Secondary Kinetic Isotope Effects in C-N Rotation of Amides

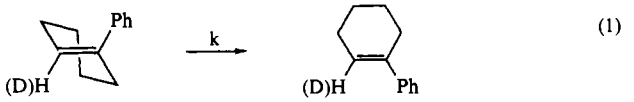
Charles L. Perrin,*,† John D. Thoburn,† and A. Jerry Kresge‡

Contribution from the Departments of Chemistry, University of California—San Diego, La Jolla, California 92093, and University of Toronto, Toronto, Ontario, M5S 1A1 Canada.
Received December 23, 1991

Abstract: A secondary deuterium kinetic isotope effect (KIE) k_H/k_D of 2.0 was recently reported for trans → cis isomerization of 1-phenylcyclohexene-*2-d*. The large value was attributed to loss of all the zero-point energy associated with the out-of-plane C-H bending mode. If this phenomenon is general, a large KIE might also be manifested in the C-N rotation of amides, whose rates can be determined by NMR methods. To demonstrate KIEs convincingly, it is necessary to measure the rates for H and D amides simultaneously in the same solution. Such measurements are possible because isotope shifts separate the signals. The kinetics of stereoisomerization were followed by line-shape analysis, saturation transfer, or selective inversion recovery. For HCONHD k_H/k_D is only 1.16 ± 0.10, and for $DCON(CH_3)_2$ it is only 1.18 ± 0.04. For $HCONDCH_3$ k_H/k_D is 1.00 ± 0.03, which is equivalent to no isotope effect at all. For $HCONDC_6H_4NO_2$-*p* k_H/k_D is 1.04 ± 0.03, which is quite small. The absence of any KIE in $HCONDCH_3$ could be confirmed by ^1H NMR. We therefore conclude that there is no large secondary KIE for C-N rotation in amides, for substitution at carbon or at nitrogen. The absence of any large effect is discussed in terms of the bending modes of reactant and transition state. The KIE in $HCONH_2$ may arise from thermal population of excited vibrational states.

Introduction

Quasiprimary Kinetic Isotope Effects. Secondary deuterium kinetic isotope effects (KIEs),[1] k_H/k_D, in organic systems are usually quite small, since the C-H or C-D bond is not being broken in the rate-limiting step. Instead, a carbon atom is often undergoing rehybridization from sp^3 to sp^2, and the change of bending frequencies and of zero-point energies leads to a k_H/k_D of only 1.15-1.20. However, a k_H/k_D of 2.0 was recently reported[2] for trans → cis isomerization of 1-phenylcyclohexene-*2-d* (eq 1), even though the nominal hybridization of the carbon remains sp^2 throughout the rearrangement.



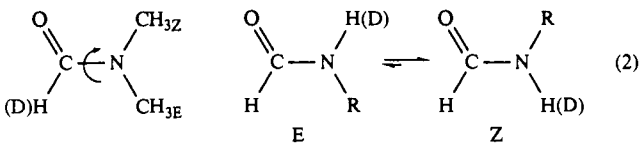
(1)

This large value was rationalized by proposing an analogy to the familiar primary kinetic isotope effect, which involves cleavage of a bond to the isotopically labeled atom. That KIE arises because a 2950-cm^{-1} C-H stretching mode is converted to a zero-frequency reaction coordinate. Since the C-H bond of the reactant has a higher zero-point energy than does the C-D bond, there results a k_H/k_D near 7. In the rotation of eq 1 it is an 820-cm^{-1} out-of-plane C-H bending mode whose zero-point energy is lost in forming the transition state. When the difference between C-H and C-D zero-point energies is taken into account, there results a k_H/k_D of 1.7, or else 1.85 according to MNDO calculations including tunneling corrections.[2] This is much larger than the usual secondary KIE because a vibrational frequency is not merely changed but is completely lost in the transition state. It is smaller than the usual primary KIE because the vibration involved is a bending mode rather than a stretching mode. Thus this KIE is primary in that all of the isotope-dependent zero-point energy is lost in the transition state, but secondary in that no bond to the isotope is broken. Such a KIE has been called a "quasiprimary" one.

A similar effect was seen in nitrogen inversion of ethylenimine,[3] where k_H/k_D for deuterium substitution on nitrogen is 2.34. This was called a "special case of a primary isotope effect", weaker because it involves bending along the reaction coordinate, rather than bond breaking.

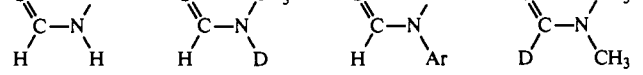
The MNDO calculations are not entirely convincing, since they require accurate evaluation of all vibrational frequencies of both the strained *trans*-cyclohexene and the biradical transition state. Although there are other examples of large secondary deuterium KIEs in rotation of excited-state *trans*-stilbene,[4] the published experimental results for *trans*-1-phenylcyclohexene can be questioned, since the rates were measured in separate samples and the deuterated substrate may have happened to contain less of a catalytically active species or more of an inhibitor. Indeed, it is known that acids can catalyze the isomerization of *trans*-cyclohexene derivatives.[5]

Proposal. Secondary KIEs in C-N Rotation of Amides. Despite these reservations, if a "quasiprimary" kinetic isotope effect is general, it might also be manifested in the C-N rotation of amides (eq 2). Here greater diversity is available since deuterium can



(2)

be substituted at either N or C of the amide, and the alkyl group R on nitrogen can be varied or doubled. The four amides that we have studied are formamide (**1**), *N*-methylformamide (**2**), *p*-nitroformanilide (**3**), and *N,N*-dimethylformamide (**4**). The



Ar = $C_6H_4NO_2$-*p*

special feature of **3** is that its nitrogen is likely to remain sp^2-hybridized at the transition state, inasmuch as X-ray and neutron-diffraction studies indicate that *p*-nitroaniline is planar.[6] This is a strong test for KIEs, since the equilibrium isotope effect vanishes exactly for **4** and almost exactly for the other amides.

Secondary kinetic isotope effects on amide rotation are of recent interest for elucidation of mechanism. In particular, the β KIEs (for deuterium substitution at the α carbon, adjacent to the carbonyl) have been measured, with conflicting results, for the

† University of California—San Diego.
‡ University of Toronto.

(1) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. Saunders, W. H., Jr. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Part 1, p 565.
(2) Caldwell, R. A.; Misawa, H.; Healy, E. F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6869.
(3) Carter, R. E.; Drakenberg, T.; Bergman, N.-Å. *J. Am. Chem. Soc.* **1975**, *97*, 6990.
(4) Courtney, S. H.; Balk, M. W.; Philips, L. A.; Webb, S. P.; Yang, D.; Levy, D. H.; Fleming, G. R. *J. Chem. Phys.* **1988**, *89*, 6697. Saltiel, J.; Waller, A.; Sun, Y.-P.; Sears, D. F., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4580.
(5) Rudolph, A.; Weedon, A. C. *J. Am. Chem. Soc.* **1989**, *111*, 8756.
(6) Trueblood, K. N.; Goldish, E.; Donohue, J. *Acta Crystallogr.* **1961**, *14*, 1009. Tichý, K.; Prelesnik, B. *Czech. J. Phys.* **1969**, *19*, 857.

