

Conformational Preferences in Hexahydro-2*H*-azepin-2-ones (Caprolactams)

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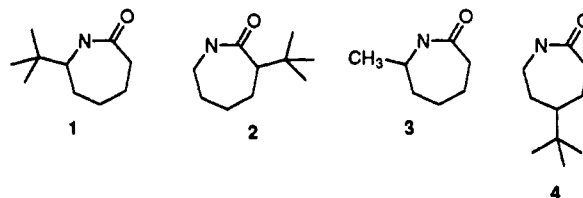
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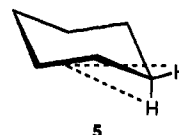
It was predicted and found that caprolactams are similar to cyclohexanes in conformational preferences. The compounds investigated were 7-methyl- and 3- and 7-(1,1-dimethylethyl)hexahydro-2*H*-azepin-2-ones. The 600-MHz NMR spectra showed discrete sets of axial and equatorial hydrogens, with the equatorial hydrogens lying "downfield" as in cyclohexane. The boat forms were surprisingly low in energy. The chair form with an axial substituent is predicted to have the highest energy of the four main conformers. Agreement between calculated and observed coupling constants is acceptable for *tert*-butyl-substituted caprolactams, but not for methyl (the energy of the axial methyl substituent appears to be too high in MM2 and especially in MM3). Some of these compounds show abnormally small coupling constants for hydrogens near the *tert*-butyl group. Calculations suggest that the effect is related to bond lengthening.

Conformational preferences in cyclohexanes have been thoroughly studied.¹ Medium rings also have received considerable attention, principally through the work of Anet and coworkers.² The present work explores seven-membered rings, i.e. caprolactams, a system not previously investigated in detail. The amide function is similar to the methylene group of cyclohexanes in rigidity, although not in size.⁴ Thus, caprolactams might be expected to show some similarity to cyclohexanes in conformation.² Interference between carbonyl and equatorial C3-substituents might be a point of difference between the amide function and a methylene group.⁵ The molecules of interest are 7- and 3-(1,1-dimethylethyl)hexahydro-2*H*-azepin-2-ones 1 and 2, respectively, and the 7-methyl compound 3. The 600-MHz NMR spectra of these compounds were simulated using LAOCON.⁶ The 5-*tert*-butyl lactam 4 was briefly investigated, but the NMR spectrum was not completely solvable due to severely overlapping resonances. The NMR data for 1-3 are listed in Chart 1.

One principle feature of the NMR spectra is the segregation of axial and of equatorial hydrogens into



discrete regions (cf. Figure 1). The equatorial hydrogens lie "downfield", due to the dominance of the longitudinal anisotropy of neighboring C-C bonds (cf. 5), similar to cyclohexanes.⁷



The energies of the conformers of 1-3 were calculated with several molecular mechanics programs (Table 1) and also by semiempirical quantum chemistry programs (Table 2). For the equatorial *tert*-butyl compounds, the chair-boat energy difference is quite small, of the order of 2 kcal/mol in most calculations. The surprising stability of the boat form represents the greatest difference between the lactams and cyclohexanes.^{2,8,9} Scheme 1 compares the differences between chair and boat caprolactams with the more familiar cyclohexanes. In cyclohexane, the main source of the 6 kcal/mol destabilization of the twist-boat form is torsional interactions, according to the MM3¹⁰ dissection of energy terms. In the caprolactams, the 2 kcal/mol destabilization is distributed over several terms, although van der Waals' interactions (largely steric) are prominent.

For the *tert*-butyl-substituted molecules, the chair form with an axial *tert*-butyl is the least-stable conformation,

