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Theoretical Analysis of Secondary Kinetic Isotope Effects in C–N Rotation of Amides

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Abstract: The deuterium kinetic isotope effects for rotations about the C–N bonds of formamide, *N*-methylformamide, and *N,N*-dimethylformamide have been calculated from the Bigeleisen equation using the program QUIVER, based upon *ab initio* harmonic vibrational frequencies for ground states and transition states, calculated with GAUSSIAN 92 at the RHF/6-31G*, RHF/6-311++G**, MP2(FC)/6-31G*, and MP2(FC)/6-311++G** levels. The predicted isotope effects are similar at the different levels and agree closely with experimental values from Perrin *et al.* (*J. Am. Chem. Soc.* **1992**, *114*, 8800). The magnitudes of the isotope effects are interpreted.

Introduction

Perrin *et al.* recently reported experimental measurements, summarized in Figure 1, of the secondary kinetic isotope effects for rotation about the C–N bonds of several amides.[1] A fuller interpretation of these results can be provided by an analysis of the changes in vibrational frequencies upon conversion of the ground to the transition state. We have calculated these isotope effects and found good agreement with experimental values. The results are analyzed to determine the origins of these effects.

Ab Initio Structures of Ground States and Transition States. The molecular structure of formamide has been determined from its microwave spectrum.[2] *Ab initio* calculations at a variety of levels are in agreement.[3–5] Our calculations are summarized in Table 1. Like Wiberg *et al.*[4] and Wright *et al.*,[5] we find that ground-state formamide optimizes to a structure with a pyramidalized amino group (HNH plane 13° to C–N bond) when second-order Møller–Plesset (MP2) corrections for electron correlation are included (Table 1). Our HF calculations optimized to a planar structure. If the MP2 optimization of formamide is constrained to C_s symmetry, the structure obtained is 0.2 kcal/mol lower in energy than the C_1 structure, and has 0.5 kcal/mol less zero-point energy but has an imaginary frequency (-355 cm^{-1}) corresponding to pyramidalization at the nitrogen. Using either structure gives a negligible difference in the magnitude of the calculated kinetic isotope effect for rotation.

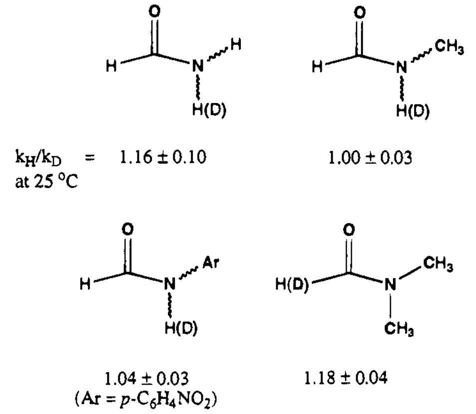

Figure 1. Summary of experimental kinetic isotope effects for CN rotation.[1]

The molecular structure of *N*-methylformamide has been determined by electron diffraction.[6] *Ab initio* calculated structures are in good agreement here as well[7] (Table 1). At the MP2/6-31G* level, the *trans* form is calculated to be more stable than the *cis* form by 1.3 kcal/mol. A small (2°) pyramidalization was found at the nitrogen atom for the *trans* form, whereas the *cis* form had C_s symmetry.

Our calculations of *N,N*-dimethylformamide at the MP2/6-31G* level are in agreement (Table 1) with the experimental structure,[8] determined by microwave spectroscopy.

As noted previously,[9] two diastereomeric conformers were found as transition states for amide rotation. During rotation about the C–N bond, pyramidalization at the nitrogen atom occurs, with the substituents on nitrogen directed toward (TS-1) or away (TS-2) from the carbonyl (Figure 2), TS-1 was found to be ≈2 kcal/mol lower in energy than TS-2 and 15–18 kcal/mol higher in energy than the ground state. Only TS-1 was calculated for *N,N*-dimethylformamide. The calculations re-

