Effects of Substitution on Nitrogen on Barriers to Rotation of Amides

2†—Evaluation of the Importance of Resonance Effects

B. Mario Pinto and Walter A. Szarek*
Carbohydrate Research Institute and Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

T. Bruce Grindley
Department of Chemistry, Dalhousie University, Halifax, Nova Scotia B3H 4J3, Canada

Analogs of *N*-acetyl- and *N*-benzoyl-azacyclohex-2-enes having an oxygen atom, a methylene-d_2 group or a carbonyl group in place of the C-4 methylene group have been synthesized. The amide rotational barriers in these compounds have been measured by the total line-shape analysis of variable-temperature ^{1}H NMR spectra. The free energies of activation for both the *N*-acetyl and *N*-benzoyl series decrease in the sequence O = CD_2 > C=O. The barriers for the first two compounds in each series are similar to those of the corresponding saturated analogs, a result which confirms recent reports that the long accepted barrier-decreasing effect of an α-olefinic substituent on nitrogen is counteracted. Evidence is presented that resonance stabilization of the rotational transition state in the unsaturated compounds still obtains. It is suggested that the introduction of an α-olefinic substituent on nitrogen has a negligible effect on the amide rotational barriers in the cases of the oxygen and methylene-d_2 analogs, since any increase in the stabilization of the transition state by resonance is offset by the accompanying decrease in the sp^3 character of the nitrogen atom. In cases in which a substituent on the olefinic group can interact directly with the lone pair on nitrogen, for example in the carbonyl analogs, then the resonance stabilization of the transition state is dominant.

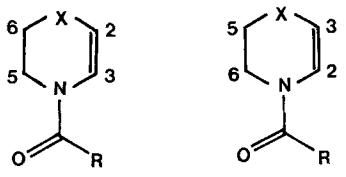
INTRODUCTION

Many studies of amides have been performed in order to determine the factors which influence the magnitudes of the rotational barriers.[2–4] Although the magnitudes of the barriers have been rationalized in terms of the relative importance of such factors as steric, resonance, hybridization and solvent effects in the ground state and the transition state for rotation, it is often difficult to evaluate clearly the size of the individual contributions in such a way that the magnitudes of the barriers in other amides can be reliably predicted.[1] Significant progress has been made, however, in the detailed evaluation of the influence of steric and electronic effects of the carbonyl substituents on the barriers to rotation.[5–7]

The effects of substituents on nitrogen on the magnitude of the rotational barriers are, however, not nearly as well understood. For instance, it is accepted[4,8,9] that the introduction of α-unsaturation into one of the substituents attached to nitrogen lowers the barrier significantly, relative to the saturated analogues. This decrease in the free energy of activation for rotation had been attributed[4] to resonance stabilization of the transition state. The effect apparently increased progressively in systems in which the α-unsaturated substituent changed from vinyl[8,9] to aryl[4] to *N*-acyl-heteroaromatic rings,[10] in which competition of the acyl group for the lone pair on nitrogen with a potentially aromatic ring disappears in the transition state. Recently, however, several puzzling results were obtained. In our earlier study,[1] it was shown that the rotational barrier in 4-benzoyl-1-thia-4-azacyclohex-2-ene (**1**) was approximately the same (60.07 kJ mol^{-1} at 300 K for the rotation process from the less populated to the more populated conformer) (the labels **1a** and **1b** in Table 5 in Ref. 1 should be interchanged) as in the saturated analogues, *N*-benzoylazacyclohexane[11a] (61.95 kJ mol^{-1} at 292 K) or *N*-benzoyl-1-thia-4-azacyclohexane (60.89 kJ mol^{-1} at 303 K; $\Delta G_c^{\neq}$ evaluated from the coalescence of the signals for C-3 and C-5 in the ^{13}C NMR spectra at 303 K measured in acetonitrile-d_3; $\Delta\nu$ was 88.9 Hz at 250 K; B. M. Pinto and W. A. Szarek, unpublished results). Fraser *et al.*[12] reported that the barrier to rotation in a 2-substituted *N*-acylazacyclohex-2-ene was 5.0 kJ mol^{-1} *greater* than that in the related saturated compound. Furthermore, they also emphasized[12] that the free energies of activation obtained for the acyclic vinyl amides[8] were calculated by an approximate method, the peak separation method, which has been recognized[13] as being inaccurate. Recalculation[12] of these results from the original data[8] using a more accurate approximate method, the coalescence method, suggested that the introduction of unsaturation into one of the substituents on nitrogen results in a much smaller reduction (*ca* 2–3 kJ mol^{-1}) in the rotational barriers relative to the saturated amides than had previously been recognized.[2–4]

* Author to whom correspondence should be addressed.
† For Part 1, see Ref. 1.

CCC-0030-4921/84/0022-0676$08.50



1 X=S, R=Ph
2 X=O, R=Me
3 X=O, R=Ph

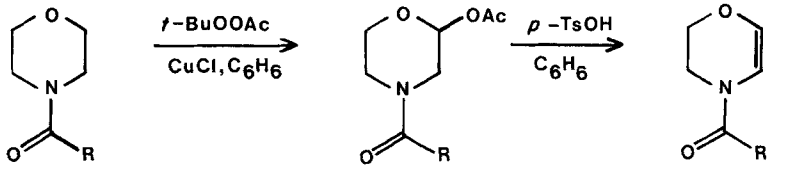
4 X=CO, R=Me
5 X=CO, R=Ph
6 X=CD_2, R=Me
7 X=CD_2, R=Ph

In order to assess the relative importance of resonance effects of substituents on nitrogen, we now report the results of the investigation of the barriers to amide rotation in the six compounds, **2–7**. Because these compounds are cyclic, one would expect that, as the resonance interactions change with the corresponding changes in the nature of the substituent, changes in geometry would be small wiith respect to those in acyclic analogs. As a result, changes in steric effects in the above series of compounds in which the R group is held constant should be minimal. These compounds exhibit ^{1}H NMR spectra which have sufficient complexity that their line shapes show significant changes over considerable temperature ranges. Thus, careful analysis of the variable temperature spectra should yield accurate values of free energies, enthalpies and entropies of activation.[14]

RESULTS AND DISCUSSION

Synthesis

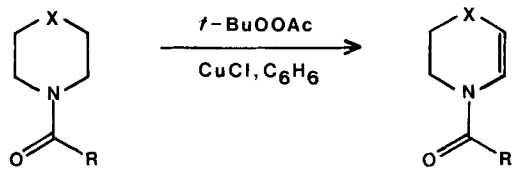
The unsaturated amides **2–7** were prepared from the corresponding saturated amides by adaptation of the peroxyester reaction of Kharasch and Sosnovsky.[15] Thus, treatment of the saturated amides **8** and **9** with *tert*-butyl peracetate in refluxing benzene in the presence of copper(I) chloride for 5.5 h by the procedure of Lawesson and Sosnovsky[16] afforded 2-acetoxy-4-acetyl-1-oxa-4-azacyclohexane (**10**) and 2-acetoxy-4-benzoyl-1-oxa-4-azacyclohexane (**11**), respectively (Scheme 1). Under similar conditions the saturated amides **12**, **13**, **14** and **15** were converted directly into the unsaturated amides **4**, **5**, **6** and **7**, respectively (Scheme 1). Berglund and Lawesson[17] have shown that *N*-benzoyloxymethyl-*N*-methylformamide can be prepared from *N*,*N*-dimethylformamide by the copper ion catalyzed thermal peroxyester reaction, and Sosnovsky[18] has prepared *N*-acetoxymethyl-*N*-methylformamide from *N*,*N*-dimethylformamide and *tert*-butyl peracetate by means of a copper ion catalyzed photochemical reaction. Similarly, the copper ion catalyzed photochemical reaction of dimethylacetamide with *tert*-butyl peracetate afforded *N*-acetoxymethyl-*N*-methylacetamide.[19] Clearly, in the reactions of **14** and **15** described above, functionalization of the carbon adjacent to nitrogen leads to the elimination products **6** and **7**, respectively. In the case of the ketones, **12** and **13**, on the basis of a report by Rawlinson and Sosnovsky,[19] who stated that substitution α to a carbonyl group is difficult, it is likely that the initial functionalization takes place on the carbon adjacent to the amide group. The results obtained in the study suggest that substitution adjacent to oxygen is preferred over substitution adjacent to an amide, the latter substitution being, in turn, more favorable than substitution α to a ketone. It is interesting that, when 1,4-oxathiane was subjected to similar conditions, substitution occurred adjacent to sulfur rather than oxygen.[19] The unsaturated compounds 4-acetyl-1-oxa-4-azacyclohex-2-ene (**2**) and 4-benzoyl-1-oxa-4-azacyclohex-2-ene (**3**) were prepared by treating **10**



8 R=Me
9 R=Ph

10 R=Me
11 R=Ph

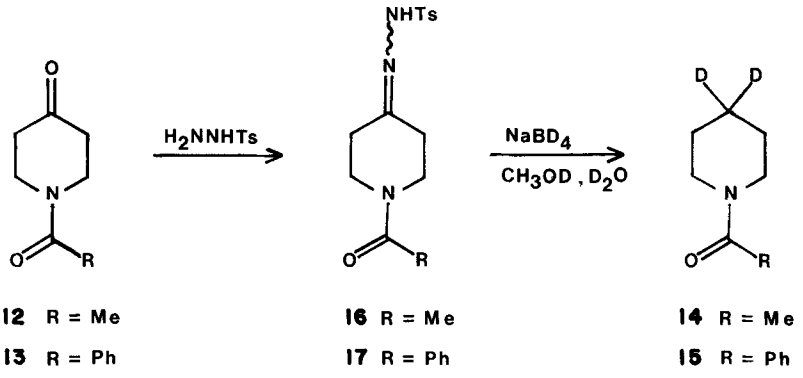
2 R=Me
3 R=Ph



12 X=CO, R=Me
13 X=CO, R=Ph
14 X=CD_2, R=Me
15 X=CD_2, R=Ph

4 X=CO, R=Me
5 X=CO, R=Ph
6 X=CD_2, R=Me
7 X=CD_2, R=Ph

Scheme 1. Syntheses of amides **2–7**.



Scheme 2. Syntheses of deuteriated starting materials.

and **11**, respectively, with refluxing benzene containing *p*-toluenesulfonic acid. The dideuterio derivatives, **14** and **15**, were prepared by treatment of the corresponding tosylhydrazones **16** and **17** with sodium borodeuteride in methanol-d_1 and deuterium oxide, as illustrated in Scheme 2. The sequence was patterned after the work of Kabalka *et al.*,[20] who described the reduction of tosylhydrazones to the corresponding dideuteriomethylene derivatives using deuteriated catecholborane and a sodium acetate–deuterium oxide complex.

Conformational analysis

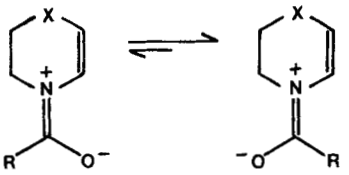
The conformational analysis of cyclic amides, such as **2–7**, is potentially complex because of the occurrence of three conformational processes, namely nitrogen inversion, ring inversion and restricted rotation about the amide bond. Although it is known that the geometry about the nitrogen atom in amides can deviate from planarity to give slightly pyramidal structures,[21,22] barriers to nitrogen inversion are low (<20 kJ mol^{-1}),[3,21] and the effect of the nitrogen inversion process is not likely to be observed in the dynamic nuclear magnetic resonance spectra in the normally accessible temperature range. It was also expected that the barrier to ring inversion would be considerably less than that for amide rotation. For example, in 4-acetyl- and 4-benzoyl-1-oxa-4-azacyclohexane, the free energies of activation for ring inversion are 28 and 31 kJ mol^{-1}, respectively;[11b] introduction of a double bond would be expected to lower this barrier. For instance, the barrier to inversion in 1,4-dioxane has been evaluated as being 40.5[23] or 41.8 kJ mol^{-1},[24] while that in 1,4-dioxene is 30.5 kJ mol^{-1}.[25] As expected, the variable temperature ^{1}H NMR spectra of compounds **2**, **3**, **4**, **6** and **7** showed no evidence of the slowing of ring inversion in the temperature ranges over which the amide rotational process was investigated. Surprisingly, the low-temperature spectra of compound **5**, in which the barrier to amide rotation is considerably lower than in the other amides, show the effects of the onset of slow ring inversion near the low-temperature limit. The consequences of this observation for the determination of the amide rotational barrier in **5** will be discussed later.

