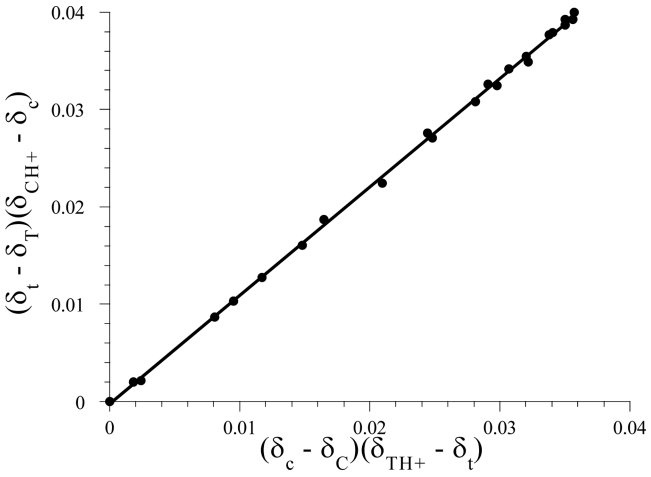

Figure 9. Linearized plot (eq 8) from chemical shifts during NMR titration of a mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazole (Scheme 16) with acid. Reproduced from ref 88. Copyright 1994 American Chemical Society.

ADVANTAGES OF NMR TITRATION

There are many advantages to NMR titration for evaluating relative acidities or basicities:

- It is highly accurate because it depends on measurement only of NMR chemical shifts, never pH or molarity or volume of titrant, as in the usual titrations.
- It is possible to use ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, etc.
- It is applicable to a mixture of isomers or stereoisomers, without any necessity for separating closely related substances.
- It is insensitive to impurities because all measurements are made in a common solution.
- It is applicable to aprotic solvents, ones in which a pH electrode would be useless.
- From the temperature dependence it is possible to separate enthalpy and entropy contributions to ΔpK_a.

Among the NMR titrations that demonstrate the power of this method are the measurements of the relative basicities of *cis*- and *trans*-4-*tert*-butylcyclohexylamine (**34**), the relative acidities of *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acid (**35**), and the relative basicities of all four stereoisomers of 2-decalylamine (**36**), synthesized as a four-component mixture.[89]

DOI: 10.1021/acs.joc.6b02390
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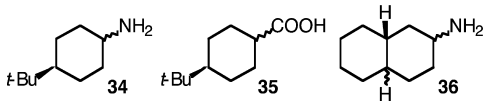
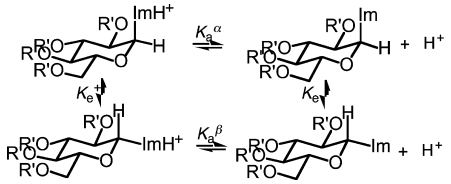


APPLICATION OF NMR TITRATION TO REVERSE ANOMERIC EFFECT

We return to the question of whether a protonated substituent has a greater preference for the axial position in sugars, as was claimed for **32**. Instead of ring inversion in a xylosylimidazole we compare anomers of glucosylimidazole and of its conjugate acids (Scheme 17). Glucose derivatives, with bulky groups (OR, CH_2OR, R = H, CH_3CO) that remain equatorial, were chosen specifically to avoid complications due to ring inversion. In principle, the magnitude of the reverse anomeric effect could be measured as the increase in the proportion of the β anomer on protonation of a mixture of anomers. However, in contrast to glucosylamines **33**, glucosylimidazoles are configurationally stable and do not equilibrate. Instead, a thermodynamic cycle permits measuring the reverse anomeric effect from the difference in pK_a of the two anomers. If the reverse anomeric effect increases the proportion of β anomer on protonation, then the α anomer must be more acidic than the β, and the NMR titration method can determine the acidity difference quantitatively.

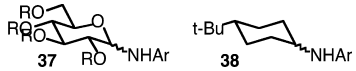
Scheme 17. Anomeric Equilibria in Glucosylimidazoles



By NMR titration it was found that K_a^{α}/K_a^{β} ranges from 0.520 to 0.970.[90] The α anomer is *less* acidic than the β. This is not a reverse anomeric effect but an enhancement of the normal anomeric effect. A protonated imidazolyl has a greater preference for the axial position than an unprotonated one does because protonated imidazolyl is more electronegative than unprotonated, which enhances the normal anomeric effect.

Similar behavior is observed for other glycosylimidazoles.[91] A protonated imidazolyl has a greater preference for the axial position than an unprotonated has. This preference outweighs the small steric effect, arising from hindrance to ionic solvation, as seen in Scheme 16. Again, these results are opposite to what is expected from the reverse anomeric effect. We conclude that there is no firm evidence for this effect, only an enhanced normal anomeric effect from cationic substituents.

The opposing roles of the anomeric effect and of steric hindrance to ionic solvation are nicely seen in the *N*-protonation-induced shifts of both the anomeric equilibrium in *N*-(tetra-*O*-methylglucopyranosyl)anilines **37** and the cis/trans equilibrium in *N*-(4-*tert*-butylcyclohexyl)anilines **38**.[92] Both K_a^{α}/K_a^{β} and K_a^{cis}/K_a^{trans} are > 0, meaning that the equilibrium shifts toward equatorial upon *N*-protonation, consistent with steric hindrance to ionic solvation. This shift is smaller for **37** than for **38**, consistent with an enhancement of the normal anomeric effect that counters the steric hindrance and reduces the shift toward the equatorial β anomer.



The contrasting substituent effects on the conformational equilibria are informative. The shift toward equatorial upon *N*-protonation decreases slightly but detectably with electron-donating substituents on the cyclohexylaniline **38**, which fine tune the steric hindrance to ionic solvation, as shown in Figure 10. In contrast, that shift increases for the glucosylanilines **37**. This is consistent with an enhancement of the normal anomeric effect due to a more localized positive charge, rather than with a reverse anomeric effect. These results thus define further the substituent dependence of the anomeric effect. More details are available in reviews.[93]

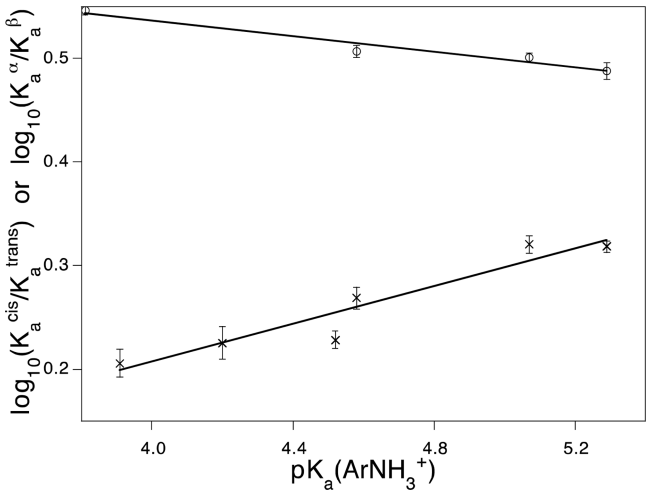
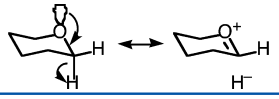


Figure 10. Plot of $\log(K_a^{\alpha}/K_a^{\beta})$ of tetra-*O*-methylglucosylanilines (x) and $\log(K_a^{cis}/K_a^{trans})$ of 4-*tert*-butylcyclohexylanilines (o) versus pK_a of the corresponding $ArNH_3^+$. Reproduced from ref 92. Copyright 2003 American Chemical Society.