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Table 1. Optimized Ground-State Structures of Amides

molecule	$HCONH_2$	HCOHNMe(*cis*)	HCONHMe(*trans*)	$HCONMe_2$
calculation	MP2/6-311++G**	MP2/6-31G*	MP2/6-31G*	MP2/6-31G*
symmetry	C_1	C_1	C_s	C_s
energy (hartrees)	−168.98579	−207.95678	−207.95839	−246.98805
zero-point energy (kcal/mol)	28.9	47.6	47.6	65.9
	Selected Bond Distances (Å) and Angles (deg)[a]			
C=O	1.2163 (1.21)	1.2267	1.2282 (1.219)	1.2293 (1.20)
C−N	1.3687 (1.35)	1.3618	1.3615 (1.366)	1.3642 (1.34)
C−H	1.1045 (1.098)	1.1063	1.1049 (1.125)	1.1054
$N-H_{cis}$	1.0074 (1.001)		1.0109 (1.027)	
$N-H_{trans}$	1.0097 (1.001)	1.0138		
$N-Me_{cis}$		1.4483		1.4470 (1.45)
$N-Me_{trans}$			1.4510 (1.459) Å	1.4501 (1.45)
N−C−O	124.7 (124.7)	124.8	125.3 (124.6)°	
H−C−O	122.8 (122.5)			122.4
$H_{trans}-N-C$	119.2 (120.0)	115.4		
$H_{cis}-N-C$	117.5 (118.5)		118.1 (118.7)	
H−C−N		112.3	112.1 (112.7)	112.1
$Me_{cis}-N-C$		124.9		122.0 (120 assumed)
$Me_{trans}-N-C$			121.4 (121.4)	120.0 (120 assumed)
$H_{trans}-N-C-O$	165.8 (180 assumed)	0.1		
$H_{cis}-N-C-O$	12.2 (0 assumed)			
Me−N−C−O		180.3		
exptl ref	2		6	8

[a] Experimental values are in parentheses.

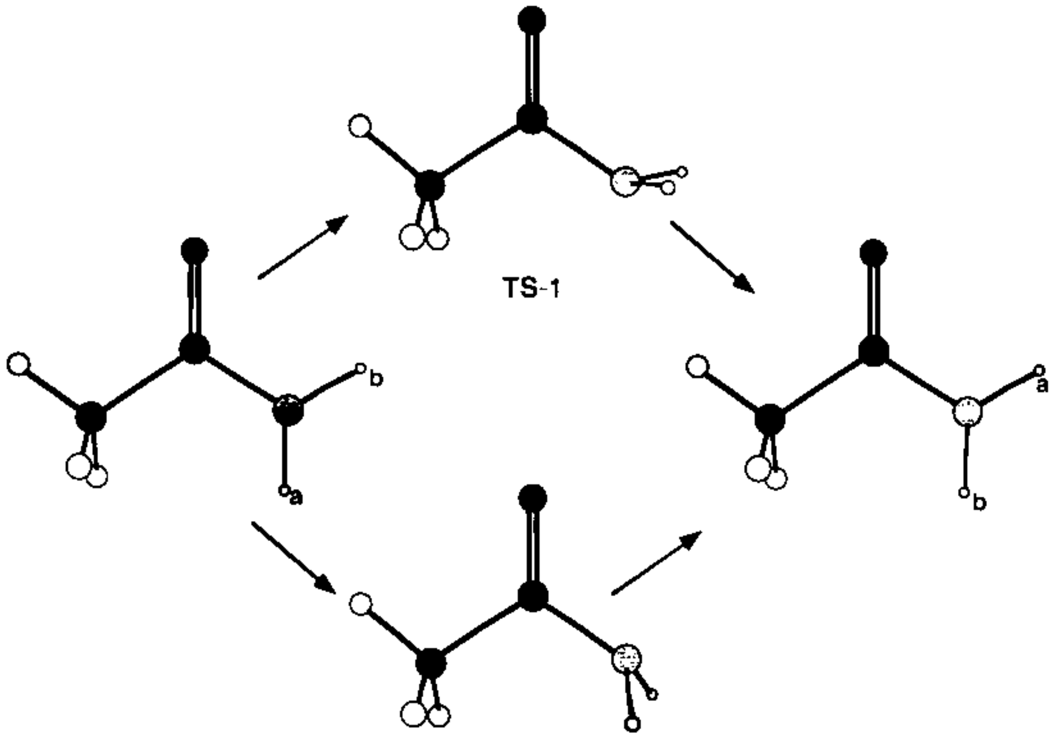

Figure 2. Transition states for CN rotation in amides. Acetamide is given as an example.

produce reasonably well the experimental barrier to rotation in amides.[10] Table 2 gives the calculated structural parameters for TS-1 of the amides.