The determination of the conformational preference of the amide group in compounds **2–7** was performed by examination of the low-temperature ^{13}C NMR spectra, as described previously.[1] Earlier workers have shown[26] that, in *N,N*-dialkylamides, the carbon *syn* to the carbonyl oxygen of an amide is shielded relative to the corresponding carbon in the *anti* conformer. Table 1 gives ^{13}C chemical shift data for the rotational

Table 1. ^{13}C chemical shift data for rotational isomers

		Chemical shifts[a]								
Compound	Isomer	C-2	C-3	C-4	C-5	C-6	Amide C=O	CH_3	Quaternary Ph	Other Ph
2	Major	129.6	105.9	—	38.8	64.8	166.4	21.0	—	—
	Minor	131.3	104.4	—	43.6	64.1	166.4	21.0	—	—
3	Major	130.6[b]	107.4	—	39.7	64.7	166.9	—	133.2	129.1[b], 128.3
	Minor	[c]	104.7	—	45.8	64.7	166.9	—	132.7	127.8
4	Major	143.7	107.6	194.3	35.3	40.1	169.4	21.7	—	—
	Minor	142.0	108.7	194.1	35.3	43.9	169.4	21.7	—	—
5	Major	147.4	106.9	194.7	36.2	42.8	171.0	—	133.6	129.9
	Minor	143.7	106.9	194.7	36.2	46.5	171.0	—	132.7	129.4
6	Major	126.0	108.0	21.9[b,d]	21.9[b]	40.2	167.8	21.3[b]		
	Minor	124.1	108.0	21.7[b,d]	21.7[b]	44.5	167.8	21.3[b]		
7	Major	130.2	107.9	21.6[d]	21.6[d]	40.8	169.2	—	134.7	128.1, 127.4
	Minor	126.6	111.0	21.3[d]	21.3[d]	47.2	168.4	—	134.4	127.1

[a] In ppm downfield from internal tetramethylsilane in chloroform-*d* at 230 K, except for the spectrum of **5**, which was recorded in acetone-d_6 at 183 K.
[b] Assignments may be interchanged.
[c] Obscured by the signals of the phenyl quaternary carbons.
[d] Chemical shift for C-4 signal in the spectrum of the non-deuteriated analog.



Scheme 3. Ground-state amide conformational preference.

isomers in compounds **2–7**. Signal assignments were made by comparison with literature data,[11a,27,28] by observation of which signals coalesced on raising the temperature and, for the olefinic carbons, by consideration of the effects of α-substitution and of resonance on chemical shifts (see Ref. 28). In all cases, the α-olefinic carbon in the major isomer is deshielded relative to that in the minor isomer, whereas the α-methylene carbon is shielded relative to the corresponding carbon in the minor isomer. (It should be noted that the carbons α to the amide group are labeled C-3 and C-5 in the cases of **2** and **3**, but C-2 and C-6 in the cases of **4–7**.) On the basis of this data we conclude that, as in compound **1**, the carbonyl group of the amide is *syn* to the methylene group in the major isomer, as illustrated in Scheme 3. With one exception, the ^{13}C chemical shifts of the β-carbons in the methylene groups are not affected by the orientation of the amide group. However, the ^{13}C NMR signals for the β-olefinic carbons for the two isomers have different chemical shifts in several cases (see Table 1), and the signal attributable to the carbon *anti* to the carbonyl group resonates at higher field than that due to the carbon *syn* to the carbonyl group. Thus, the effect of the orientation of the carbonyl group on the direction of the change in chemical shift of the α-olefinic carbons in the two isomers is opposite to that of the β-olefinic carbons in these molecules.

The ^1H NMR spectra of compounds **2–7** are shown in Fig. 1. The signal assignments were made as described previously.[1] The static parameters obtained from the LAOCN-4A analysis[29] of the ABCC'DD' systems corresponding to the olefinic and methylene protons in the two isomers in the low-temperature spectra of compounds **2–7** are given in Tables 2 and 3.

Ground-state populations

The thermodynamic parameters derived from the ground-state populations are given in Table 4. As previously observed[1] in compound **1**, the more stable amide conformation in compounds **2–7** is that in which the carbonyl group is *syn* to the methylene group. The observed free-energy differences between conformations are fairly small (ΔG^0 values at 273.2 K range from 1.6 to 4.2 kJ mol^{-1}) but are much larger than those observed for acyclic *N,N*-dialkylamides. For instance, the free-energy difference in *N*-isopropyl-*N*-methylacetamide is 0.54 kJ mol^{-1}.[30] The introduction of aryl groups as substituents on nitrogen generally results in a larger free-energy difference between isomers.[2] Destabilizing effects as a result of steric interactions between alkyl groups on nitrogen and the carbonyl group are probably small (<2 kJ mol^{-1}) since, in *N*-alkylformamides, the proportion of the isomer with the carbonyl group *syn* to the alkyl group only changes from 92 to 82% on changing of the alkyl group from methyl to *tert*-butyl.[31] That this effect is not simply the result of similar destabilization of both conformational isomers is evident from the fact that steric bulk does not affect the barriers in *N,N*-dialkylformamides.[32] When alkyl or aryl groups are present on the carbonyl carbon, the ground-state conformational populations change markedly. Hence, the major factor influencing these populations is the steric interaction between the substituent on the amide carbonyl group and the substituents on nitrogen. It has also been suggested[33] that dipole–dipole repulsion affects ground-state equilibrium populations of conjugated amides; however, this effect is probably also small for these derivatives.* With *N*-vinyl derivatives, an unexplained secondary factor may be present, since in *N*-alkylformamides the conformer in which the alkyl group is *syn* to the carbonyl group is stabilized[31] whereas the vinyl group in *N*-vinylformamides has been shown by *ab initio* calculations (STO-3G) to have little conformational preference.[34] Thus, the steric interactions between the α-methylene group and the carbonyl substituent (methyl or phenyl) in compounds **2–7** are probably more severe than those between the olefinic group and the carbonyl substituent. In agreement with this conclusion, examination of Dreiding models suggests that the equatorial methylene proton is more nearly in the plane of the amide group than is the olefinic proton. One compound in particular, namely, *N*-benzoylazacyclohex-2-en-4-one (**5**), exhibits a considerably greater free-energy difference between isomers ($\Delta G^0 = -4.2$ kJ mol^{-1}) than any of the other compounds studied here [the range for ΔG^0 (273.2 K) is -1.6 to -2.5 kJ mol^{-1}]. In compounds **4** and **5**, the nitrogen atom will be able to donate electrons to the ring carbonyl group and to the amide carbonyl. In **5**, the carbonyl group in the amide will, therefore, be able to interact more strongly with the phenyl group by resonance, and will tend to hold the phenyl group more nearly planar to the amide bond than in the other benzamides. Since non-bonded steric interactions are inversely proportional to the sixth power of the distance between the interacting atoms,[35] this change would affect the isomer with the more severe non-bonded interactions to a greater extent.

* The major evidence for this effect arises from consideration of the equilibrium populations of *N*-acetyl derivatives of dihydrobenzimidazole. In the monoacetyl derivative, the isomer with the carbonyl group *syn* to the benzene ring (*Z* isomer) is present to a greater extent than the *anti* (*E*) isomer (61:39).[33] In the *N,N'*-diacetyl derivative the proportions of the *Z,Z*, to *Z,E* to *E,E* isomers were 30:65:5. The authors claimed,[33] on the basis of the proportion in the monoacetate, that the *Z,Z* isomer should be favoured in the conformational mixture, and that the observed result was caused by a large dipolar repulsion. Statistically, from the result obtained for the monoacetate, one would predict that the proportions of *Z,Z* to *Z,E* to *E,E* isomers would be 37:48:15. Thus, the dipolar repulsion effect is small even in this case, where it should be larger than in the compounds considered in the present publication. For compounds in which such effects are important, see Ref. 10.

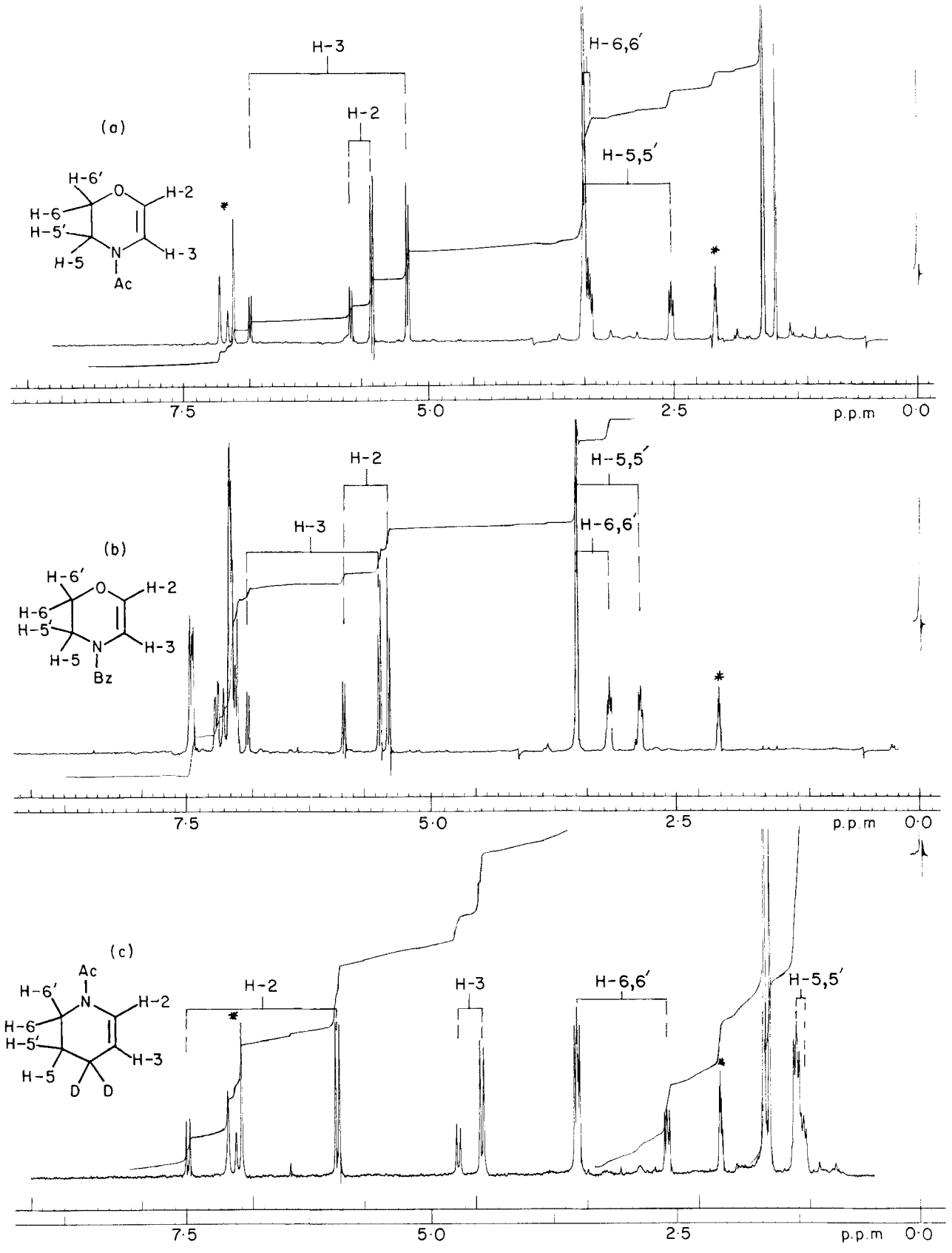


Figure 1. Low-temperature ^{1}H NMR spectra of compounds 2–7 (Bz = benzoyl) (0.5 M in toluene-d_8): (a) **2** at 220 MHz, $T = 239.4$ K; (b) **3** at 220 MHz, $T = 239.4$ K; (c) **6** at 220 MHz, $T = 233.1$ K; (d) **7** at 220 MHz, $T = 233.1$ K; (e) **4** at 100 MHz, $T = 301.4$ K; (f) **5** at 100 MHz, $T = 301.4$ K. Peaks marked with asterisks are solvent peaks.