PERLIN EFFECT

A related phenomenon is the decrease of the one-bond C−H coupling in the NMR spectra of molecules with axial C−H adjacent to the oxygen of an oxane.[94] This is known as the Perlin effect (not Perrin). It is generally interpreted in terms of an n_O-σ^*_{CH} anomeric interaction, whereby a lone pair is delocalized into the antiperiplanar C−H bond, as suggested in Scheme 18. Nevertheless, calculated coupling constants $^1J_{CH}$ in three ethers follow a cosine dependence on the COCH dihedral angle θ.[95] This is consistent with the Perlin effect, with a lower $^1J_{CH}$ at $\theta = 60°$ than at 180°. The inconsistency is that it does not follow the cos(2θ) dependence of n-σ^* delocalization, which was therefore rejected as accounting for $^1J_{CH}$. Instead the cosine dependence was attributed to an electrostatic interaction between the COC dipole and the C−H bond.

Scheme 18. Hyperconjugative Delocalization Assumed to Decrease Axial $^1J_{CH}$



To test this experimentally, one-bond carbon−carbon coupling constants $^1J_{CC}$ were measured in a series of cyclic and acyclic ethers.[96] Again, the dependence on COCC dihedral angle θ follows cos(θ), consistent with an electrostatic interaction, rather than the cos(2θ) characteristic of n-σ^* delocalization, which was rejected.

SECONDARY ISOTOPE EFFECTS ON BASICITY

Above it was stated that the CD_3 groups in **10** increase the basicity of the N to which they are attached. This is a secondary

DOI: 10.1021/acs.joc.6b02390
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isotope effect (IE) because the bond to the isotope remains intact. The evidence for such an effect came from a comparison of the basicities of $PhCH_2NH_2$ and $PhCD_2NH_2$.[97] By titration, the latter was found to be more basic, with a ΔpK_a of 0.054 ± 0.001. Thus, the deuterium is effectively electron-donating.

In contrast, deuterium retards solvolysis,[98] where it is effectively electron-withdrawing. Actually, this is not an electronic effect but is due to changes of hybridization. In solvolysis, the hybridization of carbon changes from sp^3 to sp^2, and there are decreases in vibrational frequencies and zero-point energies that account for the IE. In amines there is no obvious change of vibrational frequencies on protonation and no obvious origin for the IE on basicity.

Instead of hybridization changes, the isotope effect on amine basicity was attributed to an inductive effect.[99] This cannot be due to a simple difference in the electronegativities of H and D[100] because the Born-Oppenheimer approximation guarantees that the electronic wave function is independent of nuclear mass. Instead, it arises because the positive charge in the protonated amine interacts with the C−H or C−D dipole. Dipole moment is the product of charge separation and bond length, and the C−H bond length is greater than that of C−D, owing to anharmonicity.

I was skeptical of this explanation. A C−H bond is quite nonpolar, so that the charge separation across that bond is very small. Also, the anharmonicity leads to a difference of bond lengths of only 0.005 Å. Therefore, the contribution from an inductive effect seemed to be too small. Perhaps the IE was just experimental error. The ΔpK_a of 0.054 is near the limit of accuracy of pH titration, although the error estimate of ±0.001 appears to be genuine. A simpler explanation for an apparent IE is the presence of impurities. Because $PhCH_2NH_2$ and $PhCD_2NH_2$ come from separate preparations, each may have had different impurities, which can bias the pK_a measurement. Indeed, ΔpK_a from a repeat measurement 16 years later was different, 0.032,[101] still with the same precision (which is not the same as accuracy). In view of this uncertainty, I did not want to burden a student with the multistep synthesis of the statistical mixture of isotopologues of **10** without more confidence that the isotopic perturbation would be informative.

We therefore undertook to measure a secondary deuterium IE on basicity, but by NMR titration of a mixture of $PhCH_2ND_2$ and $PhCHDND_2$ in D_2O.[102] This sacrifices a factor of 2 relative to $PhCD_2NH_2$, but it permits ^1H NMR titration because an intrinsic isotope shift separates the signals of CH_2 and CHD. Even though it was necessary to synthesize $PhCHDNH_2$ independently, it was mixed with $PhCH_2NH_2$, so that impurities do not interfere. Small aliquots of acid were then added to this mixture, and the two chemical shifts were measured. Figure 11 shows the fit of the data to eq 8, which becomes eq 9, where δ_{h0} and δ_{d0} or δ_{hH} and δ_{dH} are for the deprotonated or protonated h and d forms, measured at the beginning or end of the titration.

$$(\delta_d - \delta_{d0})(\delta_{hH} - \delta_h) = (K_a^H/K_a^D)(\delta_h - \delta_{h0})(\delta_{dH} - \delta_d) \quad (9)$$

The least-squares slope of Figure 11 is 1.0420 ± 0.0009, and the correlation coefficient is >0.99999, attesting to the excellent linearity of the plot. The average K_a^H/K_a^D of 1.0419 ± 0.0009 from replicate titrations corresponds to a ΔpK_a of 0.0178 ± 0.0004, which is both a precision and an accuracy much better than can be achieved with a pH titration. This success is because the NMR titration method is competitive, so that even a minute difference in basicities can be detected. Similar H/D isotope

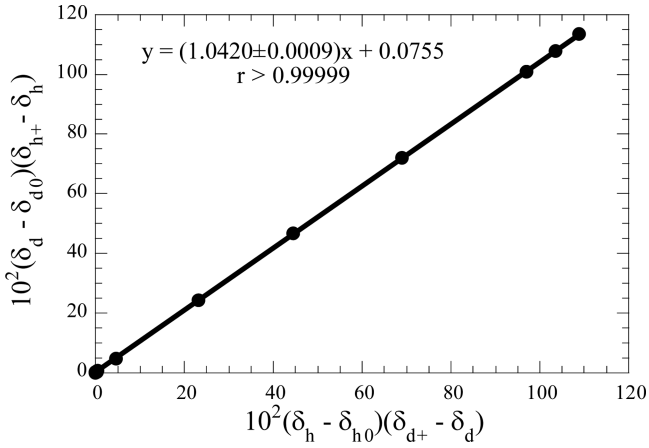

Figure 11. Linearized plot (eq 9) of CH_2 and CHD chemical shifts δ_h and δ_d of a mixture of $PhCH_2ND_2$ and $PhCHDND_2$ + acid in D_2O. Reproduced from ref 102. Copyright 2003 American Chemical Society.

effects were observed for $CH_{3-n}D_nNH_2$, CH_3NHCD_3, and $PhN(CH_3)CD_3$.