***Ab Initio* Vibrational Frequencies of Ground States and Transition States.** The infrared spectra of formamide and several of its relevant isotopomers have been obtained, and the fundamental frequencies have been assigned.[3,11] Our *ab initio* calculations of the vibrational frequencies of formamide and its isotopomers in Table 3, as well as those of previous workers,[3] give reasonable agreement with experiment. Here, the NH_2 wagging frequency (thought to be important[1] in influencing the kinetic isotope effect (KIE)) is retained by use of the pyramidalized MP2 structure; this mode is the imaginary frequency of the planar structure. While scaling of our MP2 frequencies by a factor of 0.97 gives closer agreement with the experimental frequencies, the calculated KIEs change by only about ±0.001 upon scaling. Unscaled frequencies were therefore used to calculate KIEs.

The infrared spectra of *N*-methylformamide and several of its relevant isotopomers have been reported,[12] and our calculated values are in good general agreement with them. In the same way our calculated frequencies for *N,N*-dimethylformamide agree with reported values.[13]

Calculation of Isotope Effects. The Bigeleisen equation[14] for isotope effects allows computation of KIEs using the molecular masses and symmetries, the $3n - 6$ fundamental frequencies of ground states and $3n - 7$ fundamental frequencies

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Table 2. Optimized Transition-State Structures of Amides

molecule	formamide (TS-1)	*N*-methylformamide (TS-1)	*N*,*N*-dimethylformamide
calculation	MP2/6-311++G**	MP2/6-31G*	MP2/6-31G*
symmetry	C_s	C_1	C_s
energy (hartrees)[a]	−168.96046 (−168.95683)	−207.92892 (−207.92571)	−246.95752
zero-point energy (kcal/mol)[a]	28.2 (28.0)	47.0 (46.9)	65.1
	Selected Bond Distances (Å) and Angles (deg) of TS-1 of Amides		
C=O	1.2087	1.2187	1.2191
C—N	1.4430	1.4412	1.4401
C—H	1.1009	1.1021	1.1034
N—H	1.0190	1.0231	
Me—N		1.4779	1.4699
N—C—O	125.4		
H—C—O	121.6	121.5	121.5
H—N—C	107.5	106.3	
H—C—N		113.5	113.7
Me—N—C		110.6	109.5
H—N—C—O	56.4		
Me—N—C—H		123.2	119.4
H—N—C—H		−120.4	

[a] Energy data in parentheses are for TS-2.

Table 3. MP2/6-311++G** Vibrational Frequencies (cm^{-1}) of Formamide and Deuterated Isotopomers[a]

	$HCONH_2$[b]	$DCONH_2$[b]	HCONH(*cis*-D)[c]	HCONH(*trans*-D)[c]
NH_2 wag	398 (289)	398 (*d*)		
NCO bend	566 (581)	559 (563)	536 (*b*)	501 (*b*)
NH_2 twist	620 (603)	608 (591)		
CH out of plane def.	1041 (1021)		1050 (1048)	1043 (1048)
NH_2 rock	1073 (1045)	1150 (1142)		
CN stretch	1279 (1258)	1262 (1242)	1277 (1287)	1180 (1189)
CH bend	1439 (1390)		1420 (1379)	1437 (1391)
NH_2 scissors	1630 (1577)	1626 (1582)		
CO stretch	1798 (1754)	1778 (1740)	1796 (1710)	1791 (1710)
CH stretch	3024 (2854)		2706 (2571)	2684 (2558)
NH_2 sym. stretch	3618 (3439)	3618 (3438)		
NH_2 asym. stretch	3761 (3563)	3761 (3563)		
CD out of plane def.		870 (*d*)		
CD bend		981 (955)		
CD stretch		2239 (2135)		
NHD wag			314 (*d*)	366 (*d*)
NHD twist			596 (*d*)	545 (*d*)
NHD rock			908 (*d*)	1004 (*d*)
NHD scissors			1481 (1467)	1506 (1475)
NHD sym. stretch			3023 (2874)	3024 (2874)
NHD asym. stretch			3709 (3451)	3709 (3482)

[a] Experimental values in parentheses are from refs 3 and 11. [b] Experimental frequencies measured in vapor phase. [c] Experimental frequencies measured in chloroform solution. [d] Not reported.

of transition states, and the imaginary frequencies of transition states. The equation in simplified form (symmetry numbers omitted[15]) is

$$k_H/k_D = \mathrm{KIE} = \mathrm{MMI} \times \mathrm{EXC} \times \mathrm{ZPE}$$

where MMI (mass and moment of inertia) involves the partition functions for translational and rotational states, EXC (excitation) involves the population of vibrational states above the zero-point energy level, and ZPE (zero-point energy) is the familiar term involving differences in zero-point energies.