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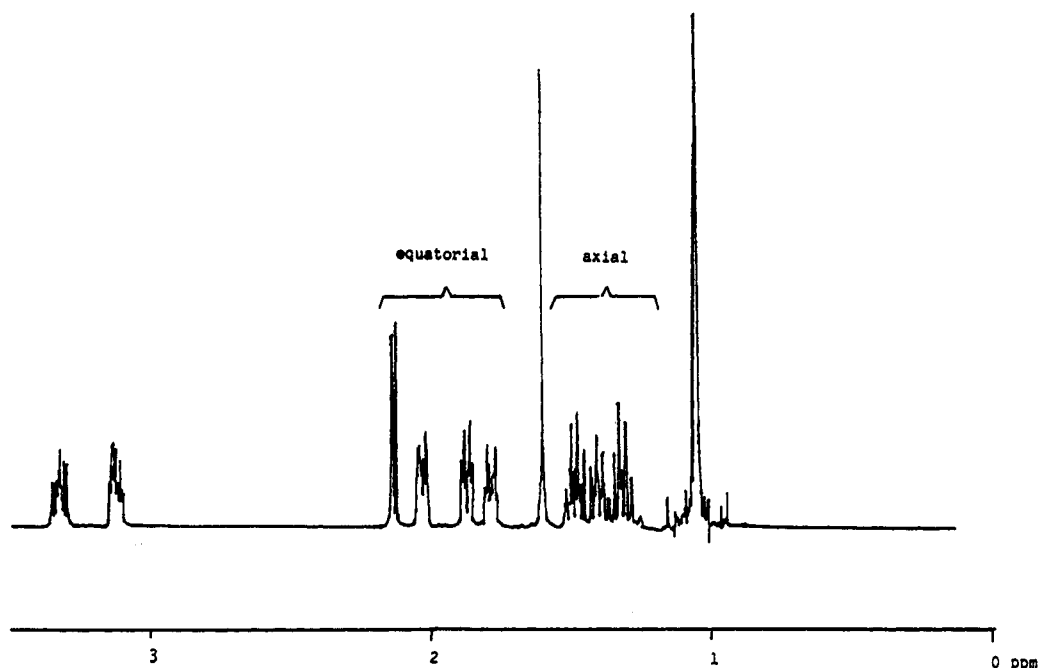
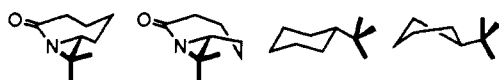


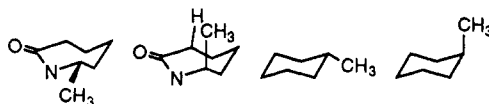
Figure 1. NMR spectrum of 3-(1,1-dimethylethyl)hexahydro-2*H*-azepin-2-one (2), showing axial and equatorial absorptions.

Scheme 1



steric energy	19.14	20.89	17.72	23.28
compression	1.50	1.54	1.30	1.51
bending	2.99	3.02	1.41	1.59
van der Waals'				
1,4	11.42	12.00	9.87	10.71
other	2.13	2.69	2.03	1.94
torsional	5.11	5.59	2.95	7.58

Scheme 2



steric energy	11.18	13.87	9.10	10.87
compression	0.53	0.47	0.38	0.45
bending	2.07	5.29	0.22	0.56
van der Waals'				
1,4	8.60	8.27	6.97	7.11
other	-0.04	0.27	-0.24	0.12
torsional	4.07	3.56	1.74	2.60

by some 4 kcal/mol, a smaller value than for cyclohexanes.¹¹ In 2, the boat form with a formally axial *tert*-butyl is more stable than a boat form with an equatorial *tert*-butyl due to interference of the latter with carbonyl. The higher energies of 2 vs 1 show the destabilizing effect of the equatorial *tert*-butyl-carbonyl interaction.

The axial-equatorial energy difference in methylcyclohexane (1.8 kcal/mol) is one of the benchmarks of organic chemistry.⁴ It is of interest to see how methyl-substituted caprolactams 3 compare. In 3, most types of calculation place the axial methyl about 2 kcal/mol less stable than the equatorial methyl.¹¹ The programs developed for biochemical applications, AMBER,¹² BIO+,¹³ and OPLS,¹⁴ appear to give rather high axial-equatorial energy dif-

ferences in 3 (ca. 2.5 kcal/mol), as does the SYBYL force field.¹⁵ MNDO and PM3 calculations suggest lower axial-equatorial energy differences (ca. 1 kcal/mol), although AM1 shows a 2 kcal/mol difference in energy difference.¹⁶

Details of the MM3 calculations for methylcyclohexane vs 3 are shown in Scheme 2. The 1.8 kcal/mol energy difference in axial vs equatorial methylcyclohexane is largely torsional, although bending and van der Waals' terms also contribute, according to the MM3 dissection of energies. In 3, the overall difference in energy is exceptionally high (2.7 kcal), and bending terms are the dominant contributor. Oddly enough, the axial methyl is not bent, but rather the ring bonds suffer rather large deviations from the optimum (e.g. C(O)-N-C, 126° (from 121°), and C(CH₃)-C-C, 117° (from 111°)). These values differ to some extent in other force-field calculations.