The value of 0.0178 is quite close to half the 0.032 observed when the experiment was repeated.[101] Therefore, I was forced to accept the existence of a secondary deuterium IE on amine basicity. But I was still skeptical of an explanation based on inductive effects and anharmonicity. Above I asserted that there is no obvious change of vibrational frequencies on protonation and no obvious origin for the IE on basicity. Of course, what is obvious depends on who you are. To me there was no obvious change of vibrational frequencies, but alkaloid chemists know about Bohlmann bands in amines.[103] These are characteristic IR absorptions at 2700−2800 cm^{-1}, lower than the 2900 cm^{-1} of a typical sp^3 C−H stretch. Upon *N*-protonation these "disappear"; actually, they revert to typical frequencies and are lost among other C−H modes. Therefore, the zero-point energy increases on protonation, but the increase is less for C−D than for C−H. Indeed, a C−H frequency increase of 100 cm^{-1} corresponds to a ΔpK_a of 0.03, comparable to the observed IEs.

The lower frequency of the Bohlmann bands is generally attributed to n-σ^* delocalization of the nitrogen lone pair into an antiperiplanar C−H antibonding orbital, as illustrated in Scheme 19. As a result, the zero-point energy of that C−H

Scheme 19. n-σ^* Delocalization of Nitrogen Lone Pair into Antiperiplanar C−H Antibonding orbital

stretching mode is decreased and to a greater extent than a C−D mode. On protonation, those zero-point energies revert to ordinary values, but the C−H increases to a greater extent. Therefore, the C−H isotopologue resists protonation.

STEREOELECTRONIC ISOTOPE EFFECT

If the IE arises from the delocalization in Scheme 19, this is a stereoelectronic effect, dependent on the orientation of the lone pair relative to the C−H bond. This can be tested experimentally with 1-benzyl-4-methylpiperidine **39**. The purpose of the CH_2Ph group is to occupy the equatorial position so that the lone pair is fixed axial. The synthesis from the imide used $LiAlD_4$ to produce primarily d_4 product, but with sufficient $LiAlH_4$ to produce some

DOI: 10.1021/acs.joc.6b02390
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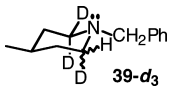
d_3 product (shown) and very little d_2. The d_3 product is a mixture of two isotopomers (isomers that differ in the position of an isotope, as distinguished from isotopologues, which differ in the number of isotopic substitutions), which differ by whether H or D is trans to the methyl. If the D is trans to the methyl, it is axial and antiperiplanar to the lone pair. If instead the H is trans to the methyl and axial, its zero-point energy is reduced by n-σ^* delocalization, so that that isotopomer ought to be less basic.



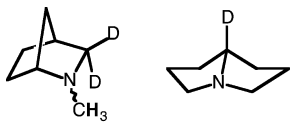
39-d_3

Experimentally, by ^{1}H NMR titration of the CHD, K_a^{eqD}/K_a^{axD} was found to be 1.060 ± 0.006, with the isotopomer with an axial D more basic. The accuracy is lower than for $PhCHDNH_2$ because the CH signals here are broadened by coupling to adjacent H. Nevertheless, this is remarkable accuracy for the difference in basicity between two species that are so very similar. Besides, it is a difference that would not be believed if it were obtained by pH titration of the separate isotopomers, somehow synthesized independently.

We therefore rejected an explanation for such IEs as arising from the inductive interaction of the C−D dipole moment with the positive charge on the protonated amine, which would be angle-independent. This is a secondary IE that arises from n-σ^* delocalization of a lone pair into an antiperiplanar C−H antibonding orbital, as in Scheme 19.

OTHER SECONDARY DEUTERIUM ISOTOPE EFFECTS ON ACIDITY

In support of secondary deuterium IEs on basicity, DFT calculations of C−H bond lengths in rotamers of CH_3NH_2 and of C−D frequencies in rotamers of DCH_2NH_2 showed that a bond antiperiplanar to the lone pair is longer and has a lower stretching frequency.[104] A lengthening and a frequency decrease are also seen with a synperiplanar lone pair, but only to about half as much as anti. These calculations were confirmed experimentally with 2-methyl-2-azabicyclo[2.2.1]heptane-d_2 (**40**) and pyrrolizidine-d (**41**). No angle-independent IE attributable to an inductive effect could be detected.



40 **41**

From the slope and intercept of the temperature dependence of the IE in CH_3NHCD_3, $\Delta\Delta H^\circ$ and $\Delta\Delta S^\circ$ were found to be −88 ± 21 cal/mol and −0.034 ± 0.072 cal/(mol K), respectively. The latter is not significantly different from zero. A temperature dependence and a non-zero $\Delta\Delta H^\circ$ are contrary to a previous study, where the effect was too small to measure.[105] This is consistent with an origin in zero-point energies, rather than in an inductive effect, which ordinarily appears in the entropy. (The most familiar example is the comparison of the acidities of formic and acetic acids.)

As an aside, it may be mentioned that $\sigma_{\Delta S}$ and $\sigma_{\Delta H}$, the errors in $\Delta\Delta S^\circ$ and $\Delta\Delta H^\circ$, respectively, must satisfy eq 10, where T_{avg} is an average temperature of measurement.[106] (Strictly, $T_{avg} = 1/((\sum(1/T)^2/n))^{1/2}$, where n is the number of temperatures.) This follows from the result that the errors σ_b and σ_a in the slope and intercept, respectively, of a linear least-squares fit to $y = a + bx$, must satisfy $\sigma_a/\sigma_b = (\sum x^2/n)^{1/2}$.

$$\sigma_{\Delta H} = T_{avg}\sigma_{\Delta S} \tag{10}$$

Secondary deuterium IEs on the basicities of various deuterated pyridines and of 2,6-lutidine-2,6-$(CD_3)_2$ were also measured by NMR titration.[107] Deuteration increases the basicity, but the IE per deuterium is largest for substitution at the 3-position and smallest for the nearby 2-position, which ought to show the largest inductive effect. DFT calculations overestimate the IEs but support an origin in vibrational frequencies and zero-point energies.