After application of the Redlich—Teller product rule, it is possible to express the KIE in terms of the vibrational frequencies alone.[15,16] Then the KIE is given by

$$k_H/k_D = (\nu_{i(H)}{}^{\ddagger}/\nu_{i(D)}{}^{\ddagger}) \times \mathrm{VP} \times \mathrm{EXC} \times \mathrm{ZPE}$$

where the MMI term has been reduced to the product of the ratio of imaginary frequencies ($\nu_{i(H)}{}^{\ddagger}/\nu_{i(D)}{}^{\ddagger}$) times a vibrational product (VP) term. The terms are

$$\mathrm{VP} = \prod_{n}^{3n-6} \nu_{n(D)}/\nu_{n(H)} \Big/ \prod_{n}^{3n^{\ddagger}-7} \nu_{n(D)}{}^{\ddagger}/\nu_{n(H)}{}^{\ddagger}$$

$$\mathrm{EXC} = \prod_{n}^{3n-6} 1 - e^{-u_n(H)}/1 - e^{-u_n(D)} \Big/ \prod_{n}^{3n^{\ddagger}-7} 1 - e^{-u_n(H)^{\ddagger}}/1 - e^{-u_n(D)^{\ddagger}}$$

$$\mathrm{ZPE} = \prod_{n}^{3n-6} e^{(u_n(H)/2)}/e^{(u_n(D)/2)} \Big/ \prod_{n}^{3n^{\ddagger}-7} e^{(u_n(H)^{\ddagger}/2)}/e^{(u_n(D)^{\ddagger}/2)}$$

where $u = h\nu/kT$ and ν are the fundamental vibrational frequencies.

The program QUIVER[17] was used to calculate the separate components of the Bigeleisen equation (the partition functions) using ground- and transition-state frequencies computed by the

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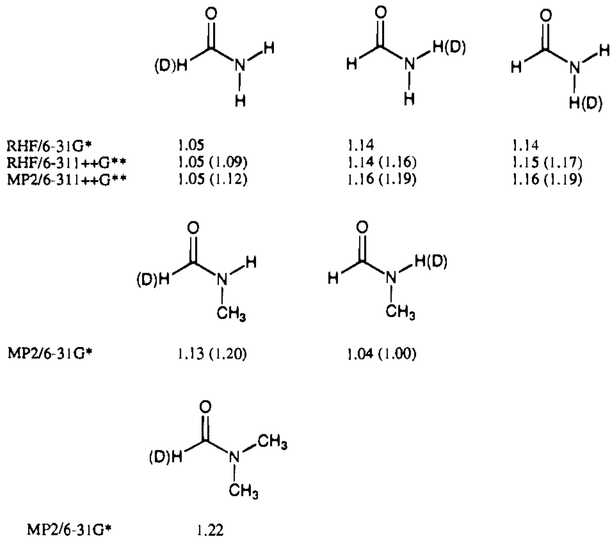

Figure 3. Summary of calculated isotope effects for CN rotation. (Values in parentheses are those calculated from the second transition structure of amide rotation).

GAUSSIAN 92[18] program. Temperatures and atomic masses were varied as desired.

The Bigeleisen equation ignores tunneling which can be included approximately by the method of Bell.[19] As seen below, Bell's correction is not large in our case, and the Bigeleisen treatment is adequate to give results in good agreement with experiment.

One interesting point concerning the partition functions is that according to isotope effect theory, (VP × EXC × ZPE) approaches unity at infinite temperature,[16] where EXC cancels VP and ZPE becomes 1. Since there is no temperature dependence of the ratio of imaginary frequencies or of the VP term, the KIE temperature dependence is controlled by the ZPE and EXC terms. The "typical" case is for EXC to vary little from unity and for ZPE to decrease with increasing temperature. This causes the KIE to decrease gradually and approach the ratio of imaginary frequencies at high temperature. In our calculations, however, this was not always the case, as described later.