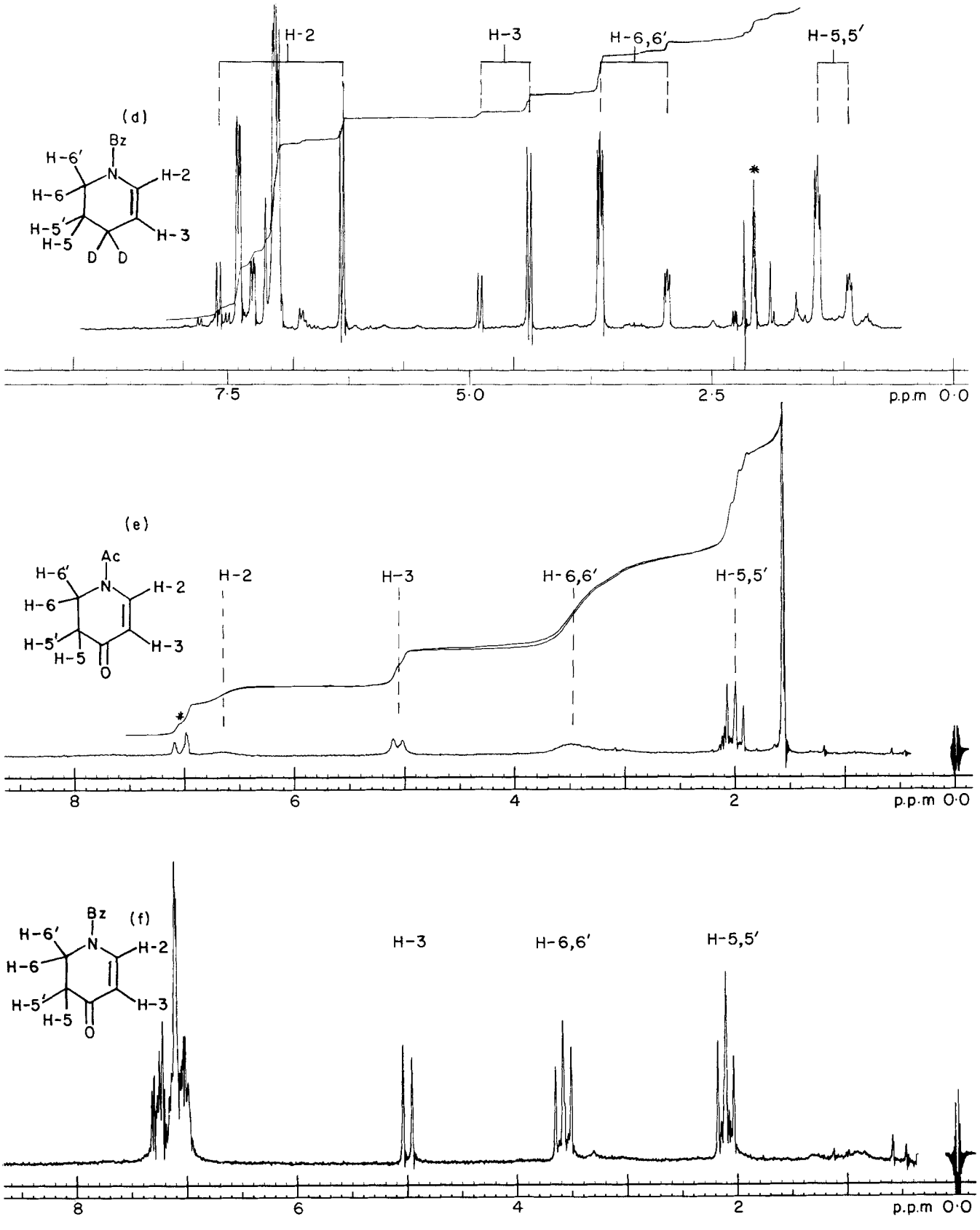


Figure 1. *Continued.*

Table 2. Chemical shifts for the ^{1}H NMR signals of olefinic and methylene protons

Compound	Temperature (K)	Isomer	Chemical shifts[a] H-2	H-3	H-5,5′	H-6,6′
2	229.8	Major	5.57	5.20	3.43	3.40
		Minor	5.78	6.80	2.53	3.35
3	229.8	Major	5.44	5.53	3.53	3.52
		Minor	5.91	6.87	2.88	3.17
4	195.5	Major	6.23	5.05	1.87	3.43
		Minor	7.79	5.21	1.84	2.46
5	195.5	Major	6.45	4.88	2.04	3.44
		Minor	7.77	5.31	1.55	2.82
6	233.1	Major	5.98	4.50	1.32	3.54
		Minor	7.52	4.74	1.25	2.66
7	233.1	Major	6.33	4.40	1.42	3.66
		Minor	7.59	4.91	1.12	3.00

[a] In ppm from tetramethylsilane in toluene-d_8.

Table 3. Coupling constants (Hz) for olefinic and methylene protons

Compound	Isomer	Coupling constants[a] $J(23)$	$J(55')$	$J(66')$	$J(56)=J(5'6')$	$J(56')=J(5'6)$
2	Major	5.0	−10.1	−8.7	3.1	6.3
	Minor	5.0	−10.6	−8.7	3.1	6.1
3	Major	5.1	−13.3	−11.1	3.0	6.6
	Minor	5.1	−13.3	−11.1	2.6	6.1
4	Major	8.3	−12.8	−9.8	5.6	9.2
	Minor	8.3	−12.8	−9.8	5.6	9.2
5	Major	8.2	−13.9	−10.3	5.8	8.6
	Minor	8.2	−13.9	−10.3	5.8	8.6
6	Major	8.3	−10.1	−10.1	3.7	7.9
	Minor	8.3	−10.7	−9.3	3.5	7.7
7	Major	8.4	−11.4	−11.4	3.3	8.0
	Minor	8.4	−11.3	−9.8	3.4	7.7

[a] In toluene-d_8.

Table 4. Thermodynamic parameters for amide conformations[a]

Compound	No. of points	ΔH° (kJ mol^{-1})	ΔS° (kJ mol^{-1} K^{-1})	ΔG° (kJ mol^{-1})[b]
2	11	−0.85	5.8	−2.45(±0.04)
3	13	−0.87	10.7	−2.04(±0.01)
4	15	−1.4	2.5	−2.08(±0.03)
5	13	−1.7	2.5	−2.42(±0.02)
6	10	−1.8	−0.7	−1.55(±0.01)
7	8	−2.58	6.2	−4.19(±0.04)

[a] For the following process: isomer with the carbonyl group *syn* to the olefinic group ⇄ isomer with the carbonyl group *anti* to the olefinic group.
[b] At 273.2 K.

Rotational barriers

The total line-shape analysis was performed by independently treating the exchange processes for the vinyl and methylene protons as AB ⇄ CD and AA′BB′ ⇄ CC′DD′, respectively; the line shapes were simulated for the exchange process for the rotation from the more populated conformer to the less populated conformer. Representative experimental and calculated DNMR spectra for compounds **3**, **4** and **6** are illustrated in Figs 2, 3 and 4, respectively. Major changes in the appearance of the spectra of all six compounds occur over a fairly wide temperature range because of the fact that each spin system consists of two components, each of which has a significantly different chemical-shift difference between the signals of the exchanging protons, a situation which permits the observation of maximum broadening at different temperatures. Since the magnitude of T_2^* does not affect the appearance of the spectra when the broadening owing to exchange is considerably greater than T_2^*, the accuracy of the line-shape matching of the DNMR spectra of compounds **2–7** does not depend on the accuracy of the assignment of T_2^* to nearly the extent that it does for two-site exchange. In the present work, values of T_2^* were taken from the spectra at the slow-exchange and the fast-exchange limits; values of T_2^* in the exchange-broadened region were then obtained by linear interpolation.

In the spectra of compound **5** the signals for the methylene protons sharpened below coalescence (minimum line width *ca* 5 Hz at 218 K) and then gradually broadened as the temperature was lowered. In contrast, the signals for the olefinic protons sharpened as the temperature was lowered below the coalescence temperature until the line width was close to that observed in the region of fast exchange. These observations are consistent with the occurrence of a second conformational process in which enantiotopic methylene protons are converted into diastereotopic methylene protons, while the olefinic protons remain unaffected. Either of the two possible conformational processes, nitrogen inversion or ring inversion, could affect the DNMR spectra in this manner, but a survey of literature results suggests that the process under observation in the spectra of **5** was that of ring inversion. For example, the barrier to nitrogen inversion in formamide is *ca* 12 kJ mol^{-1}, as estimated by microwave spectroscopy,[21a] while the barrier to ring inversion in 1,4-dioxene is 30.5 kJ mol^{-1}.[25]

The onset of broadening owing to viscosity effects as the temperature was lowered below 200 K made investigation of this process impossible in toluene-d_8. Further investigation of this conformational process in other solvents is in progress. As a result of this complication, in the present study, line-shape analysis for the DNMR spectra of **5** was performed only on the signals of the olefinic protons.