0002-7863/92/1514-8800$03.00/0

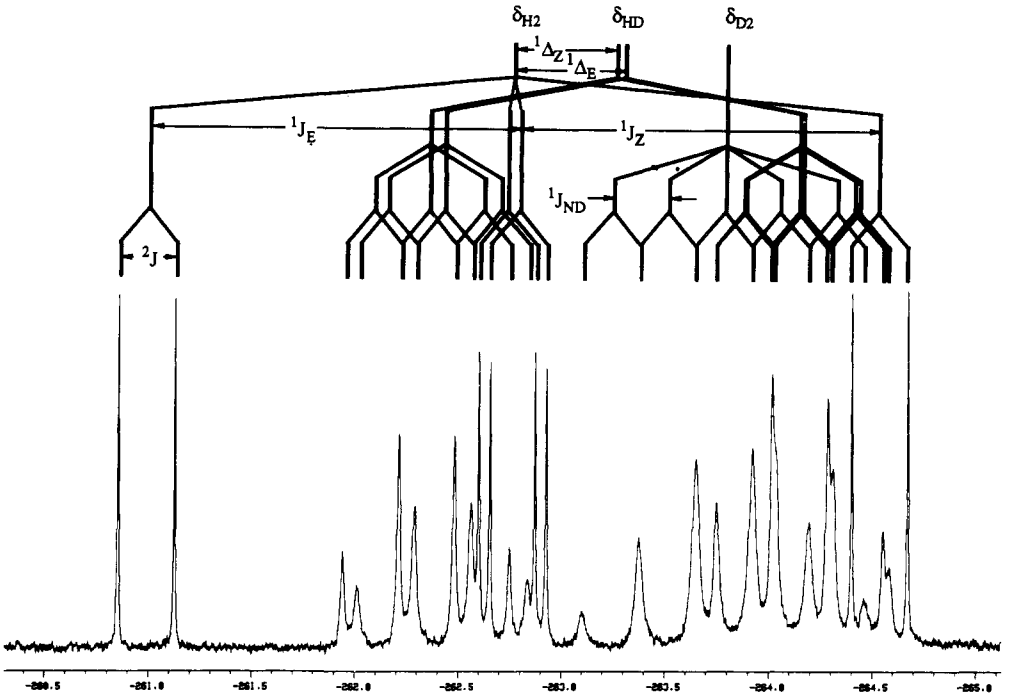


Figure 1. 50.7-MHz ^{15}N NMR spectrum of formamide-^{15}N in 50:50 H_2O/D_2O at 25 °C. Peaks of $HCO^{15}NH_2$ are centered at δ_{H2}, and those of (*Z*)-$HCO^{15}NHD$, (*E*)-$HCO^{15}NHD$, and $HCO^{15}ND_2$ are shifted by $^1\Delta_Z$, $^1\Delta_E$, and $^1\Delta_Z + {}^1\Delta_E$, respectively. Signals are further split by $^1J_{NH_Z}$, $^1J_{NH_E}$, $^1J_{ND}$, and $^2J_{NH}$.

rotation about peptidyl–proline bonds as catalyzed by the enzyme cyclophilin.[7]

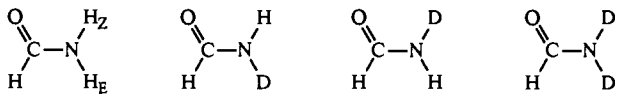
This reaction is also of historical interest. For many years the activation parameters for C–N rotation in *N,N*-dimethylformamide were uncertain, owing to systematic errors arising in part from long-range coupling to the formyl proton. To eliminate this, $DCON(CH_3)_2$ (**4-*d***) was used,[8] with the natural assumption that deuterium substitution would not lead to any measurable change in rate. Yet the above results cast new doubt on this assumption.

Kinetic Methodology. Dynamic NMR methods are the standard for determing rates of C–N rotation in amides. Activation energies required for isomerization of amides are readily accessible near room temperature. However, the simplest method, that of determining coalescence temperatures, will not succeed in the present case, since variation of even 1 °C in a reaction with 20 kcal/mol activation energy leads to an intolerable error of 10% in the rate constant. To demonstrate quasiprimary kinetic isotope effects convincingly, it is necessary to measure the rates of rotation of H and D amides in the same solution, under conditions guaranteed to be identical. However, it is necessary to distinguish the NMR signals of the isotopologues (species differing solely in isotopic content, as distinguished from isotopomers, which are isomeric owing to the position of isotopic substitution),[9] so as to measure their rates separately.

One possibility is to use coupling constants to split signals of one of the isotopologues. In particular, in the ^1H spectrum of *N*-methylformamide (**2**) the *N*-methyls of both stereoisomers are split into 5-Hz doublets by the NH proton, whereas those of **2-*d*** are not split.

Another possibility is to use isotope shifts[10] to separate the signals. NMR is sufficiently sensitive to recognize the perturbation of chemical shift by isotopic substitution. Isotope shifts by deuterium are defined as $\Delta = \delta_D - \delta_H$, where δ_D is the chemical shift of the deuterated molecule. Since substitution by a heavy isotope usually leads to an upfield shift, Δ is generally a negative quantity. Isotope shifts are customarily reported as $^n\Delta Y(Z)$, where Y is the nucleus observed, Z is the nucleus that induces the shift, and *n* is the number of bonds between Y and Z. (In contexts where Y and Z are unambiguous, isotope shifts may be abbreviated to $^n\Delta$, perhaps with a subscript to indicate stereochemistry.) Although these shifts are small, modern high-field instruments resolve the signals of isotopic molecules so that their rates can be measured separately.

For formamide (**1**) a combination of coupling constants and isotope shifts can separate signals of the various species. The room-temperature ^{15}N NMR spectrum of formamide-^{15}N in 50:50 H_2O/D_2O is shown in Figure 1. This complex spectrum from so simple a molecule arises because there are four distinct species, **1**, (*E*)-**1-*d***, (*Z*)-**1-*d***, and **1-*d*$_2$** [(*E*)-**1-*d*** and (*Z*)-**1-*d*** are isotopomers, but the others are isotopologues], each with its own isotope shift, set of coupling constants, and line width. It would be even more complex except for the fortuitous equality of the $^2J_{NH}$ to the formyl proton and the $^1J_{ND}$ of the three deuterium-containing species, which leads to peak overlap.



1 E-**1-*d*** Z-**1-*d*** **1-*d*$_2$**

The inequality[11] of ^1J_E and ^1J_Z permits measurement of the rates of stereoisomerization. This may be a special feature of formamide, since it is not seen in acetamide[12] or benzamide,[13] in which the additional complication of peak doubling due to $^2J_{NH}$ to the formyl proton would be avoided. No rate information is possible from the outer doublets of **1**, which correspond to those molecules where the ^{15}N is unaffected by rotation about the C–N bond because the two NH nuclei have the same spin. However,

(7) Harrison, R. K.; Caldwell, C. G.; Rosegay, A.; Melillo, D.; Stein, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7063.

(8) Neuman, R. C., Jr.; Jonas, V. *J. Org. Chem.* **1974**, *39*, 925.

(9) Seeman, J. I.; Paine, J. B., III. Personal communication. See: Perrin, C. L.; Engler, R. E. *J. Phys. Chem.* **1991**, *95*, 8431.

(10) Siehl, H.-U. *Adv. Phys. Org. Chem.* **1987**, *23*, 63. Forsyth, D. A. *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 6, Chapter 1. Hansen, P. E. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105; *Prog. Nucl. Magn. Reson. Spectrosc.* **1988**, *20*, 207.

(11) Sunners, B.; Piette, L. H.; Schneider, W. G. *Can. J. Chem.* **1960**, *38*, 681. Brown, A. J. R.; Randall, E. W. *Mol. Phys.* **1964**, *8*, 567. Chuck, R. J.; Gillies, D. G.; Randall, E. W. *Ibid.* **1969**, *16*, 121.

(12) Binsch, G.; Lambert, J. B.; Roberts, B. W.; Roberts, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 5564.

(13) Johnston, E. R. Ph.D. Thesis, University of California, San Diego, CA, 1980. Thoburn, J. D. Unpublished observations.

line-shape analysis of the central pair of doublets of **1** can provide the rate of that rotation. The larger splitting in that pair is $^2J_{NH}$, and the smaller is the difference $^1J_E - ^1J_Z$. The pair coalesces to a simple doublet at high temperature, when rotation becomes so fast that only an average $^1J_{NH}$ is seen. Likewise, the signals of (*E*)-**1**-*d* and (*Z*)-**1**-*d* are each doublets due to $^1J_{NH}$, split into overlapping 1:1:1 triplets by $^1J_{ND}$, and further split into doublets by an equal $^2J_{NH}$ (thus producing 1:2:2:1 quartets). The *E* and *Z* signals are separated by $^1/_2(^1J_E - ^1J_Z) \pm (^1\Delta_Z - ^1\Delta_E)$. For the upfield components of the ^1J doublet this separation is quite small, since the two terms nearly cancel. For the downfield components it is nearly 4 Hz, and line-shape analysis as they coalesce can provide the rate constant for interconversion of (*E*)-**1**-*d* and (*Z*)-**1**-*d*. In principle this same method would be applicable to the 1:3:5:5:3:1 sextets of **1**-d_2, but not only are $^1J_{ND}$ and thus the difference between ^1J_E and ^1J_Z 6.5-fold smaller but also the ^{15}N peaks are broadened by two quadrupolar deuteriums. Nevertheless, line-shape analysis provides two measurements of k_H from the central pair of doublets of **1** and four measurements of k_D from the overlapping downfield quartets of the two stereoisomers of **1**-*d*.