Kinetic Isotope Effects. Calculated kinetic isotope effects of formamide summarized in Figure 3 and in Table 4 show good agreement with experiment. Differences in theoretical isotope effects from various computational levels are small compared to the isotope effects themselves and to changes caused by varying the position of isotopic substituents. As noted earlier, the optimized structure of formamide is planar with RHF calculations but is nonplanar at the MP2 levels. The calculated KIEs using the MP2 planar structure are 0.02−0.03 smaller than those from the nonplanar structure. Tunneling corrections[19] were also performed for formamide, using RHF/6-31G* frequencies and geometries. Results with scaled ($(0.8)^{1/2}$ scaling factor) and unscaled frequencies are given in Table 5. There is a moderate correction for tunneling in cases with deuterium(s) on the nitrogen atom and no simulated methyl groups, but with either deuterium on carbon or with simulated methyl groups (see below), the tunneling correction is small.

Table 4. Components of Calculated Isotope Effects for Rotation about the C−N Bond in Formamide at 298 K[a]

	RHF/ 6-31G*	RHF/ 6-311++G**	MP2(FC)/ 6-31G*	MP2(FC)/ 6-311++G**
		$LCONH_2$ via TS-1		
$\nu_H^{\ddagger}$ (cm^{-1})	404.6	403.5	514.0	513.6
$\nu_D^{\ddagger}$ (cm^{-1})	391.0	389.8	497.3	497.2
ΔΔZPE (kcal/mol)	0.02	0.02	0.01	0.01
$\nu_H^{\ddagger}/\nu_D^{\ddagger}$	1.035	1.035	1.034	1.033
k_H/k_D(VP)	0.979	0.979	0.981	0.980
k_H/k_D(EXC)	1.001	1.000	1.000	1.000
k_H/k_D(ZPE)	1.036	1.039	1.029	1.034
k_H/k_D via TS-1	1.051	1.054	1.043	1.048
k_H/k_D via TS-2		1.093		1.119
		$HCONHL_{cis}$ via TS-1		
$\nu_H^{\ddagger}$ (cm^{-1})	404.6	403.5	514.0	513.6
$\nu_D^{\ddagger}$ (cm^{-1})	354.9	354.2	451.1	451.0
ΔΔZPE (kcal/mol)	0.00	0.01	0.02	0.04
$\nu_H^{\ddagger}/\nu_D^{\ddagger}$	1.140	1.139	1.139	1.139
k_H/k_D(VP)	0.902	0.894	0.894	0.894
k_H/k_D(EXC)	1.095	1.096	1.080	1.055
k_H/k_D(ZPE)	1.008	1.021	1.031	1.082
k_H/k_D via TS-1	1.135	1.139	1.134	1.161
kH/k_D via TS-2		1.162		1.186
		$HCONHL_{trans}$ via TS-1		
$\nu_H^{\ddagger}$ (cm^{-1})	404.6	403.5	514.0	513.6
$\nu_D^{\ddagger}$ (cm^{-1})	354.9	354.2	451.1	451.0
ΔΔZPE (kcal/mol)	−0.01	0.01	0.00	0.04
$\nu_H^{\ddagger}/\nu_D^{\ddagger}$	1.140	1.139	1.139	1.139
k_H/k_D(VP)	0.855	0.859	0.860	0.860
k_H/k_D(EXC)	1.190	1.161	1.148	1.089
k_H/k_D(ZPE)	0.982	1.010	0.998	1.089
k_H/k_D via TS-1	1.138	1.148	1.121	1.163
k_H/k_D via TS-2		1.171		1.188

[a] L indicates the position of isotopic substitution.

Table 5. Corrections to Isotope Effects (k_H/k_L) Due to Tunneling (6-31G* at 321.15 K)

	unscaled frequencies		scaled frequencies[b]	
amide[a]	uncorrected	with tunnel correction	uncorrected	with tunnel correction
$LCONH_2$	1.056	1.073	1.052	1.065
$HCONL_2$	1.242	1.355	1.257	1.346
$LCONX_2$	1.136	1.146	1.129	1.137
c-HCONLX	1.063	1.076	1.070	1.081
t-HCONLX	1.063	1.076	1.072	1.083
c-LONHX	1.107	1.122	1.102	1.114
t-LCONHX	1.112	1.128	1.106	1.118
t-HCONLH	1.129	1.191	1.134	1.182
c-HCONHL	1.129	1.191	1.136	1.185
$LCONH_2$	1.109	1.120	1.097	1.106
t-HCONLH	1.154	1.207	1.157	1.199

[a] L indicates the position of H or D substitution. X is a hydrogen atom of mass 15 used to simulate a methyl group. [b] A frequency scaling factor of $(0.8)^{1/2}$ was used.