Secondary IEs on the basicities of isotopologues of trimethylamine have also been measured.[108] Again, deuteration increases the basicity. Figure 12 shows the linearized plot (eq 9) of chemicals shifts from an NMR titration of a mixture of tri(methyl-d)- and tri(methyl-d_2)-ammonium ions in D_2O, for which the correlation coefficient is an impressive 0.999999. Again, the IE is attributed to the decrease of the CH stretching frequency and zero-point energy by n-σ^* delocalization. The dependence on dihedral angle leads to a preference for conformations with H antiperiplanar to the lone pair and D gauche. This preference then leads to a calculated nonadditivity of IEs. The exceptional accuracy made it possible to confirm this nonadditivity experimentally. In particular, the decrease in basicity per deuterium increases with the number of deuteriums. This nonadditivity is a violation of the widely assumed Rule of the Geometric Mean.

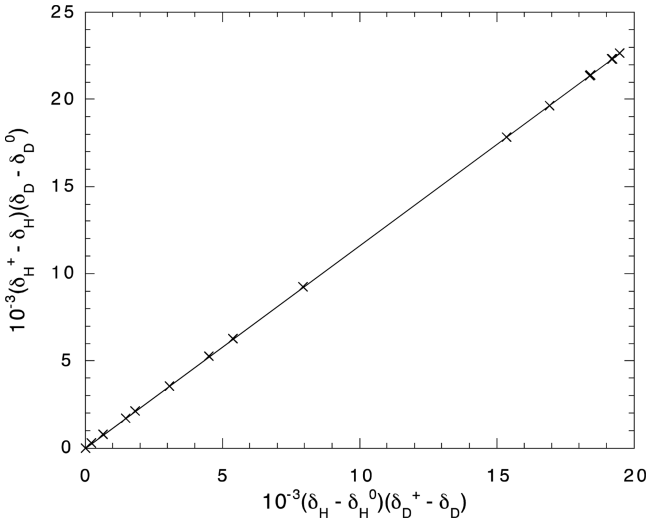


Figure 12. NMR titration of a mixture of $(CH_2D)_3ND^+$ and $(CHD_2)_3ND^+$. Reproduced from ref 108. Copyright 2008 American Chemical Society.

Secondary deuterium IEs on acidities of carboxylic acids and phenols were also measured by NMR titration.[109] Deuteration definitely decreases the acidity. Figure 13 shows the data, along with calculated IEs, but scaled down 6-fold because these DFT calculations ignore solvation and overestimate the IE. For aliphatic acids, the IEs decrease as the site of deuteration becomes more distant from the acidic OH, as expected, but IEs in both phenol and benzoic acid remain invariant as the site of deuteration moves from ortho to meta to para. The IEs originate in isotope-sensitive vibrations whose frequencies and zero-point energies are lowered upon deprotonation. For the aromatic acids the lack of a falloff with distance is evidence against an inductive origin.

DOI: 10.1021/acs.joc.6b02390
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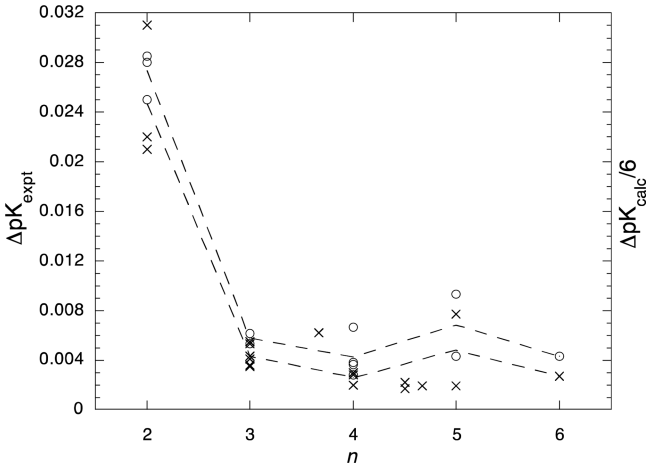

Figure 13. Secondary deuterium IEs (ΔpK_a per D) on acidities of RCOOH, phenol, and benzoic acid versus *n*, the number of bonds between D and O: (x) observed, (o) calculated, scaled down 6-fold. Reproduced from ref 109. Copyright 2007 American Chemical Society.

From the temperature dependence of the secondary IEs on acidities of formic-*d* acid, acetic-*d* and -d_2 acids, and 3,5-difluorophenol-d_3, it was possible to evaluate $\Delta\Delta H°$ and $\Delta\Delta S°$.[110] Again, the IE appears in $\Delta\Delta H°$, consistent with an origin in isotope-sensitive vibrations and zero-point energies. For DCOOH, the IE can be clearly attributed to the *n*-σ* delocalization in the anion of Scheme 20.

Scheme 20. *n*-σ* Delocalization Reduces C−H Stretching Frequency and Zero-Point Energy

The alternative interpretation is that the IE on acidity arises from the interaction of the ionic charge with the bond dipole, which differs between C−H and C−D because of anharmonicity.[111] However, we assert that it is not necessary to invoke anharmonicity to account for the IEs. The harmonic and anharmonic frequencies calculated for formic acid and formate anion do differ. Nevertheless, the IE calculated from harmonic frequencies is the same as from anharmonic.[112] We therefore conclude that if harmonic frequencies can account for the IEs, it is not necessary to invoke an inductive origin for the IEs arising from anharmonicity. More details are available in a review.[113]

Still another example of secondary IEs on acidity comes from calculated primary and secondary ^{18}O IEs on the acidities of carbon, boron, nitrogen, and phosphorus acids.[114] In some cases, in particular, HCOOH, the secondary IE was found to be larger than the primary. This is counterintuitive because the H atom that is lost is closer to the ^{18}O that is responsible for the primary IE. The relative magnitudes of the IEs might be associated with the higher vibrational frequency of the C=O stretch, compared to C−O. However, this contribution is small, and the larger secondary IE comes primarily from the moment-of-inertia factor.