For the other amides line-shape analysis is not applicable since signals separated by isotope shifts will coalesce with each other at a far lower temperature than the coalescence of signals due to separate stereoisomers or to diastereotopic nuclei. Consequently rates of stereoisomerization of these amides must be measured by ^1H and ^{13}C spin saturation transfer[14] and ^{13}C selective inversion recovery.[15]

Experimental Section

Synthesis and Sample Preparation. A concentrated aqueous solution of partially deuterated formamide-^{15}N was prepared by mixing equimolar amounts of formamide-^{15}N (0.5 mL, 99% ^{15}N, Cambridge Isotope Laboratories) and D_2O (270 μL, 99% ^2H, Aldrich). To prevent acid and base catalysis of hydrogen exchange,[16] 18 μmol of 1:1 acetate buffer was added. Sodium nitrate-^{15}N (99% ^{15}N, Cambridge Isotope Laboratories) was added as an internal standard for ^{15}N NMR.

A 5:4 mixture of $HCONHCH_3/HCONDCH_3$ (**2**/**2**-*d*) was prepared by stirring *N*-methylformamide (Aldrich, 3 mL, 51 mmol) with D_2O (Aldrich, 2 mL, 110 mmol) and H_2O (2 mL, 111 mmol) overnight, removing the water at reduced pressure (25 °C, 4 Torr), and purifying by distillation (65 °C, 4 Torr). For the ^{13}C saturation-transfer experiments, this neat sample was used. To prevent overload of the ^1H receiver coil, 0.2 mL of this material was dissolved in 0.5 mL of DMSO-d_6.

p-Nitroformanilide was synthesized from *p*-nitroaniline and acetic formic anhydride[17] and recrystallized from ethyl acetate, mp 196–198 °C (lit.[18] mp 192–194 °C). A 1:1 mixture of $HCONHC_6H_4NO_2$-*p*/$HCONDC_6H_4NO_2$-*p* (**3**/**3**-*d*) was prepared by stirring overnight 1.0 g of *p*-nitroformanilide (6 mmol) in 1 mL of H_2O (56 mmol), 1 mL of D_2O (55 mmol), and 50 mL of THF and removing the volatiles at reduced pressure. A 2.1 M solution in DMSO-d_6 was prepared.

A neat sample of 1:1 $HCON(CH_3)_2/DCON(CH_3)_2$ (**4**/**4**-*d*) was prepared from 0.5 mL of anhydrous *N*,*N*-dimethylformamide (Aldrich) and 0.5 mL of *N*,*N*-dimethylformamide-d_1 (Merck Sharp & Dohme) deuterated at the formyl position.

^1H NMR Spectroscopy. The ^1H NMR spectra of $HCONHCH_3/HCONDCH_3$ were recorded on a Nicolet NT200 spectrometer operating at 200.3 MHz. The spectrometer was run unlocked to allow for continuous low-power decoupling of deuterium at 30.7 MHz. The power and frequency of the CW proton decoupler were alternated to provide for preirradiation of the *Z* methyl site during the restoration period as well as for homonuclear decoupling of the CH of (*E*)-$HCONHCH_3$ during acquisition. Nonselective high-power 90° pulses were used for observation in order to reject any *xy* magnetization created by the preirradiation.[19] The first acquisition was discarded since the pulse programmer requires the saturation to be at the end of the pulse sequences.

^{15}N NMR Spectroscopy. ^{15}N NMR spectra were recorded on a Varian UN500 spectrometer operating at 50.7 MHz with a deuterium lock. At these high concentrations and enrichments, 16 scans, without proton decoupling, provided excellent signal-to-noise ratios. Spectra were recorded at both 25 and 48 °C.

^{13}C NMR Spectroscopy. ^{13}C NMR spectra were recorded on a Varian UN500 spectrometer operating at 125.7 MHz with a deuterium lock and WALTZ-16 proton decoupling. No deuterium decoupling was necessary because $^2J_{CD}$ and $^3J_{CD}$ are small (<0.5 Hz, based on known[20] J_{CH} corrected for the ratio of magnetogyric ratios) and because the largest coupling is to *N*-methyl resonances that are already broadened to 1.5-Hz width owing to the relatively high viscosity of the samples as well as to the quadrupolar relaxation of the adjacent ^{14}N. With neat samples and nonselective 90° pulses, eight acquisitions were more than sufficient to give good signal-to-noise ratios. Chemical shifts are reported relative to TMS using $\delta_{DMSO\text{-}d_5}$ = 39.5 ppm or $\delta_{dioxane}$ = 67.6 ppm (added to neat samples).

Saturation-Transfer Measurements. Kinetics of stereoisomerization were followed by saturating the *Z* methyls or carbonyls of *N*-methylformamide, the carbonyl, ipso, or ortho carbons of *p*-nitroformanilide, or the *E* methyls of *N*,*N*-dimethylformamide and measuring the transfer of saturation to both of the corresponding sites, as well as their spin–lattice relaxation rates. For *N*-methylformamide the ^1H or ^{13}C intensities, *I*, of the downfield *E* methyls were measured while the *Z* methyls were being irradiated at the lowest power level that would saturate them. The equilibrium intensities, I^0, of the *E* methyl peaks were obtained during off-resonance irradiation downfield by $|\delta_E - \delta_Z|$ from the *E* methyl peaks, in order to correct for spillover due to the decoupler's frequency bandwidth. While site *Z* was being saturated, apparent spin–lattice relaxation times, T_1, of the *E* site were measured by the inversion-recovery method (180° − τ − 90°). The preacquisition delay was always at least $7T_1$ to allow for complete relaxation between repetitions. Sixteen acqusitions were taken, and 0.1 Hz of line broadening was added. The same base line and scaling factors were used in all spectra to ensure that relative intensities were consistent. Intensities were based on peak heights rather than integrals since the former are more reliable. For ^{13}C measurements, nonselective composite 180° pulses ($\pi/2\text{–}\bar{\pi}\text{–}\pi/2$) were used to achieve more complete inversion. Selective homonuclear presaturation was accomplished using low power through the observe coil during the preacquisition delay, as well as during the τ delay of the T_1 measurements. Minimal (0.5 Hz) line broadening was added. For *N*,*N*-dimethylformamide the initial value of k_H/k_D had appeared to be 1.56, which is large. However, we have found this to be artifactual, arising from differential spillover of saturating irradiation, and it is essential to use minimum-power irradiation.

For *N*,*N*-dimethylformamide k_{ZE} was measured (measure I_z while saturating the *E* sites), since the *Z* methyl peaks of the two isotopologues are more clearly resolved than the *E* peaks. For *N*-methylformamide k_{EZ} was measured because this is the larger rate constant and k_{ZE} would require a slightly higher temperature, and because in the ^1H spectrum the *E* methyls are better resolved. For *p*-nitroformanilide the isomerization is faster because of the electron-withdrawing *p*-nitrophenyl group, so the smaller rate constant k_{ZE} was measured by saturation of the carbonyl, ipso, and ortho carbons of the *E* stereoisomer. Saturation-transfer experiments were performed five times and T_1 measurements three times in order to determine standard deviations for these quantities.

Selective ^{13}C Inversion-Recovery Measurements. Selective inversion-recovery experiments were performed on the *E* and *Z* ^{13}C methyl peaks of **4**/**4**-*d*. The carrier frequency was centered between the two *Z* peaks, and a nonselective 90° pulse was applied. After an evolution period of 0.786 ms = $[2(\delta_E - \delta_Z)]^{-1}$, a second nonselective 90° pulse restored the *E* magnetizations along the +*z* axis and the *Z* magnetizations along the −*z* axis. After a mixing time *t* of variable length, a 90° observe pulse was applied and the spectrum was acquired. Between pulse sequences a 90-s delay was added to allow for complete relaxation of all magnetizations. A total of 8 scans were taken for each of 15 mixing times. Only minimal line broadening (0.1 Hz) was applied. All experiments were performed three times.

Temperature Control. The optimal temperature for measuring rate constants by line-shape analysis is just below the coalescence temperature. For the doublets of formamide this is near 48 °C. For the other amides, studied by the saturation-transfer or inversion-recovery method, the temperature was adjusted to match the rate constant to the reciprocal of the spin–lattice relaxation time. At the end of each experiment the actual probe temperature was determined from peak separations in an ethylene glycol sample.[21] Temperature fluctuation during a series of experiments was <0.1 °C.