In axial methylcyclohexane, the methyl group is canted outward, whereas in 3, the effect is less apparent (from MM3).¹⁷ The transannular axial hydrogen at C3 is canted inward, and the bond angles around carbonyl and around nitrogen have widened in an attempt to distance the axial methyl from the interfering transannular hydrogen. However, semiempirical calculations suggest that the axial methyl does indeed bend outward. In the axial *tert*-butyl-substituted molecules, this group is bent outward quite severely.

NMR-Force Field Correlations

For 1-2, the major contributor to the observed NMR coupling constants is the eq-chair form. The eq-boat, and

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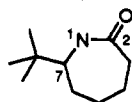
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Chart 1

7-(1,1-Dimethylethyl)hexahydro-2H-azepin-2-one (1)

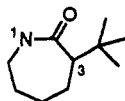


		Coupling Constants (Hz)				
		3a-4a	3a-4e	3e-4a	3e-4e	4a-5a
hydrogens:						
obsd 3J		12.6	2.1	1.6	6.9	12.9
calcd 3J		12.4	2.7	2.5	6.2	12.7
hydrogens:		4a-5e	4e-5a	4e-5e	5a-6a	5a-6e
obsd 3J		4.2	3.7	3.3	12.3	3.4
calcd 3J		3.4	3.4	4.2	12.7	3.4
hydrogens:		5e-6a	5e-6e	6a-7a	6e-7a	
obsd 3J		3.2	4.3	9.7	0.5	
calcd 3J		3.4	4.7	10.7	1.3	

Chemical Shifts (ppm)

H3a	H3e	H4a	H4e	H5a	H5e
2.52	2.44	1.56	1.87	1.50	2.03
H6a	H6e	7a			
1.22	1.94	3.03			

3-(1,1-Dimethylethyl)hexahydro-2H-azepin-2-one (2)

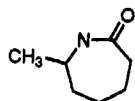


		Coupling Constants (Hz)				
		3a-4a	3a-4e	4a-5a	4a-5e	4e-5a
hydrogens:						
obsd 3J		10.3 Hz	0.5	12.8	2.7	3.9
calcd 3J		10.9	2.1	13.4	2.9	2.6
hydrogens:		4e-5e	5a-6a	5a-6e	5e-6a	5e-6e
obsd 3J		3.9	12.7	3.9	3.9	3.9
calcd 3J		4.6	13.0	3.6	3.6	3.9
hydrogens:		6a-7a	6a-7e	6e-7a	6e-7e	
obsd 3J		11.8	2.6	0.9	4.7	
calcd 3J		11.9	2.0	1.6	5.3	

Chemical Shifts (ppm)

H3a	H4a	H4e	H5a	H5e	H6a
2.13	1.32	1.87	1.49	1.78	1.40
H6e	H7a	H7e			
2.03	3.33	3.12			

7-Methylhexahydro-2H-azepin-2-one (3)



		Coupling Constants (Hz)				
		3a-4a	3a-4e	3e-4a	3e-4e	4a-5a
hydrogens:						
obsd 3J		9.6	1.7	2.5	8.8	12.5
calcd 3J		11.8	1.7	1.7	7.3	13.1
calcd $^3J^a$		11.5				12.6
hydrogens:		4a-5e	4e-5a	4e-5e	5a-6a	5a-6e
obsd 3J		2.8	3.4	4.4	12.4	3.6
calcd 3J		2.5	2.5	5.4	13.0	3.7
calcd 3J					12.4	
hydrogens:		5e-6a	5e-6e	6a-7a	6e-7a	
obsd 3J		3.6	4.2	9.9	1.0	
calcd 3J		3.7	4.6	10.8	1.6	
calcd $^3J^a$				10.0		

Chemical Shifts (ppm)

H3a	H3e	H4a	H4e	H5a	H5e
2.46	2.47	1.53	1.85	1.55	1.98
H6a	H6e	H7a			
1.38	1.77	3.50			