The rate constants derived from the line-shape analysis of the spectra of **2–7** are given in Table 5. Activation parameters for the restricted rotation about the amide bond were calculated as described in the Experimental section. The results are presented in Tables **6** and **7**. In all cases, agreement between the activation parameters obtained from the two separate analyses of the methylene-proton signals and the olefinic-proton signals was fairly good, although the two analyses were performed independently of one another. The covariances between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were, as expected, fairly large (see Table 7). The entropies of activation varied from -17.1 ± 6.9 J mol^{-1}

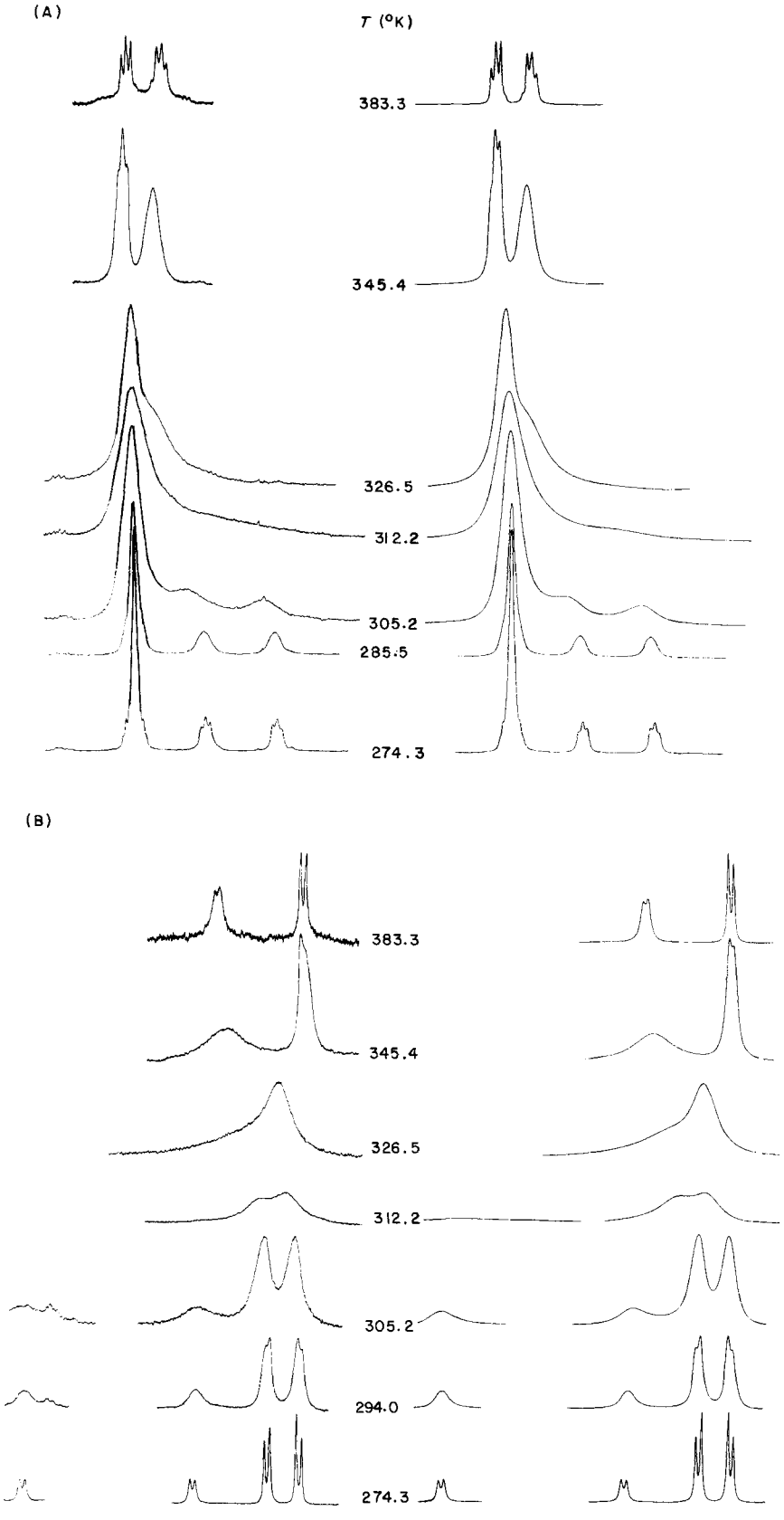


Figure 2. Experimental (left) and calculated (right) DNMR spectra of (A) methylene and (B) olefinic protons in **3**.

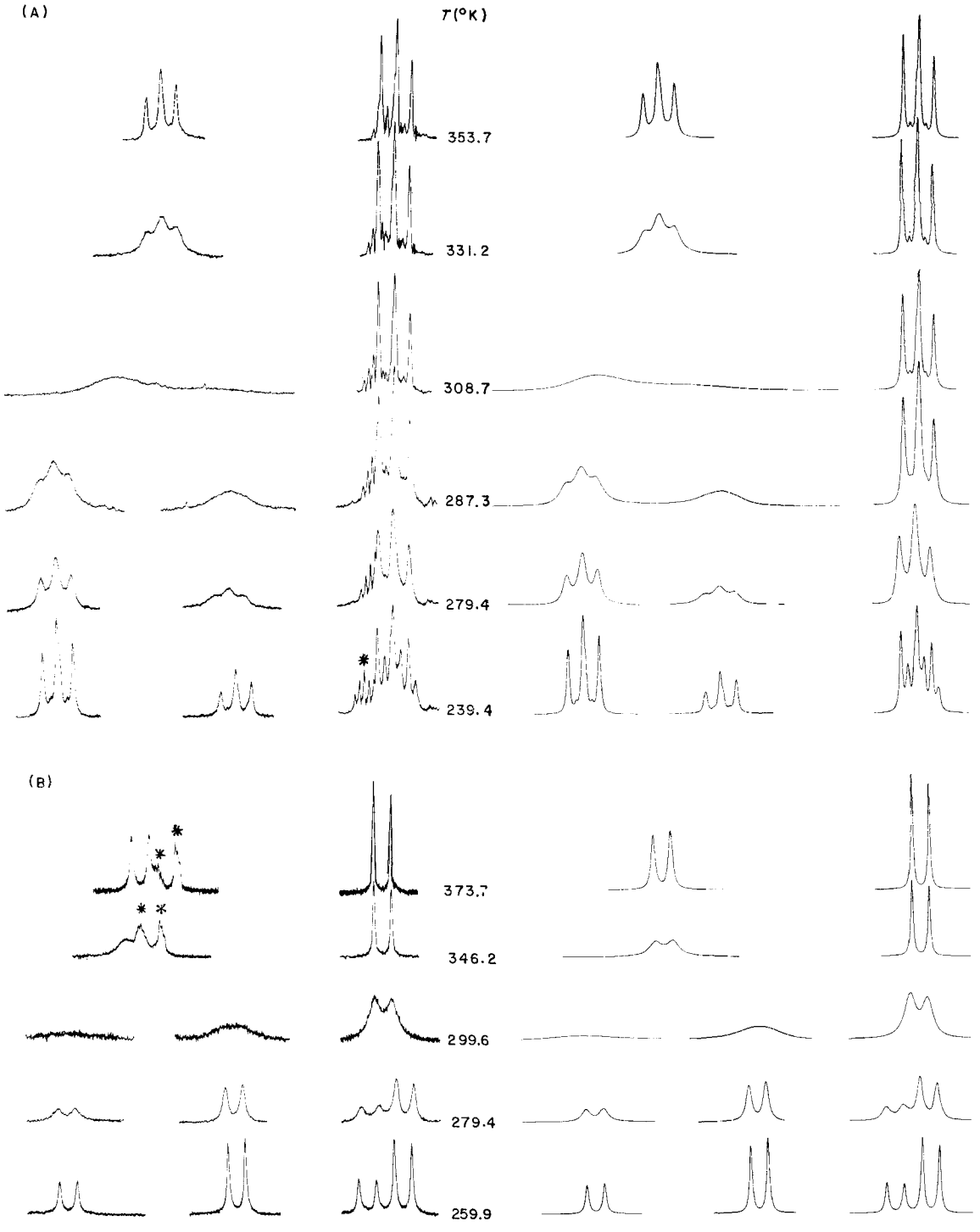


Figure 3. Experimental (left) and calculated (right) DNMR spectra of (A) methylene and (B) olefinic protons in **4**. Peaks marked with asterisks are solvent peaks.

(-4.1 ± 1.7 cal mol^{-1}) to 17.8 ± 9.2 J mol^{-1} (4.3 ± 2.2 cal mol^{-1}), the average value being 0.7 J mol^{-1} (0.2 cal mol^{-1}), with no apparent relationship with structure. The low absolute values obtained for the entropies of activation and their random distribution about zero suggest that the entropies of activation for **2–7** are approximately zero, and that the errors are larger than calculated as in the Experimental section. The errors in the rate constants, in particular, as estimated in this study are the uncertainties involved in matching calculated and experimental line shapes; however, this treatment has not included an evaluation of errors in T_2^* values or chemical shift values which were obtained by extrapolation into the exchange-broadened region. The precautions taken in the performance of this line-shape analysis should have ensured the avoidance of most systematic errors.[36] Entropies of activation for amide rotational barriers have been shown to be close to zero,[15] even when solvents containing aromatic nuclei were employed.[36] However, in systems other than amides, substantial entropies of activation have been observed for the bar-

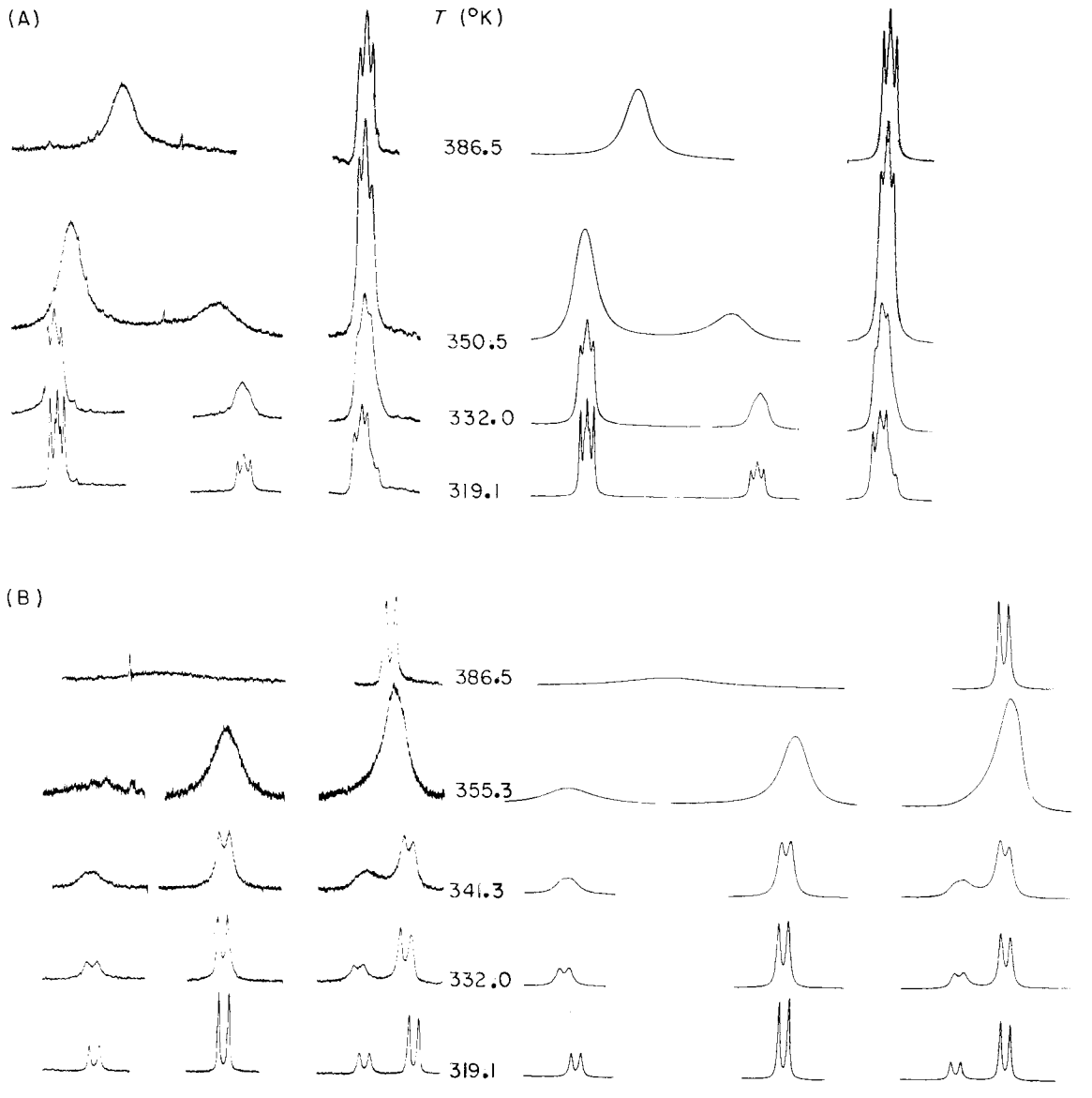


Figure 4. Experimental (left) and calculated (right) DNMR spectra of (A) methylene and (B) olefinic protons in **6**.

rier to rotation in aromatic solvents.[37–39] These effects have been explained as arising from the changes in polarization of the molecule between the ground state and the transition state, a situation which affects the tightness of solvation. It is not obvious why benzaldehyde derivatives,[39] in particular, should differ in this respect from amides. In view of the small entropies of activation observed, the following discussion of rotational barriers will employ the free energies of activation.