Calculation of Rate Constants and Error Estimates. Line-Shape Analysis of Formamide. Figure 2 shows an expanded region near δ −262.5 of the ^{15}N spectrum of Figure 1, but at 48 °C. There are two

(14) Hoffman, R. A.; Forsén, S. *Prog. Nucl. Magn. Reson.* **1966**, *1*, 15.
(15) Alger, J. R.; Prestegard, J. H. *J. Magn. Reson.* **1977**, *27*, 137.
(16) Perrin, C. L. *Acc. Chem. Res.* **1989**, *22*, 268.
(17) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315. Huffman, C. W. *J. Org. Chem.* **1958**, *23*, 727.
(18) DeWolfe, R. H.; Newcomb, R. C. *J. Org. Chem.* **1971**, *36*, 3870.
(19) Perrin, C. L.; Johnston, E. R. *J. Magn. Reson.* **1979**, *33*, 619.
(20) Dorman, D. E.; Bovey, F. A. *J. Org. Chem.* **1973**, *38*, 1719.
(21) Raiford, D. S.; Fisk, C. L.; Becker, E. D. *Anal. Chem.* **1979**, *51*, 2050.

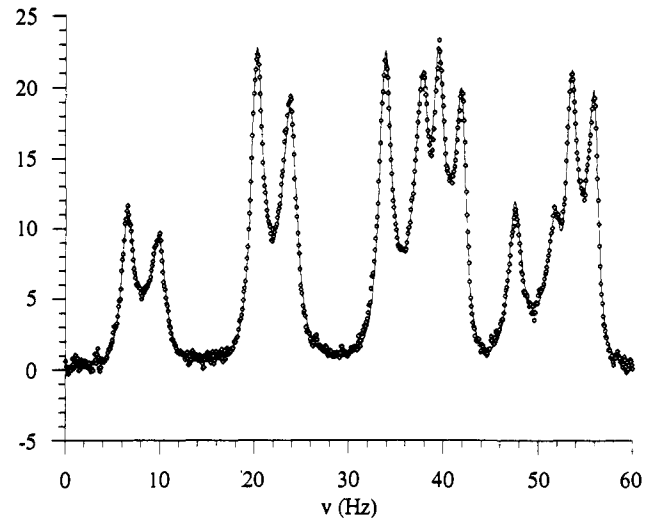


Figure 2. Region around δ −262.5 of ^{15}N NMR spectrum of formamide-^{15}N in 50:50 H_2O/D_2O at 48 °C (◊ = experimental, — = best computer fit to exchange line shape).

doublets (peaks 4 and 6, numbered from left to right) that arise from **1** and four (peaks 1, 2, 3, and 5) from **1**-*d*. It is the coalescence of these doublets that provides the separate rate constants for stereoisomerization of these two isotopologues. Each of the six doublets was independently fit by a multidimensional least squares/Newton–Raphson method to the line shape for two equally populated sites with different intrinsic line widths.[22] For HCONHD the assumption of equal populations is consistent with the near equality of total zero-point energies calculated for cis and trans isomers.[23] Initial guesses at the rate constants were estimated from the valley to peak ratio, but these are only approximate because the published tables[24] assume equal line widths.

Input parameters are ν_A and ν_B, the resonance frequencies of sites A and B, and $\delta\nu_A$ and $\delta\nu_B$, their intrinsic line widths in the slow-exchange limit. Even at 25 °C detectable exchange occurs, as evidenced by broadening of the two central doublets of **1**. (No increased broadening is seen for the outer doublets of **1**.) Rather than input parameters being taken directly from this spectrum, the same line-shape program with fixed k = 0.2–0.3 s^{-1} was used to vary them for the three different species until the best visual fit was obtained. A further complication is that the line widths of both stereoisomers of **1**-*d* increase with temperature, owing to quadrupolar broadening. To extrapolate the line widths to 48 °C, it was assumed that the *relative* effectiveness of quadrupolar broadening by *Z* or *E* deuterium is the same as at 25 °C and that the sum of these two broadenings is seen in **1**-d_2. The values of ν_A, ν_B, $\delta\nu_A$ (0.35 Hz for $HCONH_2$, 0.67 Hz for (*Z*)-HCONHD), and $\delta\nu_B$ (0.35 Hz for $HCONH_2$, 1.00 Hz for (*E*)-HCONHD) were then used to fit the spectrum at 48 °C.

With so many data points, the errors estimated statistically from the goodness of the fit are too small to contribute to the overall error. There are two other, more significant sources of error in the measurement of k, namely, the error estimated from the measurable variation of k from doublet to equivalent doublet and the error associated with uncertainties in $\nu_A - \nu_B$ and in $\delta\nu_A$ or $\delta\nu_B$ of HCONHD. These input parameters are accurate to ±0.04 Hz and ±0.1 Hz, respectively, since such changes produce detectable deviations in the 25 °C line shape and since the temperature dependences of $\delta\nu_A$ and $\delta\nu_B$ are small enough that the extrapolations to 48 °C are reliable. The temperature variation of $\nu_A - \nu_B$ cannot be substantial, since the fits are good. Besides, for significant error to be produced in the KIE, the variation for different isotopomers must be different, which is unlikely. The effects of these uncertainties on k were evaluated empirically, and the total error from both sources was estimated by propagation of errors.[25]

Saturation-Transfer Kinetics of N-Substituted Formamides. Rate constants for exchange from site j to site i were calculated according to eq 3,[26]

$$k_{ji} = t_i(j)/T_{1i}(j) \tag{3}$$

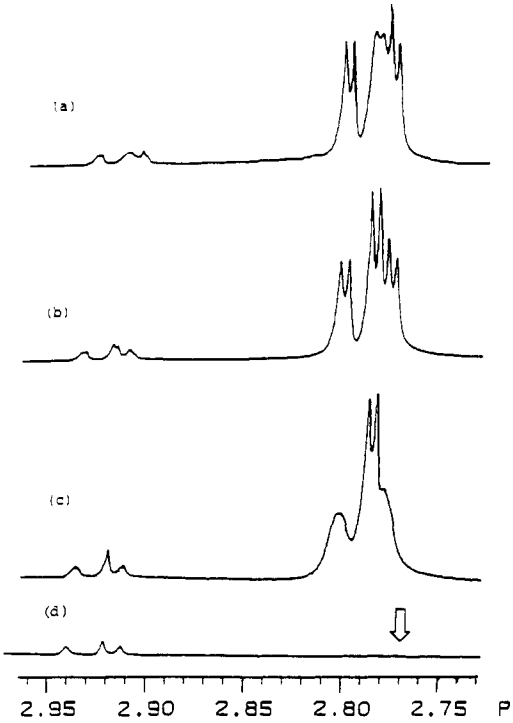


Figure 3. 200-MHz ^1H NMR spectrum of *N*-methyl region of HCONHMe + HCONDMe in DMSO-d_6: (a) without decoupling; (b) ^2H decoupled; (c) ^2H decoupled and formyl ^1H decoupled; (d) ^2H decoupled, formyl ^1H decoupled, and irradiated at site indicated by arrow.

where $t_i(j)$ is the fractional decrease in intensity (I) of site i upon saturation of site j (eq 4)

$$t_i(j) = \frac{I_i^0 - I_i(j)}{I_i^0} \tag{4}$$

and $T_{1i}(j)$ is the apparent spin–lattice relaxation time for site i while j is being saturated.

Standard deviations in the intensity were calculated from five replications of the saturation-transfer experiments. Errors in T_1 were either the standard deviation of the three T_1 measurements or the statistical errors from the fit of the data to the exponential decay, whichever was larger. Reported errors in other quantities were calculated by propagation of errors.