As for formamide, substitution of deuterium at the different positions of *N*-methylformamide gives substantially different KIEs. These are summarized in Figure 3 (where values in parentheses are those for TS-2 of amide rotation) and Table 6.

The largest KIEs were found for deuterium substitution on the carbon atom of *N*,*N*-dimethylformamide (Table 7). Here, the model calculation using simulated methyl groups on the nitrogen of formamide (MP2/6-311++G**) gives substantially different results than do the calculations with the methyl groups (H is replaced with mass of 15, that of a methyl group) explicitly included.

Comparison with Experiment. These calculations can be compared directly with three of the experimental KIE results: formamide and *N*-methylformamide with deuterium substitution on the nitrogen and *N*,*N*-dimethylformamide with deuterium substitution on the carbonyl carbon.

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Table 6. Components of Calculated Isotope Effects for Rotation about the C−N Bond in *N*-Methylformamide at 298 K[a]

	MP2(FC)/6-31G*	
	cis-Me	*trans*-Me
LCONHCH$_3$ via TS-1		
$\nu_H^\ddagger$ (cm^{-1})	327.9	327.9
$\nu_D^\ddagger$ (cm^{-1})	293.4	293.4
ΔΔZPE (kcal/mol)	0.05	0.06
$\nu_H^\ddagger/\nu_D^\ddagger$	1.118	1.118
k_H/k_D(VP)	0.919	0.895
k_H/k_D(EXC)	1.037	1.042
k_H/k_D(ZPE)	1.073	1.102
k_H/k_D via TS-1	1.143	1.148
k_H/k_D via TS-2	1.213	1.218
HCONLCH$_3$ via TS-1		
$\nu_H^\ddagger$ (cm^{-1})	327.9	327.9
$\nu_D^\ddagger$ (cm^{-1})	310.2	310.2
ΔΔZPE (kcal/mol)	−0.01	−0.01
$\nu_H^\ddagger/\nu_D^\ddagger$	1.057	1.057
k_H/k_D(VP)	0.979	0.959
k_H/k_D(EXC)	1.037	1.062
k_H/k_D(ZPE)	0.975	0.984
k_H/k_D via TS-1	1.047	1.059
k_H/k_D via TS-2	1.010	1.022

[a] L indicates the position of isotopic substitution.

Table 7. Components of Calculated Isotope Effects for Rotation about the C−N Bond in N,N-Dimethylformamide at 298 K[a]

	RHF/6-31G*	MP2(FC)/ 6-31G*	MP2(FC)/ 6-311++G** [b]
LCONMe$_2$			
$\nu_H^\ddagger$ (cm^{-1})	208.4	266.2	248.6
$\nu_D^\ddagger$ (cm^{-1})	182.4	232.3	224.8
ΔΔZPE (kcal/mol)	0.08	0.09	0.04
$\nu_H^\ddagger/\nu_D^\ddagger$	1.143	1.146	1.106
k_H/k_D(VP)	0.872	0.868	0.903
k_H/k_D(EXC)	1.054	1.045	1.038
k_H/k_D(ZPE)	1.153	1.170	1.091
k_H/k_D	1.211	1.217	1.131

[a] L indicates the position of isotopic substitution. [b] Model calculations using the geometries and force constants of formamide but changing the mass of both hydrogens of NH$_2$ to 15.

In the case of HCONLH (L = H or D), the calculations give a range of k_H/k_D = 1.14−1.17 (298 K, TS-1, average for *cis* and *trans*), depending on the basis set and method; scaled RHF/6-31G* calculations with tunneling corrections give a value of 1.184. These compare well with the experimental value of 1.16 ± 0.10 (corrected[1] to 298 K).