^a Coupling constants if the eq-ax (chair) energy difference were 1.4 kcal.

the ax-boat conformers have a small but significant effect. For the methyl compound 3, the ax-chair should also contribute. A "twist" form is also possible (cf. 7), which is quite high in energy. Using the dihedral driver option

Table 1. Energies of Conformers (kcal/mol). Force Field Calculations

	MMX ^a	MM2	MM3	MM+	AMBER ^b	BIO+ ^b	OPLS ^b	SYBYL
7-(1,1-Dimethylethyl)-2H-azepin-2-one (1)								
chair								
eq	8.6	13.19	19.12	9.50	7.6	7.1	-0.7	9.90
ax	13.3	18.08	26.76	13.90	13.4	12.2	4.9	15.49
boat								
eq	10.7	15.70	20.89	11.43	10.9	12.4	4.4	12.75
ax	10.6	16.14	23.97	11.55	10.6	9.8	0.6	12.96
3-(1,1-Dimethylethyl)-2H-azepin-2-one (2)								
chair								
eq	12.1	15.07	20.97	12.66	12.0	10.0	12.2	11.13
ax	15.4	21.71	28.32	16.50	14.7	13.4	12.9	15.72
boat								
eq	14.6	16.92	22.84	14.91	14.2	15.1	14.6	13.79
ax	12.9	19.00	24.43	14.58	13.4	13.5	14.1	13.42
7-Methyl-2H-azepin-2-one (3)								
chair								
eq	4.2	7.99	11.18	5.26	4.0	0.8	-3.4	5.92
ax	6.4	9.78	13.47	6.74	6.3	5.3	0.1	8.45
boat								
eq	7.8	9.59	13.87	7.62	9.2	9.2	10.8	9.76
ax	6.8	10.59	16.07	7.87	10.2	11.1	11.9	14.55

^a Difficultly reproducible. ^b Difficultly reproducible in HyperCard implementation.

Table 2. Energies of Conformers (kcal/mol). Semi-Empirical Calculations

	MNDO	PM3	AM1 ^a	AM1 ^b
7-(1,1-Dimethylethyl)hexahydro-2H-azepin-2-one (1)				
chair				
eq	-51.84	-78.86	-85.84	-2947.55
ax	-47.20	-75.18	-80.51	-2942.28
boat				
eq	-49.86	-75.32	-84.08	-2945.88
ax	-47.20	-73.95	-83.18	-2944.93
3-(1,1-Dimethylethyl)hexahydro-2H-azepin-2-one (2)				
chair				
eq	-48.5	-73.53	-83.81	-2945.62
ax	-44.7	-71.00	-79.81	-2941.64
boat				
eq	-46.4	-70.76	-81.18	-2943.00
ax	-46.5	-71.36	-82.30	-2944.15
7-Methylhexahydro-2H-azepin-2-one (3)				
chair				
eq	-56.61	-63.66	-72.09	-2110.89
ax	-55.55	-62.44	-70.06	-2108.84
boat				
eq	-54.2	-60.21	-69.92	-2108.78
ax	-53.54	-59.26	-66.87	-2107.57

^a AM1 using Spartan; these calculations reflect the "hexadecane" mode of solvent simulation. ^b AM1 using HyperChem.

of MM2(87) for the basic conformers, the energies and dihedral angles for each set of vicinal protons were determined for each basic conformer at 5-deg intervals.¹⁸ The coupling constant was calculated for each of these subsidiary conformations using the relationship of deLeeuw and Altona^{19,20} in the program LACA.²¹ Using the steric energies of the conformers as Boltzmann weighting factors,

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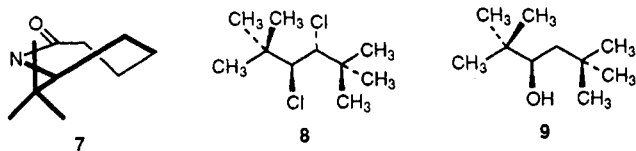
the coupling constants were weighted. Summation of the weighted individual coupling constants gives the overall predicted coupling constants for the equilibrating molecule. These data are listed in Table 1.

For the *tert*-butyl compounds, a reasonable agreement between the predicted and observed *J* values is found. The fit is not as good if the boat form is omitted from the calculation.