Inversion-Recovery Kinetics of *N*,*N*-Dimethylformamide. Determination of rate constants from inversion-recovery data is more complicated.[27] The relaxation behavior of the intensities I_E and I_Z of two sites of equal population but with unequal relaxation times T_{1E} and T_{1Z} and undergoing chemical exchange with rate constant k is described by eqs 5 and 6,

$$I_E = I_E^0 - c_1 \exp(-\lambda_1 t) + c_2 \exp(-\lambda_2 t) \tag{5}$$

$$I_Z = I_Z^0 - c_3 \exp(-\lambda_1 t) + c_4 \exp(-\lambda_2 t) \tag{6}$$

where I_E^0 and I_Z^0 are the equilibrium intensities, $c_{1,2} = [{}^1/_2 f_E I_E^0 (T_{1Z}^{-1} - T_{1E}^{-1} \mp S) - f_Z I_Z^0 k]/S$, $c_{3,4} = [f_E I_E^0 k + {}^1/_2 f_Z I_Z^0 (T_{1Z}^{-1} - T_{1E}^{-1} \pm S)]/S$, $\lambda_{1,2} = (T_{1E}^{-1} + T_{1Z}^{-1} + 2k \pm S)/2$, $S = [(T_{1E}^{-1} - T_{1Z}^{-1})^2 + 4k^2]^{1/2}$, and f_Z and f_E are corrections for imperfections that originate when pulsing does not return the *Z* and *E* magnetization to the ±*z* axis (f_Z = 2 and f_E = 0 for perfect 90° pulses). The best fit was determined by varying the seven intensity, relaxation, and rate parameters I_E^0, I_Z^0, f_E, f_Z, T_{1Z}, T_{1E}, and k so as to minimize the sum of the squares of the deviations of calculated from experimental *E* and *Z* intensities at the 15 mixing times. Errors were determined from that sum according to the propagation of errors. Further details are available.[28]

(22) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228. Sandström, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982; p 14.
(23) Tanaka, Y.; Machida, K. *J. Mol. Spectrosc.* **1976**, *63*, 306.
(24) Perrin, C. L. *Magn. Reson. Chem.* **1988**, *26*, 224.
(25) Perrin, C. L. *Mathematics for Chemists*; Wiley-Interscience: New York, 1971; p 159.
(26) Perrin, C. L.; Johnston, E. R.; Lollo, C. P.; Kobrin, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 4691.
(27) Led, J. J.; Gesmar, H. *J. Magn. Reson.* **1982**, *49*, 444. Gesmar, H.; Led, J. J. *Ibid.* **1986**, *68*, 95. Grassi, M.; Mann, B. E.; Pickup, B. T.; Spencer, C. M. *Ibid.* **1986**, *69*, 92.
(28) Thoburn, J. D. Ph.D. Thesis, University of California, San Diego, CA, 1991.

Table I. ^{13}C Chemical Shifts δ and n-Bond Deuterium-Induced Isotope Shifts $^{n}\Delta C(D)$

amide	site	δ_E, ppm	δ_Z, ppm	n	$-\Delta_E$, ppb	$-\Delta_Z$, ppb
2	methyl[a]	2.92	2.79	3	5	5
2	methyl	28.1	24.6	2	132	132
2	carbonyl	166.9	163.6	2	74	95
3	carbonyl	162.6	160.4	2	97	92
3	ipso	144.9	144.2	2	143	126
3	ortho	116.5	119.0	3	74	73
3	meta	125.3	124.9	4	<10	<10
3	para	142.6	142.5	5	<10	<10
4	methyl	35.2	30.1	3	15	52
4	carbonyl[b]	162.0	162.0	1	194	194

[a] In ^1H NMR. [b] Triplet, $^1J_{CD}$ = 29.3 Hz (**4**-*d*).

Kinetic Isotope Effects. Kinetic isotope effects were calculated from the separate k_H and k_D at temperature T and corrected to 25 °C according to eq 7. This assumes that $\Delta S_H^* = \Delta S_D^*$, but the correction is quite small.

$$(k_H/k_D)_{298} = (k_H/k_D)^{T/298} \quad (7)$$

Results

Spectral Assignments. ^1H NMR Spectra of *N*-Methylformamide. Initial experiments were conducted on **2**/**2**-*d*. The *N*-methyl region of the spectrum is shown in Figure 3. Chemical shifts and isotope shifts are included in Table I. The major, upfield set of peaks centered at δ 2.79 is well established as the *Z* methyl.[29] The ratio of *Z* to *E* isomers is about 12,[30] as confirmed by integration. The three-bond coupling $^3J_{HH}$ between the N–H and *N*-methyl protons is the same 5.0 Hz for both isomers. For the *Z* methyl the further splitting due to the $^4J_{anti}$ of 1.0 Hz is clearly resolved, but the 0.4-Hz $^4J_{syn}$ of the *E* methyl is not.

The methyl groups in the deuterated isotopologue (Figure 3a) appear as doublets, broadened into an unresolvable pair of 1:1:1 triplets (for the *Z* methyl $^4J_{anti}$ = 1 Hz, $^3J_{HD}$ = 5.0 Hz/6.5 = 0.8 Hz) which upon continuous ^2H decoupling collapses to a sharp doublet (Figure 3b). These peaks do not fall midway between the two components of the protio compound owing to an isotope shift, $^3\Delta H(D)$, of −5 ppb. Therefore the peak of the deuterated isotopologue tends to overlap with the upfield component of the protio doublet, especially for the *Z* methyls, which are broader because of the larger ^4J. The overlap is greater at higher magnetic field strengths since isotope shifts scale with field strength whereas coupling constants do not. It was therefore optimal to carry out these experiments at 200 MHz, the lowest field strength available for FT NMR. The $^4J_{syn}$ can be collapsed by homonuclear decoupling of the formyl proton to further sharpen the singlets of the *E* methyls (Figure 3c). The extra broadening of the *Z* methyls results from partial decoupling of the neighboring NH peak of (*Z*)-$HCONHCH_3$. At this field strength, and with deuterium and formyl proton decoupling, the peaks are suitably resolved to accurately measure *E* peak intensities of the protio and the deuterio compounds, both with and without saturation of the *Z* peaks.

^{13}C NMR Spectra and Signal Assignments. Chemical shifts and isotope shifts are listed in Table I. The major stereoisomer of **2** is *Z* according to the ^1H spectrum. Peak assignments for **3**[31] and **4**[32] were taken as assigned. The assignment of protio vs deuterio was based on the general observation that substitution of a heavy isotope leads to upfield NMR shifts.[10] The assignments for **4** are consistent with the generalization that anti isotope shifts are larger than syn in substituted ethylenes.[33] It should be noted that the opposite assignment of stereoisomers or diastereomeric peaks would not affect the KIEs, but the assignment of isotopologues is critical.

Table II. ^{15}N Chemical Shift, Deuterium-Induced Isotope Shifts, Coupling Constants, and Line Widths of Formamide-^{15}N Species in 50:50 H_2O/D_2O at 24 °C

formamide	$^1\Delta N(D)$, ppm	$^1J_{NH_Z}$, Hz	$^1J_{NH_E}$, Hz	$^2J_{NH}$, Hz	$\delta\nu_{1/2}$, Hz
1	−262.75[a]	−88.5	−91.3	−13.9	0.3
(*Z*)-**1**-*d*	−0.487	−13.7[b]	−91.5	−13.7	0.9
(*E*)-**1**-*d*	−0.533	−88.3	−14.0[b]	−14.0	1.4
1-d_2	−1.024	−13.8[b]	−13.8[b]	−13.8	2.0

[a] Chemical shift δ relative to $Na^{15}NO_3$. [b] J_{ND}.

Table III. Rate Constants for Rotation in $HCO^{15}NHX$ at 48 °C

peak	X	$\nu_A - \nu_B$, Hz	k, s^{-1}
1	D	−3.65	2.83 ± 0.13
2	D	−3.85	2.78 ± 0.13
3	D	−4.12	2.57 ± 0.13
4	H	−2.86	3.32 ± 0.20
5	D	−4.42	2.85 ± 0.13
6	H	−2.76	3.04 ± 0.20

Table IV. Saturation Transfer Kinetics of C–N Rotation in Amides

amide	nucleus	T, °C	sat.	k_H, s^{-1}	k_D, s^{-1}
2	Me	38	*Z*	0.092 ± 0.002	0.092 ± 0.002
2	C=O	38	*Z*	0.102 ± 0.004	0.102 ± 0.004
2	Me(^1H)	40	*Z*	0.12 ± 0.03	0.15 ± 0.03
3	C=O	26	*E*	2.50 ± 0.07	2.44 ± 0.08
3	ipso	16	*E*	0.58 ± 0.02	0.54 ± 0.02
3	ortho	26	*E*	4.4 ± 0.2	4.3 ± 0.1
4	Me	48	*E*	0.051 ± 0.002	0.043 ± 0.001

Table V. Inversion Recovery Kinetics on **4**/**4**-*d* at 48 °C

run	k_H, s^{-1}	k_D, s^{-1}	k_H/k_D
1	0.081 ± 0.004	0.069 ± 0.003	1.16 ± 0.08
2	0.059 ± 0.002	0.053 ± 0.002	1.11 ± 0.06
3	0.069 ± 0.004	0.062 ± 0.002	1.13 ± 0.07

^{15}N NMR Spectra and Signal Assignments of Formamide. For each formamide species present in 50:50 H_2O/D_2O, the isotope shift, coupling constants, and intrinsic line width can be obtained by analysis of the spectrum in Figure 1. These are all listed in Table II. The isotope shifts agree with the average value of 0.51 ppm previously observed.[34] Coupling constants are in agreement with previously observed (negative) values, expect for the earliest.[11] The coupling constant $^1J_{NH_E}$ (of (*Z*)-**1**-*d*) is of larger magnitude than $^1J_{NH_Z}$, thereby enabling assignment of the signals of the two stereoisomers of **1**-*d*. This then leads to the conclusion that the magnitude of the isotope shift of (*E*)-**1**-*d* is larger than that of (*Z*)-**1**-*d*. Thus the larger $^1\Delta_E$ and $^3\Delta_{anti}$ in formamide and *N*,*N*-dimethylformamide, respectively, are associated with the larger coupling constants, as expected.[35] It is noteworthy that the line width of (*E*)-**1**-*d* is appreciably greater than that of (*Z*)-**1**-*d*, indicating that spin–spin relaxation of ^{15}N by attached quadrupolar deuterium depends on stereochemistry, even though the coupling constants are nearly identical.