All the above IEs are secondary equilibrium IEs on acidity. The kinetic counterpart is the secondary kinetic IE (KIE) for dissociation of aqueous ammonium ion. This was measured by ^1H NMR saturation transfer on ^{15}N-labeled ammonium ion in an H_2O-D_2O mixture.[115] The secondary deuterium KIE k_H/k_D was found to be 1.07 ± 0.01.

We also measured secondary deuterium KIEs on the rates of amide C−N rotation, in connection with our studies of H exchange. This study was prompted by the report of a secondary deuterium KIE k_H/k_D of 2.0 for trans-to-cis isomerization of 1-phenylcyclohexene-2-*d*.[116] The high value was attributed to complete loss of the zero-point energy of the out-of-plane C−H bending mode. Might this also occur in amide rotation? Kinetics were followed by ^1H, ^{13}C, or ^{15}N NMR line-shape analysis, saturation transfer, or selective inversion−recovery. Isotope shifts separate the signals, so that we could measure the rates for H and D amides simultaneously in the same solution. For HCONHD k_H/k_D is 1.16 ± 0.10, and for $DCON(CH_3)_2$ it is 1.18 ± 0.04. For $HCONDCH_3$ and $HCONDC_6H_4NO_2$-*p* k_H/k_D is 1.00 ± 0.03 and 1.04 ± 0.03, which are zero or quite small.[117] The KIE in HCONHD may arise from thermal population of excited vibrational states, a feature that is readily calculated but perhaps never before observed. Ordinarily it does not contribute because normal modes involving hydrogen are too high-frequency for their excited vibrational states to be populated. What is unusual in formamide is the low frequency of the NH_2 pyramidalization mode, 289 cm^{-1},[118] or 222 cm^{-1} in $HCOND_2$.[119] With such a low frequency, excited vibrational states of HCONHD are thermally populated. Its free energy is then lowered by the resulting entropy of mixing, increasing the free energy of activation so that it rotates more slowly than $HCONH_2$.

PRIMARY KINETIC ISOTOPE EFFECTS

Finally we turn to primary deuterium KIEs on hydron transfer, where hydron is generic for proton or deuteron (or triton). Direct nitrogen-to-nitrogen hydron transfer from ammonium ion to ammonia was studied by ^1H NMR, again on a solution of ^{15}N-labeled ammonium ion in an H_2O-D_2O mixture.[120] Figure 14

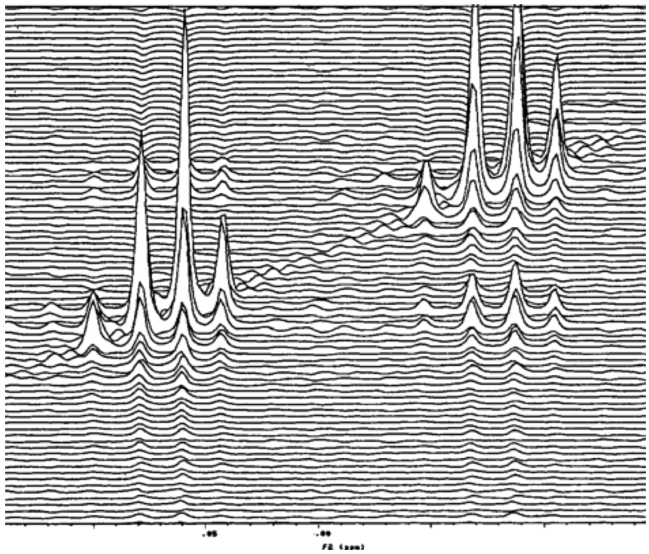

Figure 14. NH region of the 2D-EXSY spectrum of a mixture of $NH_nD_{4-n}^+$ isotopologues. Reproduced from ref 120. Copyright 1994 American Chemical Society.

shows the ^1H NH region of the pure-absorption mode 2D-EXSY spectrum of a mixture of $NH_nD_{4-n}^+$ isotopologues, each one separated by an isotope shift. The off-diagonal signals represent site-to-site exchange. From the intensities the second-order rate constant for proton transfer from ammonium ion to ammonia

DOI: 10.1021/acs.joc.6b02390
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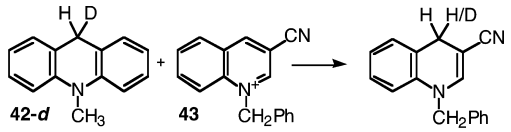
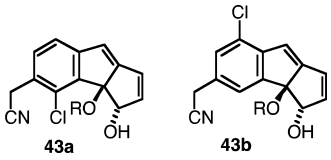
was found to be 1.6×10^8 M^{-1} s^{-1}, and the KIE k_H/k_D was found to be 1.8 ± 0.2. What is remarkable here is that although deuteron transfers are invisible to ^{1}H NMR, the 2D-EXSY rate constants do assess those rates too.

In connection with our interest in hydrogen tunneling, the intramolecular KIE for hydride transfer from 10-methyl-9,10-dihydroacridine-*d* (**42**-*d*) to 1-benzyl-3-cyanoquinolinium ion (**43**) (Scheme 21) was measured by NMR (and by mass spectrometry).[121] The result, k_H/k_D = 5−6, is a very ordinary and anticlimactic KIE, inconsistent with the unusually high intermolecular KIEs, attributed to tunneling, that were derived by fitting the kinetics of reactions of **42** and **42**-d_2 with **43** to a two-step mechanism with an intermediate complex.[122] We therefore rejected that two-step mechanism.

Scheme 21. Hydride Transfer from 10-Methyl-9,10-dihydroacridine-*d* to 1-Benzyl-3-cyanoquinolinium

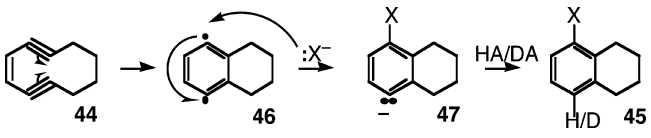


The last topic to present is an unusually low primary KIE for hydron transfer to an aryl anion. We became involved in this area of research through an inquiry from my colleague Bill Fenical at the Scripps Institution of Oceanography. He had isolated a 1:1 mixture of marine natural products (**43a**, **43b**, R = 3-oxo-4-methyl-β-fucosyl).[123] His understanding of their biosynthesis was that they arise from an enediyne, which undergoes cycloaromatization to a *p*-benzyne diradical, which then adds H and Cl. *p*-Benzynes are known to add either H atoms or Cl atoms,[124] but one of each would be too fortuitous. Therefore, he was inspired to ask whether the Cl might be added as Cl^-, from seawater.