The largest *J* values (between anti hydrogens) are most sensitive to incorrect differences in energy between basic conformers. Thus, either chair-chain interconversion or chair-boat interconversion places previously *trans* diaxial hydrogens in a conformation having a much smaller coupling constant. If the weight of the axial methyl or the boat form is incorrectly determined, the calculated 3J value will be off. As Chart 1 shows, the calculated and observed *J* values were not in agreement for the methyl compound 3, using MM2 data.

For 3, the calculated *J* values (for anti hydrogens) could be markedly improved if the ax-chair eq-chair energy difference were arbitrarily set to 1.4–1.5 kcal/mol, intermediate between the MM2 and MNDO predictions, but similar to the predictions of MM+ or PM3. Thus, either most of the force field and AM1 predictions are somewhat off, or else the Boltzmann procedure in fitting the NMR data requires refinement.

The *tert*-Butyl Effect. As Chart 1 shows, compounds 1 and 2 exhibit lower coupling constants than calculated for hydrogens near the *tert*-butyl function, i.e., the *tert*-butyl effect. This type of observation has appeared many times in the literature, e.g. for *meso*-3,4-dichloro-2,2,5,5-tetramethylhexane (8)²² and for 2,2,5,5-tetramethyl-3-hexanol (9).²³ In 8, Fahey found $^3J_{34}$ to be 5.2 Hz, considerably less than the 11–12-Hz value expected for anti hydrogens.²² In 9, the *trans* and *gauche* vicinal hydrogens show couplings of 8 and 1.8 Hz, respectively.²³



In the original work on the Karplus relationship, a caution was sounded in cases where molecular deformations were present.²⁴ This injunction was ignored at considerable risk by users of this relationship. Karplus provided rough calculations were provided for the effect of bond lengthening and of angle spreading on coupling constants.²⁴ These effects were quite large. In a more recent treatment, Imai and Osawa included a term for C–C bond stretching in their program for calculation of coupling constants.²⁵ It is noteworthy that Imai and Osawa prefer a linear dependence in bond lengthening, i.e., $-8.9222(r_{c-c} - 1.5)$.²⁵

To investigate the phenomenon in more detail, calculations on the effect of bond distance on 3J were performed

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Chart 2. Effect of Bond Distance on NMR Coupling Constant

staggered ethane			
<i>R</i>	$^1J_{C-H}$	$^3J_{1,2}$	$^3J_{1,3}$
1.43 Å	122 Hz	5.8	32.8
1.53	126	3.8	22.3
1.63	128	2.4	15.3

eclipsed ethane			
<i>R</i>	$^1J_{C-H}$	$^3J_{1,2}$	$^3J_{1,3}$
1.435	124	22.1	10.1
1.535	126	14.5	6.9
1.635	129	9.5	4.8

ethanol			
<i>R</i>	$^3J_{1,3}$	$^3J_{2,3}$	$^3J_{2,4}$
1.43	3.7	6.1	30.6
1.53	2.3	3.9	21.0
1.63	1.4	2.4	14.5

cyclopropane					
<i>r - r₀</i>	$^1J_{C-H}$	$^3J_{1,2}$	$^3J_{1,3}$	$^3J_{1,4}$	$^3J_{1,5}$
0.0	155.5	7.2	6.8	7.2	6.8
0.02	155.5	7.2	6.9	6.6	6.3
0.10	155.3	7.4	7.6	4.8	4.9

using the semiempirical program FINITE (cf. Chart 2).²⁶ For ethane, lengthening the C–C bond by 0.02 Å results in ca. 10% reduction of 3J_T or ca. 7% for 3J_G . In an ethylene system, Karplus predicted at 6% reduction of 3J for a similar change in bond distance.^{27,28}

In 1 (and 2), C2–C3 are indeed stretched ca. 0.02 Å, according to MM2 calculations (and also MNDO calculations). However, MM3 predicts 0.04 Å. The data of Table 1 show that the deviation of the observed 3J from predicted *J*'s is slightly larger than 10%.