Rate Constants for Isomerization. The results of line-shape analysis of the spectral region shown in Figure 2 are listed in Table III. The systematic increase of $|\nu_A - \nu_B|$ across the four pairs of peaks of HCONHD is real and is due to the inequality of $^1J_{ND_E}$ and $^1J_{ND_Z}$. The errors in each rate constant are based only on the precision of measurement from doublet to doublet.

The ^1H saturation-transfer spectrum of *N*-methylformamide is shown in Figure 3d. The rate constants derived from the intensities and relaxation times are included in Table IV. Saturation-transfer kinetics for the ^{13}C experiments are shown in Figures 4 and 5, and the results are listed in Table IV. The rate constants for **2** and **4** are in agreement with previous determi-

(29) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517.
(30) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337.
(31) Nakanishi, H.; Yamamoto, O. *Chem. Lett.* **1974**, 521.
(32) Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897.
(33) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. Nucl. Magn. Reson.* **1967**, *3*, 63. Baird, M. C. *J. Magn. Reson.* **1974**, *14*, 117.
(34) Lyčka, A.; Hansen, P. E. *Magn. Reson. Chem.* **1985**, *23*, 973.
(35) Frankiss, S. G. *J. Phys. Chem.* **1963**, *67*, 752.

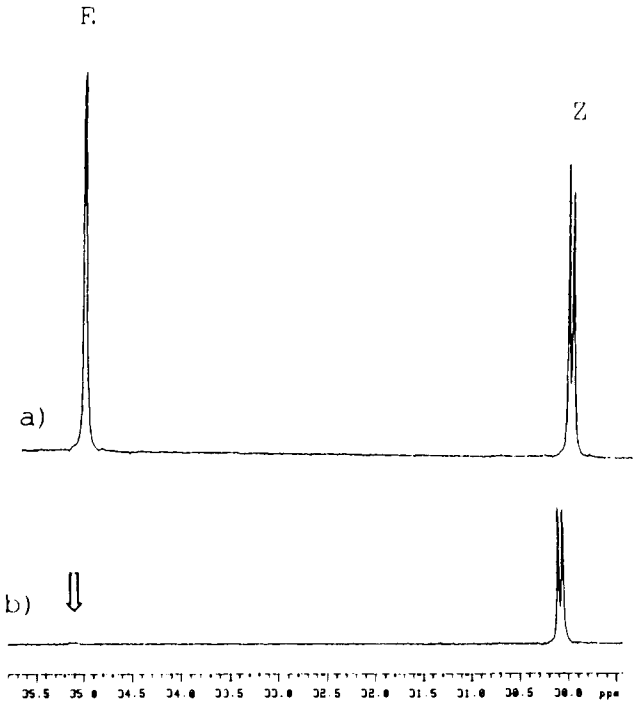


Figure 4. ^{13}C NMR saturation-transfer experiment. *N*-Methyl region of 1:1 $HCONMe_2/DCONMe_2$: (a) off-resonance irradiation; (b) irradiated at site indicated by arrow.

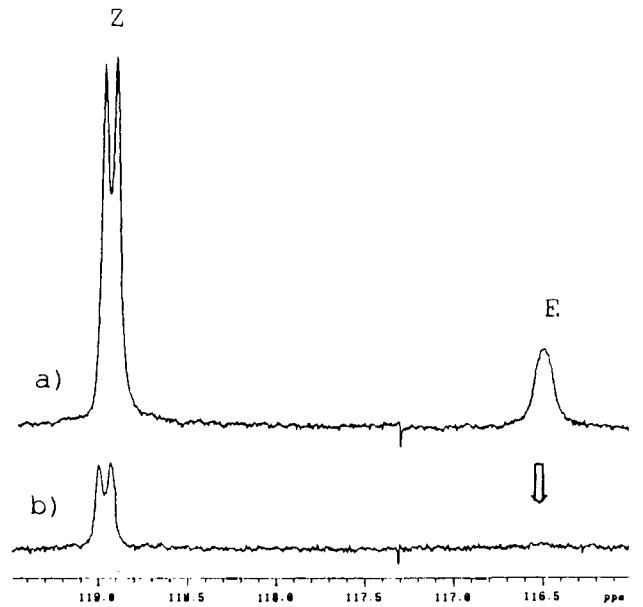


Figure 5. ^{13}C NMR saturation-transfer experiment: Ortho region of $HCONHC_6H_4NO_2$-*p*/$HCONDC_6H_4NO_2$-*p*: (a) off-resonance irradiation; (b) irradiated at site indicated by arrow.

nations.[26,36] Figures 4a and 5a show the off-resonance, or equilibrium, spectra, while Figures 4b and 5b show the spectra when saturated at the sites indicated by the arrows. The most upfield peak in Figure 4a is the *Z* methyl of $DCON(CH_3)_2$, broadened slightly by unresolved $^3J_{CD}$. It can be seen from Figure 4b that irradiation of the *E* methyls produces a greater transfer of saturation to the *Z* methyl of $HCON(CH_3)_2$, so this rotates faster than $DCON(CH_3)_2$.

To confirm the saturation-transfer results, an independent method was applied. Figure 6 shows the recovery of magnetization at *E* and *Z* methyls of **4**-*d* in a mixture with **4** after selective inversion of the *Z* methyl. The curves are sums of two exponentials, calculated using the parameters determined from the least

(36) Mann, B. E. *J. Magn. Reson.* **1977**, *25*, 91.

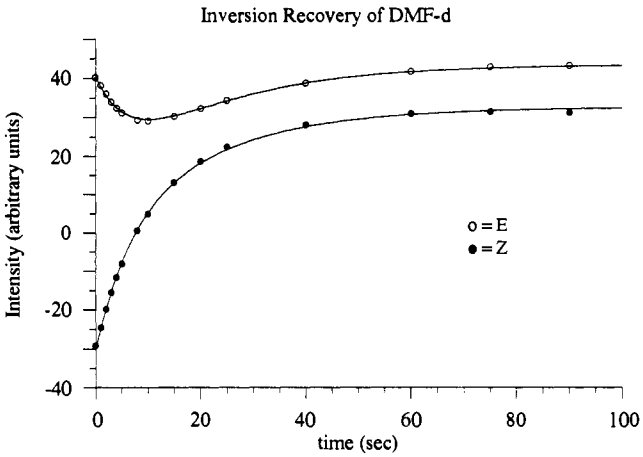


Figure 6. Selective NMR inversion-recovery experiment on *N*,*N*-dimethylformamide-*d* (○ = *E*, ● = *Z*).

Table VI. Secondary Deuterium Kinetic Isotope Effects on C–N Rotation of Amides at 25 °C

amide	nucleus	method[a]	k_H/k_D
1[b]	^{15}N	LSA	1.16 ± 0.10
2[c]	$^{13}CH_3$	ST	1.00 ± 0.06
2[c]	$^{13}C{=}O$	ST	1.00 ± 0.04
2[d]	^1H_3C	ST	0.8 ± 0.2
3[d]	$^{13}C{=}O$	ST	1.02 ± 0.04
3[d]	$^{13}C_{ortho}$	ST	1.02 ± 0.05
3[d]	$^{13}C_{ipso}$	ST	1.07 ± 0.05
4[c]	$^{13}CH_3$	ST	1.20 ± 0.05
4[c]	$^{13}CH_3$	SIR	1.14 ± 0.08

[a] LSA = line-shape analysis; ST = saturation transfer; SIR = selective inversion recovery. [b] Aqueous. [c] Neat. [d] In DMSO-d_6.

squares analysis. The rate constants and the KIEs are given in Table V. The KIE remains remarkably constant among the three runs although the individual rate constants do vary appreciably.