Comparison of the free energies of activation for the two series of compounds, namely, the acetamides and the benzamides, shows that the results in the two series are almost exactly parallel. The difference in the value of $\Delta G^{\neq}$ between the two series is 11.2± 0.6 kJ mol^{-1} (2.7 kcal mol^{-1}) for **2** and **3**, 12.9± 0.5 kJ mol^{-1} (3.1 kcal mol^{-1}) for **4** and **5** and 13.2± 0.5 kJ mol^{-1} (3.2 kcal mol^{-1}) for **6** and **7**; the average value of $\Delta\Delta G^{\neq}$ is 12.4 kJ mol^{-1} (3.0 kcal mol^{-1}). The source of the difference in $\Delta G^{\neq}$ between the acetamides and the benzamides obviously has an important steric component, since this difference is 4.2 kJ mol^{-1} for $RC(O)NH_2$,[40] 7.5 kJ mol^{-1} for $RC(O)NMe_2$[4] and 12.4 kJ mol^{-1} for the more rigid compounds considered in the present study. Thus, the effect of resonance interactions on the average angle of rotation of the phenyl group in the ground state does not appear to be substantially altered in the major isomer in the benzamide series.

Comparison of the $\Delta G^{\neq}$ values obtained for the three compounds in each series shows that the compounds having dideuteriomethylene (**6**, **7**) and oxygen (**2**, **3**) as substituents have very similar activation barriers while the compounds having carbonyl as substituents (**4**, **5**) have barriers which are *ca* 13.0 kJ mol^{-1} (3.1 kcal mol^{-1}) lower. In these two series of compounds, the γ-substituent should not alter the ring geometry substantially since the bond lengths are not significantly altered in **2**–**7**. Therefore, changes in the activation barriers should mainly be a consequence of differences in electronic effects, in which resonance effects would play an important role.

Table 5. Rate constants (k)[a] derived from line-shape analysis

		AB ⇄ CD			AA'BB' ⇄ CC'DD'				AB ⇄ CD			AA'BB' ⇄ CC'DD'		
Compound	Temperature (K)	No. of points	k (s^{-1})	Error	No. of points	k (s^{-1})	Error	Compound	Temperature (K)	No. of points	k (s^{-1})	Error	No. of points	k (s^{-1})	Error
2	326.5	8	2.5	0.5	8	2.5	0.5		358.1		5700	200		—	—
	337.1		7.0	1.0		7.5	0.5		373.7		15 000	2000		—	—
	345.4		16	2		16.0	0.5	**5**	209.6	9	1.2	0.5	Not calculated; see Results and Discussion		
	355.8		34	2		29	1		218.0		4.0	1.0			
	363.0		53	4		55	1		223.1		9.0	1.0			
	368.5		74	2		74	1		233.7		32.5	1.0			
	376.4		120	20		120	5		239.4		50	3			
	383.4		220	40		220	20		247.0		135	5			
3	274.3	14	2.7	0.3	13	2.8	0.2		252.0		210	10			
	285.5		7.0	0.5		7.0	1.0		260.0		370	20			
	294.1		13.7	0.4		15	1		268.2		800	100			
	305.2		35	2		40	2	**6**	327.4	12	5.7	0.5	8	5.0	1.0
	312.2		108	5		105	10		332.0		8.0	0.5		8.5	1.0
	315.9		115	10		115	5		336.6		16.0	1.0		17	2
	320.0		160	20		140	15		341.3		18.5	0.5		19.5	1.0
	326.5		225	5		245	7		346.3		28	1		29	2
	331.6		350	20		410	20		350.5		44	4		46	4
	337.1		500	50		520	20		355.1		67	2		68	3
	345.4		1100	100		1200	100		361.6		95	10		—	—
	355.8		2100	150		2300	200		369.9		175	15		—	—
	368.5		4000	300		—	—		373.6		205	10		—	—
	383.3		10 000	2000		10 000	2000		378.2		340	20		—	—
4	259.9	13	1.0	0.2	11	1.0	0.2		386.5		650	100		650	70
	279.4		6.0	1.0		8.2	0.5	**7**	264.8	14	2.5	0.5	13	2.8	0.5
	287.3		16	2		18.5	1.0		270.6		3.8	0.3		3.8	0.3
	294.6		28.5	1.0		35	1		282.5		12.5	0.5		11.5	1.0
	299.6		53	3		55	2		288.0		21	1		23.0	2
	301.4		66	2		65	2		292.3		41	2		42.0	2
	308.7		72	3		72	2		299.7		55	5		—	—
	318.3		—	—		300	15		312.2		170	15		175.0	7
	320.4		450	50		—	—		319.1		280	20		280	20
	322.1		520	50		—	—		327.4		540	30		550	20
	331.2		—	—		860	20		336.6		1500	50		1500	100
	333.5		950	100		—	—		341.3		1750	75		1750	150
	342.8		—	—		1950	50		346.3		2200	100		2300	200
	346.2		2500	200		—	—		350.5		2700	100		3000	100
	353.7		—	—		4500	300		355.1		4500	300		4700	400

[a] For the process for rotation from the more populated to the less populated conformer.

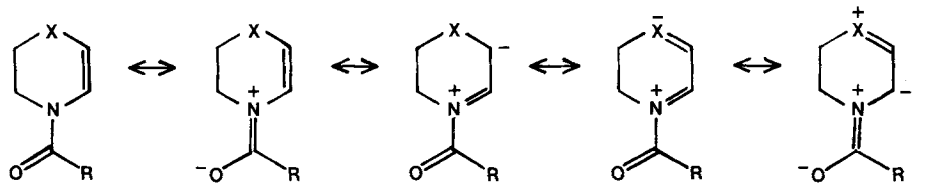
These effects can be evaluated in a simple manner by considering possible canonical structures for **2–7** (see structures A–E.

The magnitude of the rotational barrier should depend on the relative importance of B and E as opposed to A, C and D in the ground and transition states. It would be expected that structures B and E would not contribute to the transition state, whereas C and D should be much more important in the transition state than in the ground state. The fact that the

Table 6. Activation parameters for the restricted rotation about the amide bond[a]

Compound	Process analysed	No. of points	E_a (kJ mol^{-1})	Log A	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})[b]
2	AB ⇄ CD	8	73.3±2.5	12.3±0.4	70.4±2.5	−19.7±6.8	76.3±0.4
	AA'BB' ⇄ CC'DD'	8	75.3±2.5	12.5±0.4	72.3±2.5	−14.5±6.9	76.7±0.4
	Average		74.3±2.5	12.4±0.4	71.4±2.5	−17.1±6.9	76.5±0.4
4	AB ⇄ CD	10	72.3±2.1	14.3±0.4	69.6±2.1	19.6±6.8	63.7±0.2
	AA'BB' ⇄ CC'DD'	12	71.0±2.9	14.1±0.5	68.4±2.9	16.0±9.2	63.6±0.2
	Average		71.7±2.9	14.2±0.5	69.0±2.9	17.8±9.2	63.7±0.2
6	AB ⇄ CD	12	82.1±2.3	13.9±0.3	79.1±2.2	10.5±6.5	76.0±0.3
	AA'BB' ⇄ CC'DD'	8	85.5±2.6	14.4±0.4	82.5±2.6	20.8±7.6	76.3±0.4
	Average		83.8±2.6	14.2±0.4	86.8±2.6	15.7±7.6	76.3±0.4
3	AB ⇄ CD	13	68.3±1.6	13.3±0.3	65.7±1.6	1.0±5.2	65.4±0.1
	AA'BB' ⇄ CC'DD'	13	67.1±1.4	13.1±0.2	64.5±1.4	−1.9±4.2	65.1±0.1
	Average		67.7±1.6	13.2±0.3	65.1±1.6	−0.5±5.2	65.3±0.2
5	AB ⇄ CD	9	49.2±1.4	12.5±0.3	47.2±1.4	−12.0±6.0	50.8±0.3
7	AB ⇄ CD	14	66.2±1.2	13.4±0.2	63.6±1.2	2.0±3.8	63.0±0.1
	AA'BB' ⇄ CC'DD'	13	65.2±1.3	13.2±0.2	62.6±1.3	−1.3±4.0	62.9±0.1
	Average		65.7±1.3	13.3±0.2	63.1±1.3	0.4±4.0	63.0±0.1

[a] For the process for rotation from the more populated to the less populated conformer.
[b] Values for $\Delta G^{\neq}$ were calculated at 300 K.



A B C D E

Table 7. Statistical data for the activation process

Compound	NMR process	Covariances $\Delta H^{\neq}$ and $\Delta S^{\neq}$	Correlation coefficients
2	AB ⇄ CD	−1.99	−1.000
	AA'BB' ⇄ CC'DD'	−2.11	−1.000
3	AB ⇄ CD	−0.69	−0.998
	AA'BB' ⇄ CC'DD'	−1.01	−0.998
4	AB ⇄ CD	−1.75	−0.997
	AA'BB' ⇄ CC'DD'	−3.22	−0.998
5	AB ⇄ CD	−1.00	−0.999
	AB ⇄ CD	−1.77	−0.999
6	AA'BB' ⇄ CC'DD'	−2.40	−0.999
7	AB ⇄ CD	−0.51	−0.996
	AA'BB' ⇄ CC'DD'	−0.61	−0.997

Table 8. Comparison of rotational barriers in saturated and unsaturated six-membered ring cyclic amides

		Magnitude of the barrier[b] (kJ mol^{-1})			
				Unsaturated Derivative	
Carbonyl substituent	γ-Substituent[a]	Saturated derivatives	Ref.	Minor → major	Major → minor
Ph	O	59.1	11b	65.3	63.3
Ph	CH_2	62.2	11a	63.0	60.7
Ph	CO	58.9	11a	50.8	46.6
Ph	S	60.9	[c]	61.8	60.1
CH_3	O	69.2	11b	76.5	74.1
CH_3	CHR	71.0	11a	76.2	74.0

[a] In the ring.
[b] $\Delta G^{\neq}$ at 300 K.
[c] This work.

barriers for the 1-oxa-4-azacyclohexane derivatives, **2** and **3**, are very similar to those for the azacyclohexane derivatives, **6** and **7**, suggests that structure E is unimportant even in the former cases.

It thus appears that the resonance interaction of a nitrogen substituent having a double bond is largely independent of the type of substitution on the double bond, provided that there is no direct interaction between the latter substituent and the amide nitrogen. Infrared intensity studies[41] similarly showed that the resonance effect of a substituent is independent of other substituents present on a double bond. In **4** and **5**, a carbonyl group is present at the γ-position, and direct interaction between the substituents on the double bond is possible, as represented by D. This effect will occur to a much greater extent in the transition state than in the ground state and, hence, the barrier will be lowered. Comparison of the results obtained for **2**–**7** with that for **1** can be performed qualitatively, since the effect of changing from an aromatic solvent to acetonitrile is to increase the barrier only slightly[7] (*ca* 4 kJ mol^{-1}). The magnitude of the rotational barrier in **1** [$\Delta G^{\neq} = 61.9 \pm 0.4$ kJ mol^{-1} (14.8 kcal mol^{-1})] in acetonitrile-d_3 is less than those for **3** and **7** in toluene-d_8, rather than greater. In a compound containing a sulfur atom at the γ-position, the resonance canonical structure D may be important. The electron-accepting property of sulfur atoms is well known,[42] and has been explained in terms of the polarizability of second-row elements.[42] In addition, changes in geometry might affect the barrier; the long C—S bonds probably open the C—N—C bond angle. This change would cause more severe steric interactions with the amide group and lead to destabilization of the ground state. However, the barrier in *N*-benzoyl-1-thia-4-azacyclohexane (60.89 kJ mol^{-1}) is only slightly less than that in *N*-benzoylazacyclohexane (61.95 kJ mol^{-1});[11] this latter effect is, therefore, probably small.