This hypothesis was tested in collaboration with my colleague Joe O'Connor and his Ph.D. student Betsy Rodgers. We could show experimentally that the enediyne cyclodeca-1,5-diyn-3-ene **44**, in the presence of lithium halide in DMSO-d_6, is converted to 1-halotetrahydronaphthalene **45** (Scheme 22).[125] The kinetics are first order in **44** but zero order in halide, consistent with rate-limiting cycloaromatization to a *p*-benzyne biradical **46** that rapidly adds halide to form aryl anion **47**, which is then protonated. This is an entirely new type of reaction, nucleophilic addition to a biradical, as manifested by the combination of two-electron and one-electron arrows. Moreover, DFT calculations attest to the feasibility of this reaction.

Scheme 22. Quenching of an Aryl Anion Formed by Halide Addition to the *p*-Benzyne Resulting from Cycloaromatization of an Enediyne



Other anionic nucleophiles, such as azide and thiocyanate, also add to **46**. Although the rate of reaction is independent of the concentration of nucleophile, competition experiments provide their relative reactivities.[126] Smaller ions, such as Cl^-, are less reactive because they are more heavily solvated.

Deuterium incorporation in **45** was detected by both ^{1}H NMR and GC−MS. The deuterium source must be DMSO-d_6, or CD_3CN in some subsequent experiments. Only a very strong base, like aryl anion **47**, would be capable of hydron removal from so weak an acid as DMSO-d_6 or CD_3CN, in competition with trace water or added carboxylic acid. Competition experiments showed that **47** is remarkably unselective toward hydronating agents, with H_2O only 3.6 times as reactive as CH_3CN and only 16 times as reactive as DMSO, despite many orders of magnitude difference in acidities.[127] The H/D KIEs are also low, 1.2 for water, 2.2 for acetonitrile, and 2.5 for DMSO.

The same selectivities are seen with $Bu_4N^+I^-$ as with Li^+I^-, showing that in neither case can an aryllithium be formed. Besides, hydronation of an authentic aryllithium or aryl Grignard is fully selective toward water over acetonitrile or DMSO. Therefore, the **47** that is formed by nucleophilic addition to **46** is a "naked" aryl anion, not coordinated to Li or stabilized by H-bonding to solvent.

■ TOPICS OMITTED

Some topics were omitted from this discussion because their pursuit did not develop logically from other projects. Among these are (1) the pH dependence of the rates of NH exchange of aqueous biotin,[128] (2) variable-temperature NMR without a variable-temperature probe,[129] (3) an unusually strong dependence of conformation on solvent, arising from steric hindrance to solvation of a neutral amine that is hydrogen-bonded to water,[130] (4) isotopic perturbation of resonance,[131] (5) adaptation of a More O'Ferrall−Jencks diagram to support a mechanism involving electron transfer concerted with heavy-atom motion,[132] (6) measurement of a solvent KIE, leading to the *complete* mechanism of aldol condensation.[133]

■ CONCLUSIONS

This review has presented definitive results across a wide range of topics, addressed with a variety of powerful experimental techniques, some of which were developed specifically for a particular project. We have obtained much fundamental knowledge, not of any obvious practical application, but providing a better understanding of how molecular structure determines chemical reactivity. I hope that this presentation will be instructive in showing both how the results of one project expose additional questions and how logic is applied to answer those questions.

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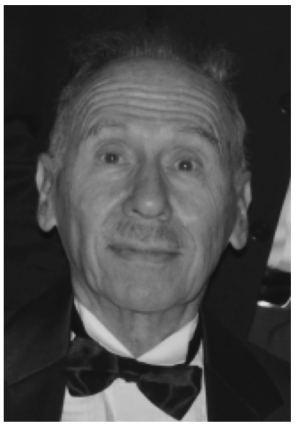
Notes

The author declares no competing financial interest.

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

Biography



Born in Pittsburgh in 1938, Charles L. Perrin graduated from Harvard College in 1959 and received his Ph.D. in 1963 from Harvard University, under the direction of the late F. H. Westheimer. Following an NSF Postdoctoral Fellowship at UC Berkeley, he joined the founders of the new campus at UC San Diego, where he is now Distinguished Professor of Chemistry (not emeritus). His research spans a broad range of structural and mechanistic chemistry, including anomeric effects, stereoelectronic control, isotope effects, dynamic NMR, solvation, reactive intermediates, and hydrogen bonding.

■ ACKNOWLEDGMENTS

This research was supported by a continuous series of NSF grants, the most recent of which is CHE11-48992. I am deeply indebted to my many excellent co-workers, included among the references. I am grateful to the American Chemical Society for the James Flack Norris Award in Physical Organic Chemistry, and I thank *The Journal of Organic Chemistry* and C. Dale Poulter for the invitation to submit this Perspective.