Secondary Deuterium Kinetic Isotope Effects. Secondary deuterium KIEs for isomerization about the C–N bond of the four amides are collected in Table VI. These are derived from the rate constants k_H and k_D in Tables III, IV, and V, extrapolated to 25 °C. The KIE for formamide is specifically k_{HCONH_2}/k_{HCONHD}. Errors in the KIE are calculated from propagation of errors in the individual rate constants. In summary, the kinetic isotope effects, averaged over the various reporter nuclei and NMR methods, are 1.16 ± 0.10 for formamide (**1**), 1.00 ± 0.03 for *N*-methylformamide (**2**), 1.04 ± 0.03 for *p*-nitroformanilide (**3**), and 1.18 ± 0.04 for *N*,*N*-dimethylformamide (**4**).

Discussion

Reliability of Kinetic Isotope Effects. Rate constants k_H and k_D in Tables III–V differ by hardly more than their experimental error, so that the reliability of their ratio may seem questionable. Nevertheless, the errors reported for the KIEs in Table VI are acceptably small. Admittedly, the errors were derived from replication and represent only a lower bound since they cannot take into account systematic errors. The most convincing evidence for the reliability of the KIEs is that the values are the same from different reporter nuclei and different NMR techniques.

The inescapable conclusion from these experiments is that there is no large KIE for C–N rotation in amides, for substitution at either carbon or nitrogen. This is apparent in Figures 4 and 5, where both on-resonance and off-resonance experiments show little difference in the relative intensities of the two isotopologues. As a measure of the sensitivity of the saturation-transfer technique, the small KIE in *N*,*N*-dimethylformamide (**4**) can be clearly seen in the relative peak heights of Figure 4. The potential error is certainly small enough that so large a k_H/k_D as 2 can be rejected. Likewise, the fit in Figure 6 is good enough to reject a large KIE. Even Figure 3 shows that there is no KIE, despite the inaccuracy

of the ^1H NMR rates. Therefore we conclude that the "quasiprimary" kinetic isotope effect is certainly not general.

The KIE in formamide is less certain, because it is obtained from fitting one ^{15}N spectrum, without corroboration from another method. Figure 2 indicates that the fit is quite good, so that the statistical errors in k_H and k_D are small. The larger sources of error are ±2–4% as judged from the agreement of k from doublet to doublet, ±3–4% from uncertainties in $\nu_A - \nu_B$, and ±2–4% from uncertainties in $\delta\nu_A$ and $\delta\nu_B$ of HCONHD. Therefore the overall error of ±9% in k_H/k_D is a conservative estimate. The value of 1.16 is definitely not near 2. It is significantly greater than 1, as is apparent from the fact that the two doublets of $HCONH_2$ (peaks 4 and 6) in Figure 2 are more coalesced than the four of HCONHD (peaks 1, 2, 3, and 5), even though the latter are intrinsically broader, and the greater coalescence of the former is more than can be accounted for by its smaller doublet separation.

Quasiprimary Isotope Effect. There is a sharp contrast between amide rotation (eq 2) and C=C rotation (eq 1), since only the latter shows a large KIE. Are these rotations really comparable? The C=C rotation is about a true double bond, whereas the C—N bond of an amide has only a partial double bond character. In fact the double bond of a *trans*-cyclohexene is severely twisted,[37] so that the activation energy for isomerization is only 12.1 kcal/mol,[2] actually lower than the $\Delta G^{\ddagger}$ of 17–21 kcal/mol for stereoisomerization of these amides. These double bonds are further similar in that both alkenes and amides[38] can be photoisomerized. Thus these two reactions have in common a rigid reactant and hydrogens or deuteriums that are rotating to produce a perpendicular transition state.

We ought not to have expected a large KIE. Despite the proposed rationalization[2] of the large effect in C=C rotation, in the amide rotation an out-of-plane C–H or N–H bending mode is *not* simply converted to a zero-frequency reaction coordinate. Instead, all of the out-of-plane modes mix to form the reaction coordinate, including the heavy-atom motions. Indeed, the transition state is a twisted amide with independent HC(=O) and NHR or NR_2 units, just as in aldehydes or amines. Therefore we expect that a full vibrational analysis, now in progress,[39] will show the following: (1) The out-of-plane C–H and N–H bending modes persist in the transition state. (2) Whatever zero-point energy is lost arises primarily from the other bending modes and is nearly independent of deuterium substitution. (3) There is no substantial loss of C–H or N–H zero-point energy nor any substantial secondary KIE. This is quite different from nitrogen inversion of ethylenimine,[3] where the N–H bending mode in the planar transition state really is the reaction coordinate, and its isotope-dependent zero-point energy is totally lost.

Are the previous calculations[2] on alkenes misleading? Much depends on the assertion that the frequency of the 820-cm^{-1} out-of-plane C–H bend becomes very low in the transition state for rotation and on the MNDO result that this bend dominates while other normal modes involving the C–H or C–D are well compensated between reactant and transition state. It is not clear how reliably any calculations can reproduce the potential-energy surface in the vicinity of a (singlet) biradical transition state, with one electron on each carbon. An advantage of amide rotation is that its transition state is closed-shell, with two electrons in a nitrogen lone pair, and thus more readily calculated. Such calculations are in progress.[39]

Why might k_H/k_D be unusually large for stereoisomerization of *trans*-1-phenylcyclohexene? In agreement with the calculations, it is likely that the frequency of the out-of-plane C–H bend is indeed considerably lower in the biradical transition state, as judged by the 369-cm^{-1} mode observed in the isopropyl radical.[40] The familiar rehybridization may also contribute, since the carbon of a *trans*-cyclohexene is pyramidalized and becomes sp^2 in the transition state. There may be an additional contribution from hyperconjugation, as in isomerization of cyclopropanes,[41] where a β hydrogen stabilizes the biradical transition state better than a β deuterium. All of these contributions reinforce one another, so that together they may lead to a large KIE of 2.0 that is special to the rotation of ethylenes. However, the quasiprimary KIE is not a general phenomenon, and it is not operative in amides.

Small KIEs in C–N Rotation of Amides. A rigorous interpretation requires a full vibrational analysis of each amide and its rotated transition state. The easiest KIE to interpret is that of *N,N*-dimethylformamide (**4**), since there is no rehybridization of the carbon to which the isotope is attached. The most extensive vibrational analysis available is of the parent formamide,[42] for which the C–H out-of-plane bending frequency is 1021 cm^{-1}. Total loss of this zero-point energy would lead to a large k_H/k_D, near 2.0. Yet only a small k_H/k_D of 1.18 ± 0.04 is observed.

Clearly the reaction coordinate is not derived exclusively from the C–H bend. Instead the C–H bend couples with C–O and $N-CH_3$ out-of-plane bends to form the torsional reaction coordinate and two other normal modes. Only the zero-point energy associated with the torsional mode is lost at the transition state. To the extent that C–O and $N-CH_3$ motions contribute to this mode, the zero-point energy is reduced and is also less sensitive to isotopic substitution. The zero-point energy of the C–H mode, although isotope dependent, is then present in both reactant and transition state. Consequently the KIE is expected to be low.

The KIE does not vanish because the 1021-cm^{-1} C–H bend is a high-frequency out-of-plane bend. In the transition state the frequency is reduced, as judged from the 764-cm^{-1} bend in CH_3CHO, which is reduced to 674 cm^{-1} in CH_3CDO.[43] Therefore there is a small reduction of zero-point energy and a small but detectable KIE.

The KIE for N-deuteration is more complicated because of the possibility of rehybridization. In parallel to the above analysis, the relevant normal mode of formamide is the 602.8-cm^{-1} C–N twisting frequency,[42] which becomes 470 cm^{-1} in $HCOND_2$.[23] Complete loss of its zero-point energy would lead to a k_H/k_D near 1.2. Yet for $HCONDCH_3$ (**2**) k_H/k_D is 1.00 ± 0.03, which is equivalent to no effect at all. For $HCONDC_6H_4NO_2$-*p* (**3**) k_H/k_D is 1.04 ± 0.03, barely beyond experimental error. Therefore this analysis is again oversimplified. The other bending modes also contribute to the reaction coordinate, so that the zero-point energy of the N–H or N–D bend remains in the transition state.

It is possible that the low KIE is due to a fortuitous cancellation, arising from an increase in the frequency of N–H bending modes in a pyramidalized nitrogen. However, **3** also shows essentially no KIE, even though its nitrogen is likely to remain planar.[6] The difference between **3** and **2** is in the expected direction, but it is not statistically significant.