In acyclic compounds, the introduction of a vinyl substituent on nitrogen causes a slight decrease in the barrier relative to the saturated compounds (see Introduction). Comparison of the results obtained in the present study and in the earlier study[1] with those for the corresponding saturated compounds (see Table 8) shows that the introduction of unsaturation into one of the nitrogen substituents causes an increase in the barrier to rotation for six-membered cyclic amides. That resonance effects are still present is evident from the results for *N*-acetyl- and *N*-benzoyl-azacyclohex-2-en-4-one, **4** and **5**, respectively. Ford *et al.*[43] have estimated that the through-resonance interaction in the ground state of *trans*-4-(dimethylamino)but-3-en-2-one is almost 32 kJ mol^{-1}. In **4** and **5**, the resonance interaction of the nitrogen with the ring carbonyl groups in the transition state should be similar to that in the above-mentioned compound. Grindley *et al.*[44] and Ford *et al.*[43] have demonstrated that rotational barriers can be related to Hammett σ parameters. On the basis of this approach,[43,44] the through-resonance interaction in the ground state between the nitrogen atom and the ring carbonyl atom will be equal to the product of the through-resonance interaction in the transition state times a factor $(\sigma^+ - \sigma^0)$ amide/$(\sigma^+ - \sigma^0)$ NMe_2 which measures the changes in the through-resonance effect. (Since the resonance effects of $—CH_2CH_3$ and —CHCHO are similar,[45] those of $—NMe_2$ and a group —NRCOR' having a geometry in which the nitrogen lone pair is parallel to the C=O plane should also be similar.) The required σ^+ values are −0.6 for NHC(O)CH and −1.7 for NMe_2,[46] and the σ^0 values are +0.02 for NHC(O)CH and −0.44 for NMe_2.[47] Therefore, an interaction energy of *ca* 16 kJ mol^{-1} is calculated for the resonance interaction in the ground state. The difference between the ground and transition-state resonance interactions, 16 kJ mol^{-1}, is approximately similar to the observed

decrease (12.5 kJ mol^{-1}) in the rotational barrier on introduction of a carbonyl group at the γ-position of **6** or **7**. Since the through-resonance stabilization of the transition state is present to about the extent expected, it is likely that the expected resonance stabilization of the transition state in **2**, **3**, **6** and **7** is present. In addition, the observed increase in rotational barriers in the unsaturated compounds **2**, **3**, **6** and **7**, relative to the corresponding saturated compounds, in contrast to the analogous situation with acyclic amides, suggests that other factors must also be important in influencing the magnitude of the barriers in these cyclic systems. Fraser *et al.*[12] reported that the barrier in an *N*-acetylazacyclohex-2-ene, in which the unsaturated ring was fused across carbons-2 and -3 to a six-membered ring, was 5.0 kJ mol^{-1} greater than that in the related saturated compound. These compounds have strong repulsive steric interactions between the equatorial α-methylene group of the fused ring and either the carbonyl oxygen or the methyl group of the acetyl function in the ground state. Comparison of the barrier in **6** with that of the unsaturated compound of Fraser *et al.*[12] gives a value of 19.4 kJ mol^{-1} for this interaction; for the saturated analogs (see Ref. 12 and Table 8) the difference in barriers is 19.2 kJ mol^{-1}. Apparently, the steric strains introduced when a six-membered ring is fused (at positions 2 and 3) to *N*-acetylazacyclohex-2-ene or to *N*-acetylazacyclohexane are identical. The value obtained should represent the strain introduced when an equatorial methyl group is added at position 2 of an *N*-acetylazacyclohexane.

Fraser *et al.*[12] have also recalculated the barrier reported[9] for the acyclic *N*-vinylamides using a better approximate equation, and have found that the decrease in the barriers in the unsaturated compounds relative to those in the saturated compounds is small (*ca* 2.5 kJ mol^{-1}). It would thus appear that the introduction of α-unsaturation into acyclic amides reduces the barrier by *ca* 2.5 kJ mol^{-1}, whereas a similar introduction of α-unsaturation into an *N*-acylazacyclohexane causes the barrier to increase by *ca* 5 kJ mol^{-1}.

The cause of this difference between the cyclic and acyclic derivatives will be considered first. In the saturated systems, the magnitude of the barrier is very slightly less for the six-membered cyclic system than for the acyclic compounds (barriers 71 and 72 kJ mol^{-1}, respectively). Comparison of x-ray results for cyclic and acyclic amides of the type being considered here indicates that the ground states for these molecules are similar in geometry and, hence, are probably similar in energy.[48] Since the magnitudes of their rotational barriers are similar, there is probably also little difference in energy between their transition states. The opposite trends observed in the barriers on introduction of unsaturation into a substituent on nitrogen in acyclic amides as compared with cyclic amides must, therefore, result from differences in the barriers in the unsaturated derivatives. This difference can be accounted for by consideration of the steric interactions in the ground and transition states for the cyclic and acyclic derivatives. For example, the manifestation of strong resonance interactions with the double bond in the transition state for the cyclic derivative should result in the co-planarity of five of the atoms in the ring; the situation would cause considerable strain due to bond-angle and eclipsing effects and, hence, resonance interactions would be inhibited. On the other hand, the transition state for the unsaturated acyclic derivative should not experience this strain and would thus be expected to be stabilized relative to the transition state for the unsaturated cyclic derivative. The steric interactions in the *ground state* of the cyclic and acyclic derivatives would be expected to be significantly different if the carbonyl substituent and the α-olefinic hydrogen were eclipsed in the more stable conformers of the cyclic derivatives. However, this situation prevails only when the amide group and the olefinic group are co-planar and, since there is less resonance interaction between the nitrogen atom and olefinic group in the ground state, an effect which results in coplanarity of the aforementioned groups, it is unlikely that there will be eclipsing interactions between the carbonyl substituent and the α-olefinic hydrogen. This conclusion is supported by the ground-state equilibrium populations for the cyclic unsaturated amides **2–7**, since a preference for the conformation in which the carbonyl substituent is *syn* to the olefinic group is observed in all cases. Thus, the lower rotational barriers in the acyclic unsaturated amides as compared with the cyclic unsaturated derivatives are probably caused by the extra strain in the transition state for the cyclic derivatives.

It is apparent that the effect of introducing an olefinic substituent on nitrogen on amide rotational barriers is considerably smaller than expected[4] on the basis of resonance stabilization of the transition state. The actual magnitude of the anticipated resonance stabilization can be calculated by the method developed by Ford *et al.*[43] They evaluated the resonance stabilization of an ethylenic derivative by a substituent as being $25\sigma_R^0$ kcal mol^{-1}; the σ_R^0 value used is that of the substituent.[43] Thus, in the ground state of the acyclic compound, a value of 31 or 43 kJ mol^{-1} is calculated depending on the source[45,49] of the σ_R^0 value for the amide group. In the transition state, if it is assumed that the resonance effect of the nitrogen is like that of NMe_2, a resonance stabilization of 55 kJ mol^{-1} is obtained and a difference in resonance energy between the ground state and the transition state of 12–24 kJ mol^{-1} results. If this range is even approximately correct, the experimental results are only consistent with there being more strain in the transition state than in the ground state of both the acyclic and cyclic olefinic amides as compared with the analogous states of the saturated amides; the latter effect would result in a destabilization of the transition state, which would counterbalance the tendency for the stabilization of the transition state through resonance interactions in the olefinic amides. The origin of this effect can be deduced by consideration of the structures of the transition states. During the rotational process, the hybridization of the bonding orbitals at the nitrogen atom may be regarded qualitatively as changing from sp^2 to sp^3. Any factor which favours this rehybridization process will stabilize the transition state, whereas any factor that disfavours the rehybridization process, for example, π-delocalization of the nitrogen lone pair, will tend to flatten the pyramidal

transition state and will thus destabilize the transition state. Thus, the rotational transition state for amides having saturated substituents is stabilized by rehybridization of the nitrogen atom from sp^2 to sp^3. The magnitude of such a stabilization should be approximately similar to the inversion barrier of trisubstituted amines,[50] *ca* 27 kJ mol^{-1}. However, rehybridization of the nitrogen atom to sp^3 in the rotational transition state for amides with unsaturated substituents is disfavoured because of π-delocalization of the nitrogen lone pair. Since the two effects oppose one another, one would expect some diminution of the resonance interaction in the transition state. Consequently, the observed resonance stabilization of the transition state in these compounds would be considerably less than expected if the significant rehybridization factor was ignored. The experimental results suggest that the gain in stability of the transition state for the acyclic unsaturated derivatives owing to resonance interaction is only slightly greater than the loss of stabilization owing to rehybridization of the nitrogen atom from sp^3 to sp^2.

EXPERIMENTAL

Toluene-d_8 was obtained from Stohler Isotope Chemicals. Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected. Proton (^{1}H NMR) spectra at 60 MHz were recorded on a Varian EM-360 or Bruker HX-60 spectrometer in chloroform-*d* with TMS as the internal standard, unless stated otherwise. ^{13}C NMR spectra were recorded on a Bruker HX-60 spectrometer equipped with an FT 60 M Fourier transform accessory at 15.1 MHz, in chloroform-*d* with TMS as the internal standard, unless stated otherwise; chemical shifts are given in parts per million downfield from TMS. A 22° pulse was employed. The probe thermocouple was used for temperature calibration (error ±1 K). The mass spectra were recorded on a CEC 21-104 mass spectrometer operating at 70 eV ionizing voltage. Thin-layer chromatography (TLC) was performed with silica gel G as the adsorbent in the following solvent systems (V/V): (A) benzene–ethyl acetate, 1:1; (B) 1:2; (C) 4:1; (D) ethyl acetate–ethanol, 20:1; (E) ethyl acetate. The developed plates were air dried, exposed to UV light and/or sprayed with a solution of cerium(IV) sulfate (1.0%) and molybdic acid (1.5%) in 10% sulfuric acid, and heated at *ca* 150 °C. Column chromatography was performed on Brinkmann silica gel (70–325 mesh). Solvents were evaporated under reduced pressure below 40 °C.

The variable temperature ^{1}H NMR spectra of compounds **2**, **3**, **6** and **7** were recorded at 220 MHz on a Varian HR 220 spectrometer at the Canadian 220 MHz Centre; the solutions were 0.5 M in toluene-d_8. Because the coalescence temperatures for the ^{1}H NMR signals for compounds **4** and **5** were comparable to the lowest temperature accessible on the HR-220 spectrometer, the spectra of these compounds were measured on a Varian HA-100 spectrometer at the Atlantic Regional Laboratories; the solutions were 0.5 M in toluene-d_8. Temperatures were measured as described in our earlier work.[1] Temperature gradients within the sample region of the HR-220 spectrometer are considered to be negligible because of the large distance between the heating unit and the probe; temperatures are believed to be accurate to ±1 °C. In the HA-100 spectrometer it is likely that there are temperature gradients over the sample; temperatures are believed to be accurate to ±1.5 °C. Spectra required for simulation were recorded using a 500 Hz sweep width for the spectra at 220 MHz and a 250 Hz sweep width for the spectra at 100 MHz. Coupling constants and chemical shifts were obtained by analysis of several spectra recorded at temperatures at which exchange was slow on the NMR time scale using the iterative program NMR-LAOCN-4A.[29] Coupling constants were observed to be temperature invariant. Values for populations and line widths in the exchange-broadened region were derived by a linear extrapolation of the values obtained at the low temperatures. The effects of long-range coupling and deuterium–proton coupling were incorporated by appropriate adjustment of the line width parameters.