An adjustment to the calculation program LACA used to predict *J* values for the effect of bond lengthening due to steric hindrance seems to take care of the bulk of the *tert*-butyl effect. The following correction was used:

(25) (a) Imai, K.; Osawa, E. *Magn. Res. Chem.* 1990, 28, 668. (b) In a subsequent publication, Osawa, E.; Ouchi, T.; Saito, N.; Yamato, M.; Lee, O.-S.; Seo, M.-K. *Magn. Res. Chem.* 1992, 30, 1104. Prof. Osawa expresses reservations concerning the technique of refs 25a and of the present paper, citing errors as high as 1 Hz between observed and calculated coupling constants. We consider error ranges of that magnitude acceptable progress toward refining the technique.

(26) (a) Pople, J. A.; McIver, J. W., Jr.; Ostlund, N. S.; *J. Chem. Phys.* 1968, 49, 2960; 1968, 49, 2965 (b) Ostlund, N. S. Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN, QCPE no. 224.

(27) In theory, the C–H bond distance should also effect the magnitude of H–C–H coupling. MM2(3) did not indicate much variation in C–H distances. Other reports suggest that some changes do occur: Wolfe, S.; Pinto, B.; Varma, V.; Leung, R. *Can. J. Chem.* 1990, 68, 1051; cf. Schafer, L.; Siam, K.; Ewbank, J.; Osawa, E. *THEOCHEM* 1986, 32, 125. Anet, F. A. L.; Bourn, A. J. R.; Carter, P.; Winstein, S. *J. Am. Chem. Soc.* 1965, 87, 5249. Imai and Osawa (ref 25) have discarded this term, finding it of little benefit in improving the fit of calculated and observed coupling constants.

(28) FINITE calculates only the Fermi contact contribution and not orbital motion, etc. terms, which are believed to be small. Jameson, C. J.; Mason, J. *Multinuclear NMR*, Mason, J.; Jameson, C. J., Eds., Plenum Press: London, 1987; p 10.

$$J_c = J_o - J_o[0.5(B_L - B_o) + 300(B_L - B_o)^2]$$

where B_L is the bond distance given by MM2 for the C-C bond lying along the H-C-C-H coupling pathway. B_o is the unperturbed bond distance from MM2. If MM3 is used, the coefficients should be reduced, as larger $B_L - B_o$ deviations are predicted.

Using the bond distance correction, for 1, predicted 3J_T is reduced from 10.7 to 10.2 Hz (observed $^3J = 9.7$ Hz), whereas for 3J_G less of an improvement is found (1.3 to 1.2 Hz; observed, 0.5 Hz). For *meso*-3,4-dichloro-2,5-dimethylhexane (8), where the central bond is lengthened 0.04 Å, 3J changes from a predicted 7.5 to 5.0 Hz (observed $^3J = 5.2$ Hz). For 2,5-dimethyl-3-hexanol (9), 3J_T changes from a predicted 9.5 to 8.3 Hz (observed $J = 8.0$ Hz). For 3J_G , the change again is not as pronounced, i.e., from a predicted 2.3 to 2.0 Hz (observed $^3J = 1.8$ Hz).

With regard to bond angle changes, Karplus made an estimate of the effect of variations in bond angle on 3J .²⁴ In the basic Karplus equation, $J = A + (B)\cos\phi + (C)\cos(2\phi)$, the following adjustments for angular deformations were used: $A = 4.2 - 0.1(\delta\phi)$; $B = -0.5 - 0.05(\delta\phi)$; $C = 4.4 - 0.12(\delta\phi)$, where $\delta\phi$ is the variation in bond angle for the coupled hydrogen from the standard value. A rather large change in 3J is predicted for a 10-deg variation in bond angle, namely -20% for anti hydrogens or -36% for gauche hydrogens. In more recent work, Imai and Osawa also use a substantial correction: $-0.2058\{(\omega_1 + \omega_2)/2 - 110\}$.²⁵

FINITE calculations predict a more complicated dependence of 3J on bond angle (Chart 3). As the bond angle is widened for one coupled hydrogen (all other atoms held constant in position), couplings of gauche hydrogens generally decrease, but couplings of anti hydrogens increase. A more complicated effect is seen when the bond angle to the OH function of ethanol is widened, keeping the geometry of all C-H groups constant. Gauche hydrogens may undergo an increase or a decrease in 3J depending upon the orientation (gauche or anti) with respect to hydroxyl. The effect is rather large compared to the effects of bond angle variations of the coupled hydrogens themselves. Widening the C-C-C bond of propane also results in a positive correction for 3J_T and one 3J_G , similar to the data for ethanol.