Excitation Term in KIE of Formamide. The KIE of 1.16 ± 0.10 for $HCONH_2$ relative to HCONHD is somewhat uncertain but significantly different from unity. It might be due to loss of the zero-point energy of the 602.8-cm^{-1} C–N twisting mode that is converted into the reaction coordinate. However, this does not lead to appreciable KIEs for the other two N-deuterated amides **2** and **3**.

It is likely that a contributor to the KIE is the Boltzmann excitation factor (eq 8,[1] where the first product is over all vibrations of the reactant and the second is over all vibrations of the transition state). Ordinarily this does not contribute, since normal modes

$$\left(\frac{k_H}{k_D}\right)_{EXC} = \prod \frac{1-\exp(-h\nu_{iH}/kT)}{1-\exp(-h\nu_{iD}/kT)} \prod \frac{1-\exp(-h\nu_{jD}^{*}/kT)}{1-\exp(-h\nu_{jH}^{*}/kT)} \quad (8)$$

involving hydrogen are of too high a frequency for their excited

(37) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734. Verbeek, J.; van Lenthe, J. H.; Timmermans, P. J. J. A.; Mackor, A.; Budzelaar, P. H. M. *J. Org. Chem.* **1987**, *52*, 2955.
(38) Song, S.; Asher, S. A.; Krimm, S.; Shaw, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 1155.
(39) Schaad, L. J. Personal communication.
(40) Pacansky, J.; Koch, W.; Miller, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 317.
(41) Baldwin, J. E.; Carter, C. G. *J. Am. Chem. Soc.* **1979**, *101*, 1325.
(42) Sugawara, Y.; Hamada, Y.; Tsuboi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1045.
(43) Hollenstein, H.; Günthard, H. H. *Spectrochim. Acta* **1971**, *27A*, 2027.

vibrational states to be thermally populated. The unusual feature of formamide is that the frequency of the wagging (pyramidalization) mode of the NH_2 is only 289 cm^{-1},[44] which decreases to 222 cm^{-1} in $HCOND_2$.[23] In the pyramidalized transition state this mode becomes an ordinary high-frequency bending vibration. This is not the reaction coordinate, but its excited states are more heavily populated for $HCOND_2$ or HCONHD. The free energy of these reactants is lowered by this degeneracy, thereby raising the free energy of activation so that they rotate more slowly than $HCONH_2$.

From the above frequencies the wagging mode can be calculated to contribute a factor of 1.07 to k_H/k_D at 48 °C. This value is small, but it must contribute to the isotope effect, and it is consistent with the experimental value of 1.16 ± 0.10. To the best of our knowledge this is the first example of a contribution of the excitation term to a KIE. Unfortunately it is not possible to test the temperature dependence of eq 8, since the line-shape method is accurate only over an exceedingly narrow range of rate constants.

(44) King, S. T. *J. Phys. Chem.* **1971**, *75*, 405.

Conclusions

There is no substantial secondary kinetic isotope effect for C–N rotation in amides, for substitution of deuterium at either carbon or nitrogen. The small effects seen can be attributed to slight changes in zero-point energies of out-of-plane bending modes, rather than conversion of C–H or N–H bends into the reaction coordinate. The large KIE in ethylenes may be a special case. Formamide may also be a special case for which the thermal population of excited vibrational states of HCONHD (or $HCOND_2$) renders the deuterium-substituted amide less reactive toward rotation.

Acknowledgment. This research was supported by National Science Foundation Grant CHE90-25113 (to C.L.P.). Purchase of the 500-MHz NMR spectrometer at UCSD was made possible by NIH Grant RR04733 and NSF Grant CHE88-14866.

Registry No. 1, 75-12-7; **2**, 123-39-7; **3**, 16135-31-2; **4**, 68-12-2; D_2, 7782-39-0.

Evidence for a 1,4-Dioxy Diradical as an Intermediate in the Thermal Decomposition of 3,3-Dibenzyl-1,2-dioxetane

Waldemar Adam* and Markus Heil

Contribution from the Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-8700 Würzburg, Germany. *Received May 11, 1992*

Abstract: The thermal decomposition of 3,3-dibenzyl-1,2-dioxetane (**1**) in $CDCl_3$ and CH_2Cl_2 solutions afforded the expected decomposition product 1,3-diphenyl-2-propanone (**2**) and the novel rearrangement ketone 1-(benzyloxy)-3-phenyl-2-propanone (**3**) in ratios of (73 ± 10):(27 ± 10). A plausible mechanism for the formation of ketone **3** involves homolytic cleavage of the dioxetane peroxide bond with subsequent β cleavage of the benzyl group in the 1,4-dioxy diradical and in-cage combination of the resulting radicals. Moreover, several control experiments render a benzyl radical-induced decomposition of dioxetane **1** unlikely. Thus, the ratio of **2** and **3** was found to be essentially independent of the initial dioxetane concentration, and the presence of radical scavengers did not affect the product ratio and reaction rate. With the electron-rich 1,4-dioxene, the dioxetane **1** afforded the cycloadduct *cis*-3,3-dibenzyl-2,5,7,10-tetraoxabicyclo[4.4.0]decane (**4**) as major product.

The most characteristic reaction of 1,2-dioxetanes[1] is their thermal cleavage to afford efficiently electronically excited carbonyl fragments. While a concerted[2] and a two-step biradical[3] mechanism have been suggested, the "merged mechanism"[4] unifies these two contrary decomposition modes. In a recent theoretical study[5] a decomposition mechanism was proposed in which the formation of the singlet dioxy diradical occurs essentially without activation energy; in fact, the thermal activation is supposedly derived from the production of the triplet diradical. Although the present-day experimental data seem to speak in favor of the biradical mechanism,[3] the only direct evidence constitutes the trapping of the intermediary 1,4-dioxy diradical by 1,4-cyclo-

Table I. Thermal Decomposition of Dioxetane **1**[a]

entry	[1] (M)	solvent[b]	additive[c]	product distribution[d] 2	3
1	ca. 4.0	none		44	56
2	1.03	CH_2Cl_2		64	36
3	0.108	CH_2Cl_2		79	21
4	0.010	CH_2Cl_2		80	20
5	0.001	CH_2Cl_2		83	17
6	0.223	$CDCl_3$		63	37
7	0.245	$CDCl_3$	2,6-di-*tert*-butyl-4-methylphenol (11%)	65	35
8	0.210	$CDCl_3$	galvinoxyl (7%)	78	22

[a] At room temperature (ca. 25 °C); ca. 48 h were required for complete consumption of the dioxetane **1**, except entry 1 for which only 18 h were necessary. [b] Also in CCl_4, CH_3OH, CH_3CN, and toluene substantial amounts of the rearrangement ketone **3** were observed by ^1H NMR. [c] In parentheses, mol % relative to dioxetane **1**. [d] Determined by integration of the appropriate ^1H NMR signals (250 MHz), normalized to 100%, error ca. 5% of the stated values, 100% consumption of the dioxetane, the mass balance was >90% in every case.

(1) For recent reviews, cf. (a) Cilento, G.; Adam, W. *Photochem. Photobiol.* **1988**, *48*, 361. (b) Baumstark, A. L. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press Inc.: Greenwich, CT, 1988; Vol. 1, p 31. (c) Adam, W.; Heil, M.; Mosandl, T.; Saha-Möller, C. R. In *Organic Peroxides*; Ando, W., Ed.; Wiley & Sons, Chichester, in press.

(2) (a) McCapra, F. *J. Chem. Soc., Chem. Commun.* **1968**, 155. (b) Kearns, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 6554. (c) Turro, N. J.; Lechtken, P.; Schore, N. E.; Schuster, G.; Steinmetzer, H.-C.; Yekta, A. *Acc. Chem. Res.* **1974**, *7*, 97.

(3) (a) O'Neal, H. E.; Richardson, W. H. *J. Am. Chem. Soc.* **1970**, *92*, 6553. (b) Richardson, W. H.; Anderegg, J. H.; Price, M. E.; Tappen, W. A.; O'Neal, H. E. *J. Org. Chem.* **1978**, *43*, 2236. (c) Richardson, W. H.; Montgomery, F. C.; Yelvington, M. B.; O'Neal, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 7525.

(4) (a) Turro, N. J.; Devaquet, A. *J. Am. Chem. Soc.* **1975**, *97*, 3859. (b) Adam, W.; Baader, W. J. *J. Am. Chem. Soc.* **1985**, *107*, 410.

(5) Reguero, M.; Bernardi, F.; Bottoni, A.; Olivucci, M.; Robb, M. *J. Am. Chem. Soc.* **1991**, *113*, 1566.

0002-7863/92/1514-8807$03.00/0