In the case of HCON(CH$_3$)L, MP2(FC)/6-31G* calculations that explicitly include the methyl group give k_H/k_D = 1.053 (298 K, TS-1, average for *cis* and *trans*). This value is somewhat outside the range of the stated experimental error for this amide, which was k_H/k_D = 1.00 ± 0.03. However, as noted by Perrin *et al.*, the experimental errors are standard deviations from replication of experiments and represent only a lower bound to the true errors,[1] so there may still be overlap between the calculated and observed values. In any case, this KIE is correctly predicted by the calculations to be smaller than those calculated for *N*-deuterioformamide and *C*-deuterio-*N,N*-dimethylformamide.

For LCON(CH$_3$)$_2$, a KIE of k_H/k_D = 1.18 ± 0.04 (298 K) was measured, whereas the MP2/6-31G*-calculated KIE is k_H/k_D = 1.22, in agreement with the experimental result.

Detailed Analysis of Calculated KIEs. The KIEs and individual partition functions at 298 K are given in Tables 4, 6, and 7 for isotopomers of formamide, *cis*- and *trans*-*N*-methylformamide, and *N,N*-dimethylformamide.

Several points are worthy of note in these tables. One is that the ratios of imaginary frequencies often deviate significantly from unity. There is much isotopic motion in the rotation, so the reaction coordinate is sensitive to isotopic substitution. Also, this ratio, like the KIE, varies depending upon substitution. Heavy substituents seem to concentrate the rotational effect on the opposite side of the C−N bond. That is, when there is rotation about a bond, inertial effects cause the motion in the transition state to involve mainly the lighter atoms or groups. This inertial effect seems related to the lowering of the frequency of vibration for a given force constant by a larger mass.

In formamide, this means that the hydrogen and oxygen atom on one side are moving less in the transition state than the two hydrogens on the other end of the C−N bond. A small KIE is seen with deuterium on the carbon, but a larger KIE is seen with deuterium on the nitrogen. However, if a methyl group is placed on the nitrogen, a counterbalancing mass effect concentrates the motion more onto the carbonyl group. This effect is similar with either an actual methyl group or a simulated methyl group (Table 7) and thus cannot be considered to be due to coupling of the torsional mode with internal modes of the methyl group.

At 298 K, the high-temperature limit (unity) of the VP × EXC × ZPE product is approached rather closely. This quantity varies only from 1.00 to 1.03 and is less than the KIE in each case. This is because the hydrogen and deuterium frequencies (ν's) involved in amide rotation are low, which has the same effect on $h\nu/kT$ as does high temperature (T).

The ZPE term is most often invoked as "dominating" KIEs; this has a certain validity in cases where the high-temperature limit has not been closely approached. In the case of amide rotational KIEs near room temperature, there are significant contributions from all of the terms in the Bigeleisen equation. For example, as pointed out by Perrin *et al.*, the EXC term can be significantly greater than unity for formamide; this is because a low-frequency wagging mode in the ground state disappears in the transition state. This becomes significant when deuterium is placed on the nitrogen and the frequency of this wagging mode decreases; this has the result of increasing the population of excited vibrational states of the ground-state conformer.[1] We also find that *N*-methylformamide has a non-negligible EXC term with deuterium on either the carbonyl or the nitrogen.

Some of the isotope effects were calculated over a 500° temperature range to study their temperature dependence. In cases with deuterium substitution on the carbon, the KIE simply decreases, eventually approaching the ratio of imaginary frequencies, as predicted by Bigeleisen−Mayer theory. The temperature dependence when deuterium is placed on the nitrogen is more interesting, however. In the case of *N,N*-dideuterioformamide (calculated by multiplying the KIEs for *cis* and *trans* *N*-deuterioformamide rotation), the KIE generally decreases with increasing temperature, but around 350 K it increases temporarily as the temperature increases (Figure 4). At that point, thermal population of low-lying vibrationally excited states of the ground-state conformer occurs over a relatively small temperature range, with the result that the increase in the EXC term temporarily outweighs the decrease in the ZPE term. However, the increase of the EXC term eventually slows, and the decrease in ZPE dominates until the high temperature limit is achieved. Also interesting is the case of the *N*-methylformamides (*cis* and *trans*) with deuterium substitution on the nitrogen (Figure 5). The ZPE term is unusual here because it is less than unity: the transition state is "tighter" than the ground state in terms of the vibrational force constants experienced by the hydrogen isotope attached to nitrogen. As