■ REFERENCES

(1) Perrin, C. L. *249th ACS National Meeting*, Denver CO, March 2015; American Chemical Society: Washington, DC, 2015; Abstract ORGN305.
(2) Perrin, C. L. *Isr. J. Chem.* **2016**, *56*, 46.
(3) Perrin, C. L. *J. Phys. Org. Chem.* **2015**, *28*, 203.
(4) Perrin, C. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 2773.
(5) Perrin, C. L. *J. Am. Chem. Soc.* **1964**, *86*, 256.
(6) Perrin, C. L.; Skinner, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 3389.
(7) Perrin, M. H.; Gouterman, M.; Perrin, C. L. *J. Chem. Phys.* **1969**, *50*, 4137.
(8) (a) Perrin, C. L. *Science* **1974**, *183*, 551. (b) Ramirez, G.; Karlsson, B.; Perrin, C. L. *Brain Res.* **1974**, *79*, 296. (c) Hydén, H.; Lange, P. W.; Perrin, C. L. *Brain Res.* **1977**, *119*, 427.
(9) Vold, R. L.; Daniel, E. S.; Chan, S. O. *J. Am. Chem. Soc.* **1970**, *92*, 6771.
(10) Perrin, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 5628.
(11) Neuman, R. C., Jr.; Hammond, G. S. *J. Phys. Chem.* **1963**, *67*, 1659.
(12) Perrin, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 5631.
(13) Perrin, C. L.; Schiraldi, D. A.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 196.
(14) Perrin, C. L.; Johnston, E. R. *J. Magn. Reson.* **1979**, *33*, 619.
(15) Perrin, C. L.; Johnston, E. R.; Lollo, C. P.; Kobrin, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 4691.
(16) Menger, F. M.; Saito, G. *J. Am. Chem. Soc.* **1973**, *95*, 6838.
(17) Perrin, C. L.; Johnston, E. R. *J. Am. Chem. Soc.* **1979**, *101*, 4753.
(18) Perrin, C. L.; Johnston, E. R. *J. Am. Chem. Soc.* **1981**, *103*, 4697.
(19) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(20) Perrin, C. L.; Johnston, E. R.; Ramirez, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 6299.
(21) Perrin, C. L. *Org. Magn. Reson.* **1981**, *16*, 11.
(22) Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* **1990**, *90*, 935.
(23) Perrin, C. L.; Gipe, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 4036.
(24) Perrin, C. L.; Dwyer, T. J.; Rebek, J., Jr.; Duff, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 3122.
(25) Perrin, C. L.; Lollo, C. P.; Johnston, E. R. *J. Am. Chem. Soc.* **1984**, *106*, 2749.
(26) Perrin, C. L.; Lollo, C. P. *J. Am. Chem. Soc.* **1984**, *106*, 2754.
(27) Perrin, C. L.; Johnston, E. R. *Can. J. Chem.* **1981**, *59*, 2527.
(28) Perrin, C. L.; Lollo, C. P.; Hahn, C.-S. *J. Org. Chem.* **1985**, *50*, 1405.
(29) Perrin, C. L.; Thoburn, J. D. *J. Org. Chem.* **1989**, *54*, 764.
(30) Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 6693.
(31) Perrin, C. L.; Chen, J.-H.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 2448.
(32) Bunton, C. A.; Yatsimirsky, A. K. *Langmuir* **2000**, *16*, 5921.
(33) Hart-Cooper, W. M.; Sgarlata, C.; Perrin, C. L.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 15303.
(34) Perrin, C. L. *Acc. Chem. Res.* **1989**, *22*, 268.
(35) (a) Perrin, C. L.; Gipe, R. K. *J. Am. Chem. Soc.* **1986**, *108*, 1088. (b) Perrin, C. L.; Gipe, R. K. *Science* **1987**, *238*, 1393.
(36) (a) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press:, Oxford; 1997. (b) Scheiner, S. *Hydrogen Bonding: A Theoretical Perspective*; Oxford University Press: Oxford, 1997.
(37) Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33.
(38) Larson, J. W.; McMahon, T. B. *Inorg. Chem.* **1984**, *23*, 2029.
(39) (a) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 11552. (b) Cleland, W. W.; Kreevoy, M. M. *Science* **1994**, *264*, 1887. (c) Cleland, W. W. *Adv. Phys. Org. Chem.* **2010**, *44*, 1.
(40) (a) Saunders, M.; Telkowski, L.; Kates, M. *J. Am. Chem. Soc.* **1977**, *99*, 8070. (b) Siehl, H.-U. *Adv. Phys. Org. Chem.* **1987**, *23*, 63.
(41) (a) Wilson, E. B.; Smith, Z. *Acc. Chem. Res.* **1987**, *20*, 257. (b) Baughcum, S. L.; Duerst, R. W.; Rowe, W. F.; Smith, Z.; Wilson, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 6296.
(42) Perrin, C. L.; Kim, Y.-J. *J. Am. Chem. Soc.* **1998**, *120*, 12641.
(43) Levine, I. N. *Quantum Chemistry*, 2nd ed.; Allyn & Bacon: Boston, 1974; p 289ff.
(44) Perrin, C. L.; Kim, Y.-J.; Kuperman, J. *J. Phys. Chem. A* **2001**, *105*, 11383.
(45) Perrin, C. L.; Kim, Y.-J. *Inorg. Chem.* **2000**, *39*, 3902.
(46) (a) Peterson, S. W.; Levy, H. A. *J. Chem. Phys.* **1958**, *29*, 948. (b) Darlow, S. F.; Cochran, W. *Acta Crystallogr.* **1961**, *14*, 1250. (c) Ellison, R. D.; Levy, H. A. *Acta Crystallogr.* **1965**, *19*, 260. (d) Bartl, H.; Küppers, H. *Acta Crystallogr.* **1975**, *A31*, S174. (e) Gonschorek, W.; Küppers, H. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 1068. (f) Küppers, H.; Kvick, A.; Olovsson, I. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1981**, *B37*, 1203.
(47) (a) Ellison, S. L. R.; Robinson, M. J. T. *J. Chem. Soc., Chem. Commun.* **1983**, 745. (b) Tanaka, N.; Araki, M. *J. Am. Chem. Soc.* **1985**, *107*, 7780. (c) Knight, W. B.; Weiss, P. M.; Cleland, W. W. *J. Am. Chem. Soc.* **1986**, *108*, 2759.
(48) Perrin, C. L.; Arrhenius, T. *J. Am. Chem. Soc.* **1978**, *100*, 5249.
(49) Perrin, C. L.; Magde, D.; Berens, S. J.; Roqué, J. *J. Org. Chem.* **1980**, *45*, 1705.
(50) Perrin, C. L.; Flach, A.; Manalo, M. N. *J. Am. Chem. Soc.* **2012**, *134*, 9698.
(51) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 8010.
(52) Mavri, J.; Hodoscek, M.; Hadzi, D. *J. Mol. Struct.: THEOCHEM* **1990**, *209*, 421.
(53) Perrin, C. L. *Science* **1994**, *266*, 1665.
(54) Perrin, C. L.; Nielson, J. B. *J. Am. Chem. Soc.* **1997**, *119*, 12734.
(55) Perrin, C. L.; Lau, J. S.; Kim, Y.-J.; Karri, P.; Moore, C.; Rheingold, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 13548.
(56) Eberson, L.; Wadsö, I. *Acta Chem. Scand.* **1963**, *17*, 1552.
(57) Garcia-Viloca, M.; González-Lafont, A.; Lluch, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 9198.