Chemical shifts in the exchange-broadened region were derived by the following process. A least-squares program APARAM was written which used the observed chemical shifts of the exchanging protons in the slow exchange region, and the averaged chemical shifts and extrapolated populations in the fast exchange region, to derive a quadratic fit of chemical shift versus temperature. Five or six low-temperature chemical shift values and three to five high-temperature values were used in this process. Simulated spectra in the exchange-broadened region below coalescence were then generated using the computer program DNMR3[51] and the calculated chemical shifts. Comparison of the calculated spectra with the experimental spectra indicated in certain cases that a further adjustment of chemical shifts was required. The adjusted values obtained in this region were used in the program APARAM, together with the chemical shift values from the spectra at the extreme temperatures used earlier to generate a more accurate fit for the temperature dependence of the chemical shift values. The signals for the methylene protons in **5** showed considerable broadening below about 218 K, which was not evident in the signals for the olefinic protons in this compound. This broadening marks the onset of slow ring inversion in **5** and, thus, these signals were not used for analysis of the amide rotational barrier. The ring inversion process in this compound is currently under investigation. Calculation of simulated line shapes was performed by use of a slightly modified version of the DNMR3 program[51] on a CDC-6400 computer equipped with a CALCOMP plotter.

Rate constants were obtained by visual comparison of the experimental spectra with those calculated for various rates; the errors were considered to be the ranges in rates over which it was impossible to distinguish between the experimental and calculated spectra. Activation parameters and errors were calculated by the use of a weighted, linear least-squares program (RATES). The program calculates both Eyring and Arrhenius parameters from an equation of the form $y = a + bx$. The sums of the squares of the y and x

residuals are both minimized; the equations for the algorithm underlying the program were obtained from Wolberg.[52] The program weights the data in accordance with their estimated errors, and specifically treats errors in both temperatures and rate constants. Uncertainties in extrapolated values of y ($\ln k$) calculated at specific values of x were obtained from the equation for the unbiased estimate of the variance of y at that value of x.[52] The reported errors in $\Delta G^{\neq}$ at 273.2 K (Table 6) was obtained directly from the above uncertainties in y. Errors in $\Delta G^{\neq}$ values were obtained by use of the following equation[53] for the linearized relative statistical error:

$$(\sigma\Delta G^{\neq}/\Delta G^{\neq})^2 = [\ln(k_B T/hk)]^{-2}(\sigma_k/k)^2 + \{1+[\ln(k_B T/hk)]^{-1}\}^2(\sigma_T/T)^2$$

General procedure for the Kharasch–Sosnovsky reaction

To a stirred solution of the saturated amide (1 g) in benzene (40 ml) containing copper(I) chloride (20 mg), under an atmosphere of nitrogen at 81 °C, was added *tert*-butyl peracetate (0.8 equiv.) in benzene (15 ml) over a period of 2–4 h. The mixture was stirred at 81 °C for an additional 3–5 h. The mixture was cooled, diluted with benzene (30 ml), washed successively with aqueous sodium hydrogen carbonate solution (2× 25 ml) and water (25 ml), and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was fractionated on silica gel to yield the product and unreacted starting material. Yields are based on reacted starting material.

2-Acetoxy-4-acetyl-1-oxa-4-azacyclohexane (10)

4-Acetyl-1-oxa-4-azacyclohexane (**8**) (2 g) was treated as described above. TLC indicated the presence of two new components having R_F values of 0.52 and 0.32 together with unreacted starting material **8** (R_F 0.23). Chromatography using solvent D as eluant gave the three components. The component having an R_F value of 0.52 was isolated as a syrup (65 mg) and was not identified. The component having an R_F value of 0.32 was isolated as a syrup and was identified as being 2-acetoxy-4-acetyl-1-oxa-4-azacyclohexane (**10**) (0.255 g, 16%). ^{1}H NMR data: δ 1.94 (s, 6H, OAc, NAc), 4.3–2.7 (m, 6H, H-3, H-5, H-6), 5.76 (br s, 1H, H-2). ^{13}C NMR data: δ 20.9 (OAc, NAc), 41.0, 43.5 (C-5), 45.4, 48.8 (C-3), 61.3 (C-6), 89.2 (C-2). The component having an R_F value of 0.23 was isolated as a liquid and was identified as being unreacted starting material **8** (0.90 g).

4-Acetyl-1-oxa-4-azacyclohex-2-ene (2)

A solution of 2-acetoxy-4-acetyl-1-oxa-4-azacyclohexane (**10**) (0.255 g, 1.37 mmol) in benzene (50 ml) containing *p*-toluenesulfonic acid monohydrate (*ca* 10 mg) was refluxed for 1 h. TLC (solvent D) indicated the disappearance of starting material and the appearance of a new component having an R_F value of 0.58. The mixture was cooled and washed with aqueous sodium hydrogen carbonate (30 ml) and water (15 ml), and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a syrup which was chromatographed using solvent D as eluant. The component having an R_F value of 0.58 was isolated as a liquid and was identified as being 4-acetyl-1-oxa-4-azacyclohex-2-ene (**2**) (0.151 g, 87%); *M* calculated for $C_6H_9NO_2$, 127; found, *m/e* 127.

4-Benzoyl-1-oxa-4-azacyclohex-2-ene (3)

A solution of 2-acetoxy-4-benzoyl-1-oxa-4-azacyclohexane (**11**) (0.237 g, 0.95 mmol), prepared from 4-benzoyl-1-oxa-4-azacyclohexane (**9**) as described by Pinto *et al.*,[27] in benzene (20 ml) containing *p*-toluenesulfonic acid monohydrate (*ca* 15 mg) was refluxed for 2 h. TLC (solvent C) indicated the absence of starting material and the presence of a faster moving component having an R_F value of 0.51. The mixture was cooled and washed successively with aqueous sodium hydrogen carbonate (10 ml) and water (10 ml), and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a liquid which was filtered through a short silica gel column to yield a clear colourless liquid which was identified as being 4-benzoyl-1-oxa-4-azacyclohex-2-ene (**3**) (0.118 g, 66%); *M* calculated for $C_{11}H_{11}NO_2$, 189; found, *m/e* 189.

N-Acetylazacyclohex-2-en-4-one (4)

N-Acetylazacyclohexan-4-one (**12**) (1 g, 7.08 mmol) was treated as described in the general procedure. TLC (solvent D) indicated the presence of a component having an R_F value of 0.44, together with unreacted starting material **12** (R_F 0.21). After chromatography with solvent D as eluant, the component having an R_F value of 0.44 was isolated as a syrupy solid and was identified as being *N*-acetylazacyclohex-2-en-4-one (**4**) (0.237 g, 37%); *M* calculated for $C_7H_9NO_2$, 139; found, *m/e* 139. The component having an R_F value of 0.21 was isolated as a liquid and was identified as being unreacted starting material (**12**) (0.352 g).

N-Benzoylazacyclohex-2-en-4-one (5)

N-Benzoylazacyclohexan-4-one (**13**) (1.0 g, 4.9 mmol) was treated as described in the general procedure. TLC (solvent B) indicated the presence of a component having an R_F value of 0.51, together with unreacted starting material (R_F 0.34). After chromatography with solvent B as eluant, the component having an R_F value of 0.51 was isolated as a syrupy solid and was identified as being *N*-benzoylazacyclohex-2-en-4-one (**5**) (0.278 g, 74%). The sample crystallized on standing and was recrystallized from ethanol; m.p. 121–122 °C; *M* calculated for $C_{12}H_{11}NO_2$, 201; found, *m/e* 201. The component having an R_F value of 0.34 was isolated as a syrup and was identified as being unreacted starting material (**13**) (0.621 g).

N-Acetyl-4,4-dideuterioazacyclohex-2-ene (6)

N-Acetyl-4,4-dideuterioazacyclohexane (**14**) (2 g, 15.6 mmol) was treated as described in the general procedure. TLC (solvent A) indicated the presence of a component having an R_F value of 0.38, together with unreacted starting material (R_F 0.13). Chromatography with solvent A yielded the pure components. The component having an R_F value of 0.38 was isolated as a clear colourless liquid, and was identified as being *N*-acetyl-4,4-dideuterioazacyclohex-2-ene (**6**) (0.37 g, 63%); *M* calculated for $C_7H_9D_2NO$, 127; found, *m/e* 127. The component having an R_F value of 0.13 was isolated as a liquid and was identified as being unreacted starting material (**14**) (1.4 g).

N-Benzoyl-4,4-dideuterioazacyclohex-2-ene (7)

N-Benzoyl-4,4-dideuterioazacyclohexane (**15**) (3 g, 15.9 mmol) was treated as described in the general procedure. TLC (solvent A) indicated the presence of a component having an R_F value of 0.67, together with unreacted starting material (R_F 0.49). Chromatography with solvent C yielded the pure components. The component having an R_F value of 0.67 was isolated as a clear colourless liquid and was identified as being *N*-benzoyl-4,4-dideuterioazacyclohex-2-ene (**7**) (0.535 g, 56%); *M* calculated for $C_{12}H_{11}D_2NO$, 189; found, *m/e* 189. The component having an R_F value of 0.49 was isolated as a liquid and was identified as being unreacted starting material (**15**) (2.05 g).

N-Acetyl-4,4-dideuterioazacyclohexane (14)

A solution of *N*-acetylazacyclohexan-4-one tosylhydrazone (**16**) (2 g, 6.5 mmol) in methanol-d_1 (30 ml) and deuterium oxide (8 ml) containing sodium borodeuteride (0.376 g, 9 mmol) was gently refluxed for 24 h. The methanol was evaporated, water (15 ml) was added and the mixture was extracted with chloroform (3 × 15 ml). The extracts were dried over anhydrous magnesium sulfate and concentrated to yield a liquid, which was purified by chromatography using solvent E as eluant. *N*-Acetyl-4,4-dideuterioazacyclohexane (**14**) was obtained as a clear colourless liquid (0.72 g, 86%). ^{1}H NMR data: δ 1.15–1.67 (m, 4H, H-3, H-5), 1.92 (s, 3H, NAc), 3.0–3.72 (m, 4H, H-2, H-6). ^{13}C NMR data: δ 21.4 (NAc), 25.4, 26.3 (C-3, C-5), 42.5, 47.4 (C-2, C-6), 168.7 (CO).

N-Benzoyl-4,4-dideuterioazacyclohexane (15)

A solution of *N*-benzoylazacyclohexan-4-one tosylhydrazone (**17**) (1 g, 2.69 mmol) in methanol-d_1 (12 ml) and deuterium oxide (4 ml) containing sodium borodeuteride (0.169 g, 4.04 mmol) was refluxed for 24 h. The methanol was evaporated, water (20 ml) was added and the mixture was extracted with chloroform (3 × 15 ml). The extracts were dried over anhydrous magnesium sulfate and concentrated to yield a syrup, which was purified by column chromatography using solvent A as eluant. *N*-Benzoyl-4,4-dideuterioazacyclohexane (**15**) was obtained as a clear colourless liquid (0.45 g, 88%). ^{1}H NMR data: δ 1.1–1.85 (br m, 4H, H-3, H-5), 2.9–3.9 (br m, 4H, H-2, H-6), 7.32 (s, 5H, Ph). ^{13}C NMR data (275 K): δ 25.6, 26.4 (C-3, C-5), 42.8, 48.5 (C-2, C-6), 126.7, 128.3, 129.3, 136.5 (Ph), 169.8 (CO).