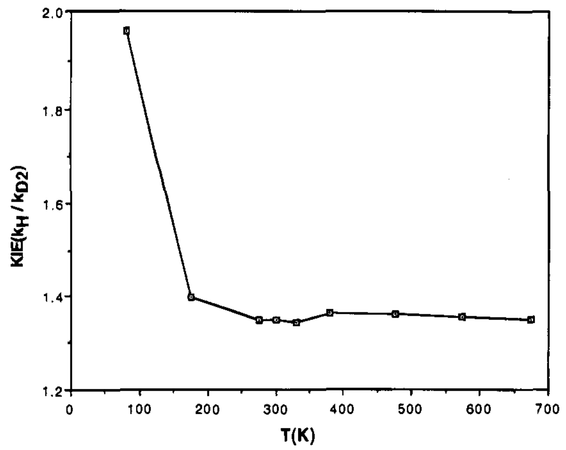

Figure 4. Calculated KIE for $HCONH_2(D_2)$ as a function of temperature.

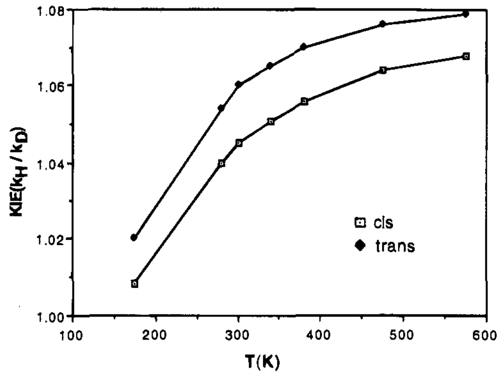

Figure 5. Calculated KIE for HCONMeH(D) as a function of temperature.

the temperature increases, both the ZPE and EXC terms increase in magnitude, so the calculated KIE continues to increase with increasing temperature, a very unusual situation, indeed.

It is not possible to compare directly the calculated KIEs with the KIE reported for HCONLAr (Ar = *p*-nitrophenyl), which was $k_H/k_D = 1.04 \pm 0.03$ at 298 K. This is an interesting case, because the amino group may be planar in the rotated transition state.[1] Consequently, this was considered to be a reasonable model for the rotation of alkenes, which give a much larger KIE.[20] Our results suggest that such planarity might indeed increase the KIE to some extent if the transition state has low frequencies associated with the N−H vibrations. This might be counteracted by the mass effect of a heavy group (such as an aryl substituent) attached to the same atom as the isotopic substituent.

The ratio of imaginary frequencies in the transition states for nondeuterated and deuterated substrates is sensitive to isotopic substitution when rotation of the isotope is part of the reaction coordinate motion. This should be a general phenomenon in rotational KIEs. Also, this ratio is temperature-independent and is responsible for the KIE at sufficiently high temperature;[16] what constitutes a sufficiently high temperature will depend on the vibrational frequency characteristics of the molecule undergoing the internal rotation. In a range where the KIE gradually approaches this limiting value, very little temperature dependence should be observed.

Conclusions

Our results support the prediction by Perrin *et al.*[1] that amide rotations are an unusual case where the EXC term of the isotope effect deviates significantly from unity. The low out-of-plane N−H frequencies of ground-state amides result in significant thermal population of excited vibrational states at or near room temperature. Although at low temperatures the ZPE term dominates the KIE, at room temperature, all of the terms (including EXC) are important and no particular term can be said to dominate.

Perrin's conclusion[1] that an out-of-plane C−H or N−H bending mode is not simply converted into the imaginary-frequency reaction coordinate is found to be correct. A number of modes couple to form the reaction coordinate. Part of the reason that amide rotational KIEs are so low (relative to alkenes[20]) when deuterium is on the nitrogen is due to partial cancellation of the rotational KIE by a 2° KIE caused by rehybridization of the nitrogen. While the rotation of a deuterium-substituted rotor is slowed by deuterium substitution (as reflected in the ratio of imaginary frequencies), the simultaneous increase in bending frequencies causes the rotation involving deuterium to be accelerated relative to that with hydrogen. The experiment using an aryl-substituted amide (believed to have planar nitrogen in the transition state[1]) is not a good test of this assertion because there is an inertial effect in amide rotations. When a heavy substituent is on one end of the C−N bond, rotational motion is concentrated on the opposite end. This is reflected in the magnitude of the KIEs.

The results here indicate that moderate level *ab initio* calculations can reproduce rotational isotope effects and provide means for detailed analysis of the origins of the effects as well as temperature dependencies.

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