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838

(58) Perrin, C. L.; Ohta, B. K. *J. Am. Chem. Soc.* **2001**, *123*, 6520.
(59) Perrin, C. L.; Lau, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 11820.
(60) Perrin, C. L.; Ohta, B. K. *Bioorg. Chem.* **2002**, *30*, 3.
(61) Perrin, C. L.; Ohta, B. K. *J. Mol. Struct.* **2003**, *644*, 1.
(62) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 282.
(63) (a) Perrin, C. L.; Nielson, J. B. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511. (b) Perrin, C. L.; Nielson, J. B.; Kim, Y.-J. *Ber. Bunsenges. Phys. Chem.* **1998**, *102*, 403. (c) Lau, J. S.; Perrin, C. L. In *Isotope Effects in Chemistry and Biology*; Kohen, A., Limbach, H. H., Eds.; CRC Press, 2005; Chapter 8. (d) Perrin, C. L. *Pure Appl. Chem.* **2009**, *81*, 571. (e) Perrin, C. L. *Acc. Chem. Res.* **2010**, *43*, 1550.
(64) Perrin, C. L.; Karri, P.; Moore, C.; Rheingold, A. L. *J. Am. Chem. Soc.* **2012**, *134*, 7766.
(65) Bogle, X. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 17172.
(66) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 8559.
(67) Perrin, C. L.; Burke, K. D. *J. Am. Chem. Soc.* **2014**, *136*, 4355.
(68) Deslongchamps, P.; Barlet, R.; Taillefer, R. J. *Can. J. Chem.* **1980**, *58*, 2167.
(69) Gipe, R. K. Ph.D. Thesis, University of California, San Diego, 1986.
(70) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.
(71) Deslongchamps, P.; Chênevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 1601.
(72) (a) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 4048. (b) Lehn, J.-M.; Wipff, G. *Helv. Chim. Acta* **1978**, *61*, 1274.
(73) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253.
(74) Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 2839.
(75) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1987**, *109*, 522.
(76) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1986**, *108*, 5997.
(77) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 3140.
(78) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 610.
(79) Perrin, C. L.; Young, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 4446.
(80) Perrin, C. L.; Young, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 4451.
(81) Perrin, C. L.; Engler, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 585.
(82) Perrin, C. L. *Acc. Chem. Res.* **2002**, *35*, 28.
(83) (a) Szarek, W. A., Horton, D., Eds. *The Anomeric Effect: Origin and Consequences*; ACS Symposium Series No. 87; American Chemical Society: Washington, DC; 1979. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983. (c) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995. (d) Thatcher, G. R. J., Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series No. 539; American Chemical Society: Washington, DC; 1993.
(84) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715.
(85) Perrin, C. L.; Nuñez, O. *J. Chem. Soc., Chem. Commun.* **1984**, 333.
(86) Paulsen, H.; Györgydeák, Z.; Friedmann, M. *Chem. Ber.* **1974**, *107*, 1590.
(87) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825.
(88) Perrin, C. L.; Fabian, M. A.; Armstrong, K. B. *J. Org. Chem.* **1994**, *59*, 5246.
(89) Perrin, C. L.; Fabian, M. A. *Anal. Chem.* **1996**, *68*, 2127.
(90) Fabian, M. A.; Perrin, C. L.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 8398.
(91) Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 6911.
(92) Perrin, C. L.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 8846.
(93) Perrin, C. L. *Pure Appl. Chem.* **1995**, *67*, 719. Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901.
(94) Perlin, A. S.; Casu, B. *Tetrahedron Lett.* **1969**, *10*, 2921.
(95) Cuevas, G.; Martínez-Mayorga, K.; López-Mora, N.; Fernández-Alonso, M. C.; Perrin, C. L.; Jiménez-Barbero, J.; Juaristi, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 2360.
(96) Perrin, C. L.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 6168.
(97) Halevi, E. A.; Nussim, M.; Ron, A. *J. Chem. Soc.* **1963**, 866.
(98) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326.
(99) Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.
(100) Weston, R. E., Jr. *Tetrahedron* **1959**, *6*, 31.
(101) Bary, Y.; Gilboa, H.; Halevi, E. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 938.
(102) Perrin, C. L.; Ohta, B. K.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 15008.
(103) (a) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157. (b) Nakanishi, K.; Goto, T.; Ohashi, M. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 403. (c) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417.
(104) Perrin, C. L.; Ohta, B. K.; Kuperman, J.; Liberman, J.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 9641.
(105) Van der Linde, W.; Robertson, R. E. *J. Am. Chem. Soc.* **1964**, *86*, 4505.
(106) Perrin, C. L. *J. Phys. Org. Chem.* **2013**, *26*, 269.
(107) Perrin, C. L.; Karri, P. *J. Am. Chem. Soc.* **2010**, *132*, 12145.
(108) Perrin, C. L.; Dong, Y. *J. Am. Chem. Soc.* **2008**, *130*, 11143.
(109) Perrin, C. L.; Dong, Y. *J. Am. Chem. Soc.* **2007**, *129*, 4490.
(110) Perrin, C. L.; Flach, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7674.
(111) Halevi, E. A. *New J. Chem.* **2014**, *38*, 3840.
(112) Perrin, C. L. *New J. Chem.* **2015**, *39*, 1517.
(113) Perrin, C. L. *Adv. Phys. Org. Chem.* **2010**, *44*, 123.
(114) Perrin, C. L.; Burke, K. D. *J. Phys. Chem. A* **2015**, *119*, 5009.
(115) Perrin, C. L.; Engler, R. E. *J. Phys. Chem.* **1991**, *95*, 8431.
(116) Caldwell, R. A.; Misawa, H.; Healy, E. F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6869.
(117) Perrin, C. L.; Thoburn, J. D.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 8800.
(118) King, S. T. *J. Phys. Chem.* **1971**, *75*, 405.
(119) Tanaka, Y.; Machida, K. *J. Mol. Spectrosc.* **1976**, *63*, 306.
(120) Perrin, C. L.; Dwyer, T. J.; Baine, P. *J. Am. Chem. Soc.* **1994**, *116*, 4044.
(121) Perrin, C. L.; Zhao, C. *Org. Biomol. Chem.* **2008**, *6*, 3349.
(122) Lu, Y.; Zhao, Y.; Handoo, K. L.; Parker, V. D. *Org. Biomol. Chem.* **2003**, *1*, 173.
(123) (a) Buchanan, G. O.; Williams, P. G.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2005**, *7*, 2731. (b) Oh, D. C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021.
(124) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.
(125) Perrin, C. L.; Rodgers, B. L.; O'Connor, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4795.
(126) Perrin, C. L.; Reyes-Rodríguez, G. J. *J. Phys. Org. Chem.* **2013**, *26*, 206.
(127) Perrin, C. L.; Reyes-Rodríguez, G. J. *J. Am. Chem. Soc.* **2014**, *136*, 15263.
(128) Perrin, C. L.; Dwyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 5163.
(129) Perrin, C. L. *J. Magn. Reson.* **1980**, *40*, 391.
(130) Perrin, C. L.; Fabian, M. A.; Rivero, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 1044.
(131) Perrin, C. L.; Kim, Y.-J. *J. Phys. Org. Chem.* **2000**, *13*, 752.
(132) Perrin, C. L. *J. Phys. Chem.* **1984**, *88*, 3611.
(133) Perrin, C. L.; Chang, K.-L. *J. Org. Chem.* **2016**, *81*, 5631.

DOI: 10.1021/acs.joc.6b02390
J. Org. Chem. 2017, 82, 819−838