N-Acetylazacyclohexan-4-one tosylhydrazone (16)

A solution of *N*-acetylazacyclohexan-4-one (**12**) (2 g, 0.015 mol) in ethanol (60 ml) containing tosylhydrazine (2.9 g) was refluxed for 12 h. The mixture was cooled and the solid that precipitated was filtered and washed with ethanol. The solid was identified as being *N*-acetylazacyclohexan-4-one tosylhydrazone (**16**) (3.5 g, 81%), m.p. 179–182 °C (dec.). ^{1}H NMR data: δ 2.2 (s, 3H, CH_3), 2.53 (s, 3H, NAc), 2.3–2.83 (m, 4H, H-3, H-5), 3.3–3.97 (m, 4H, H-2, H-6), 7.45, 7.95 (AB quartet, 4H, Ph), 8.6 (br. s, 1H, NH). ^{13}C NMR data (305 K): δ 21.6 (CH_3), 27.3, 27.8 (C-3), 33.1, 33.8 (C-5), 39.1, 41.6 (C-2), 43.7, 45.6 (C-6), 128.0, 129.6, 135.5, 135.6, 143.9, 144.1, 156.5, 156.9 (Ph), 169.8, 169.6 (CO). ^{13}C NMR data (350 K, DMSO-d_6): δ 21.0 (CH_3), 27.7 (C-3, C-5), 33.1 (C-2, C-6), 127.5, 129.2, 136.7, 143.0, 158.1 (Ph), 168.5 (CO). *M* calculated for $C_{14}H_{19}N_3O_3S$, 309; found, *m/e* 153 (309-*p*-tosyl).

N-Benzoylazacyclohexan-4-one tosylhydrazone (17)

A solution of *N*-benzoylazacyclohexan-4-one (**13**) (2 g, 9.84 mmol) in ethanol (60 ml) containing tosylhydrazine (2 g, 10.8 mmol) was refluxed for 8 h. The ethanol was evaporated and the residue was purified by column chromatography using solvent B as eluant. The component having an R_F value of 0.53 was isolated as a foam and was identified as being *N*-benzoylazacyclohexan-4-one tosylhydrazone (**17**) (3.3 g, 90%). ^{1}H NMR data: δ 2.36 (s, 3H, CH_3), 2.5–5.0 (br pks, H-2, H-3, H-5, H-6), 7.36 (s, 5H, NBz), 7.23, 7.72 (AB quartet, 4H, Ph). ^{13}C NMR data (350 K, DMSO-d_6): δ 21.0 (CH_3), 27.8 (C-3, C-5), 33.4 (C-2, C-6), 126.8, 127.6, 128.4, 129.4, 136.2, 136.8, 143.1, 157.8 (Ph), 169.7 (CO). *M* calculated for $C_{19}H_{21}N_3O_3S$, 371; found, *m/e* 279 (371-*p*-tolyl).

Acknowledgements

The authors are grateful to NSERC Canada for financial assistance in the form of grants (to T.B.G. and W.A.S.) and a scholarship (to B.M.P.). They also thank Dr G. McInnes for the use of the HA-100 spectrometer at the Atlantic Regional Laboratory and Dr A. Grey of the Canadian 220 MHz NMR Centre for use of the HR-220 spectrometer.

REFERENCES

1. T. B. Grindley, B. M. Pinto and W. A. Szarek, *Can. J. Chem.* **55,** 949 (1977).
2. W. E. Stewart and T. H. Siddall, III, *Chem. Rev.* **70,** 517 (1970).
3. H. Kessler, *Angew. Chem., Int. Ed. Engl.* **9,** 219 (1970).
4. L. M. Jackman, in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, edited by L. M. Jackman and F. A. Cotton, Chapt. 7. Academic Press, New York (1975).
5. M. D. Wunderlick, L. K. Leung, J. A. Sandberg, K. D. Meyer and C. H. Yoder, *J. Am. Chem. Soc.* **100,** 1500 (1978).
6. D. Kost and N. Kornberg, *Tetrahedron Lett.* 3275 (1978); J. Sandström, *Tetrahedron Lett.* 639 (1979).
7. L. M. Jackman, T. E. Kavanagh and R. C. Haddon, *Org. Magn. Reson.* **1,** 109 (1969).
8. D. G. Gehring, W. A. Mosher and G. S. Reddy, *J. Org. Chem.* **31,** 3436 (1966).
9. See Table 6 in Ref. 1 and Table 4 in Ref. 12 for summaries of this effect on the introduction of a vinyl substituent.
10. (a) K.-I. Dahlqvist and S. Forsen, *J. Phys. Chem.* **73,** 4124 (1969); (b) T. Matsuo and H. Shosenji, *Chem. Commun.* 501 (1969); (c) G. Yamamoto and M. Raban, *J. Org. Chem.* **41,** 3788 (1976); (d) A. Cipiciani, P. Linda, D. Macciantelli and L. Lunazzi, *J. Chem. Soc., Perkin Trans. 2* 1045 (1979); (e) J. Elguero, C. Marzin and M. E. Peek, *Org. Magn. Reson.* **6,** 445 (1975).
11. (a) J. A. Hirsch, R. L. Augustine, G. Koletar and H. G. Wolf, *J. Org. Chem.* **40,** 3547 (1975); (b) P. LeCam and J. Sandström, *Chem. Scr.* **1,** 65 (1971).
12. R. R. Fraser, J.-L. Rouston and J. R. Mahajan, *Can. J. Chem.* **57,** 2239 (1979).
13. I. O. Sutherland, in *Annual Reports on NMR Spectroscopy*, Vol. 4, edited by E. F. Mooney, p. 196. Academic Press, New York (1971).
14. D. A. Kleier, G. Binsch, A. Steigel and J. Sauer, *J. Am. Chem. Soc.* **92,** 3787 (1970).
15. H. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.* **80,** 756 (1958).
16. S.-O. Lawesson and G. Sosnovsky, *Angew. Chem., Int. Ed. Engl.* **3,** 269 (1964).
17. C. Berglund and S.-O. Lawesson, *Ark. Kemi* **20,** 225 (1963).
18. G. Sosnovsky, *Tetrahedron* **21,** 871 (1965).
19. D. J. Rawlinson and G. Sosnovsky, *Synthesis* 1 (1972).
20. G. W. Kabalka, D. T. C. Yang, J. H. Chandler and J. D. Baker, Jr., *Synthesis* 124 (1977).
21. (a) C. C. Costain and J. M. Dowling, *J. Chem. Phys.* **32,** 158 (1960); (b) A. Rauk, L. C. Allen and K. Mislow, *Angew. Chem., Int. Ed. Engl.* **9,** 400 (1970); (c) N. R. Carlsen, L. Radom, N. V. Riggs and W. R. Rodwell, *J. Am. Chem. Soc.* **101,** 2233 (1979).
22. M. Kitaus and K. Kuchitsu, *Bull. Chem. Soc. Jpn.* **47,** 67 (1974); F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.* **59,** 169 (1971); A. B. Biswas, E. W. Hughes, B. D. Sharma and J. N. Wilson, *Acta Crystallogr., Sect. B* **24,** 40 (1963).
23. F. A. L. Anet and J. Sandström, *Chem. Commun.* 1558 (1971).
24. F. R. Jensen and R. A. Neese, *J. Am. Chem. Soc.* **93,** 6329 (1971).
25. R. H. Larkin and R. C. Lord, *J. Am. Chem. Soc.* **95,** 5129 (1973).
26. D. A. Torchia, V. R. Lyerla, Jr. and C. M. Deber, *J. Am. Chem. Soc.* **96,** 5009 (1974); W. MacFarlane, *Chem. Commun.* 418 (1970); C. G. Levy and G. L. Nelson, *J. Am. Chem. Soc.* **94,** 4897 (1972); W. Walter, W. Ruback and C. O. Neese, *Org. Magn. Reson.* **11,** 612 (1978).
27. B. M. Pinto, D. M. Vyas and W. A. Szarek, *Can. J. Chem.* **55,** 937 (1977).
28. J. B. Stothers, *Carbon-13 NMR Spectroscopy*, p. 184. Academic Press, New York (1972).
29. J. A. Musso, NMR-LAOCN-4A, Quantum Chemistry Program Exchange, Program 232.
30. L. Isbrandt, W. C.-T. Tung and M. T. Rogers, *J. Magn. Reson.* **9,** 461 (1973).
31. L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.* **85,** 3728 (1963).
32. T. H, Siddall, III, W. E. Stewart and F. C. Knight, *J. Phys. Chem.* **74,** 3580 (1970).
33. G. V. Garner, O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc. C* 1234 (1971).
34. D. Ajo, G. Granozzi and E. Tondello, *J. Mol. Struct.* **41,** 131 (1977).
35. E.g. J. B. Hendrickson, *J. Am. Chem. Soc.* **89,** 7047 (1967).
36. R. R. Shoup, E. D. Becker and M. L. McNeel, *J. Phys. Chem.* **76,** 71 (1972); T. Drakenberg, K.-I. Dahlqvist and S. Forsen, *Acta Chem. Scand.* **24,** 694 (1970); H. S. Gutowsky, J. Jonas and T. H. Siddall, III, *J. Am. Chem. Soc.* **89,** 4300 (1967).
37. R. Osman, A. Zunger and Y. Shvo, *Tetrahedron* **34,** 2315 (1978); R. Osman and Y. Shvo, *Tetrahedron* **34,** 2312 (1978).
38. U. Berg and U. Sjostrand, *Org. Magn. Reson.* **11,** 555 (1978).
39. R. E. Klinck and J. B. Stothers, *Can. J. Chem.* **54,** 3267 (1976).
40. W. Walter, E. Schaumann and H. Rose, *Org. Magn. Res.* **5,** 191 (1973).
41. G. P. Ford, A. R. Katritzky and R. D. Topsom, in *Correlation Analysis in Chemistry*, edited by N. B. Chapman and J. Shorter, Chapt. 7. Plenum, London (1978).
42. N. D. Epiotis, R. L. Yates, F. Bernardi and S. Wolfe, *J. Am. Chem. Soc.* **98,** 5435 (1976).
43. G. P. Ford, A. R. Katritzky and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2* 1378 (1975).
44. T. B. Grindley, A. R. Katritzky and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2* 443 (1975).
45. R. T. C. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell and R. D. Topsom, *J. Am. Chem. Soc.* **90,** 1757 (1968).
46. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.* **80,** 4979 (1958).
47. C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.* **2,** 323 (1964).
48. T. B. Grindley, B. M. Pinto and W. A. Szarek, *J. Org. Chem.*, submitted for publication.
49. R. W. Taft, F. Price, I. R. Fox, I. C. Lewis, K. K. Anderson and G. T. Daves, *J. Am. Chem. Soc.* **85,** 3146 (1963).
50. M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.* **93,** 401 (1971); C. H. Bushweller, J. W. O'Neill and H. S. Bilofsky, *Tetrahedron* **28,** 2697 (1972).
51. D. A. Klier and G. Binsch, DNMR3: A computer program for the calculation of complex exchange-broadened NMR spectra. Modified version for spin systems exhibiting magnetic equivalence or symmetry. Quantum Chemistry Program Exchange, Program 165, Indiana University (1970).
52. J. R. Wolberg, *Prediction Analysis*, Chapt. 3. Van Nostrand, New York (1967).
53. G. Binsch, in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, edited by L. M. Jackman and F. A. Cotton, Chapt. 3. Academic Press, New York (1975).

Received 23 July 1981; accepted (revised) 3 March 1984