Neither the MM2 nor the MM3 force field indicates that much angle bending is present for the hydrogen attached to *C-tert*-butyl in 1 and 2, although the C-C-*tert*-butyl angle does flatten. Along the H-C-C-H coupling path, the bond angles for hydrogens are not distant from 109°, e.g., for 2, the deviation is 0.6° in the major conformer. No correction for bending was attempted in LACA at the present time in view of the complexity of the phenomenon predicted by FINITE, plus the small deviations from 109° in 1-3.

Experimental Section

2-(1,1-Dimethylethyl)cyclohexanone Oxime. A mixture of 5.0 g (0.032 mol) of 2-(1,1-dimethylethyl)cyclohexanone and 5.0 g (0.072) of hydroxylamine hydrochloride in 20 mL of water was refluxed for 1 hour. Crystals appeared upon cooling, which were filtered and air-dried, giving 4.8 g of crude product, mp 61-63 °C (lit.²⁹ mp 71-72 °C). Two isomers were evident in the NMR spectrum, which were not separated.

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Chart 3. Effect of Bond Angle Changes on NMR Coupling Constants

staggered ethane							
θ	$^3J_{12}$	$^3J_{13}$	θ	$^3J_{1,2}$	$^3J_{1,3}$		
101.9°	4.0	21.8	116.9	3.7	22.6		
106.9	3.9	22.0	121.9	3.7	23.1		
111.9	3.8	22.3					
ethanol (OH anti to coupled H)							
θ	$^3J_{1,3}$	θ	$^3J_{1,3}$				
101.32	2.6	116.32	2.3				
106.32	2.5	121.32	2.2				
111.32	2.3	126.32	2.2				
ethanol (OH gauche to coupled H)							
θ'	$^3J_{2,3}$	$^3J_{2,4}$	θ'	$^3J_{2,3}$	$^3J_{2,4}$		
95.0	4.5	19.8	115.0	3.8	21.4		
100.0	4.3	20.2	120.0	3.7	21.9		
105.0	4.1	20.6	125.0	3.6	22.5		
110.0	3.9	21.0					
ethanol (bending involves OH function)							
θ''	$^3J_{1,3}$	$^3J_{2,3}$	$^3J_{2,4}$	θ''	$^3J_{1,3}$	$^3J_{2,3}$	$^3J_{2,4}$
94.7	1.4	4.2	18.3	114.7	2.8	3.6	22.4
99.7	1.7	4.0	19.4	119.7	3.3	3.5	23.4
104.7	2.0	3.9	20.4	124.7	3.4	3.4	24.5
109.7	2.3	3.7	21.4				

Compounds 1 and 2 were prepared by placing 2.0 g (0.012 mol) of the oxime precursor in a 50-mL flask with 4 mL of sulfuric acid (5:1 H₂O:concentrated H₂SO₄). The black reaction mixture was heated slowly with magnetic stirring on a low-heat hot plate until a uniform appearance of bubbles was evident. The solution was cooled in an ice bath to below 10 °C, and 24% sodium hydroxide solution was slowly added to low temperature until the mixture was basic. The inorganic precipitate was removed by filtration and washed with chloroform. The filtrate was extracted with 5 × 20 mL of chloroform. The combined chloroform extracts were concentrated by distilling off solvent. The residue formed white crystals which were air-dried, giving a mixture of caprolactams, mp 61-63 °C. The isomers were separated by column chromatography on silica gel. Compound 2 was eluted with 60% cyclohexane-40% ethyl acetate, giving 0.4 g (20% yield), mp 154.3-154.8 °C as white crystals. Compound 1 was eluted with 40% cyclohexane-60% ethyl acetate, giving 1.1 g (55%) of white crystals, mp 127.3 °C. MS for 2 (C₁₀H₁₉NO): m/z 169.1462 (-2.7 ppm), base peak (C₁₀H₁₁NO) m/z 113.0842 (+0.9 ppm); for 1, MS: (C₁₀H₂₀NO, M + H⁺), 170.1538 (-4.12 ppm); base peak (C₇H₁₄N) m/z 112.1127 (+0.39 ppm). This rather strange difference between isomers (one giving an ordinary molecular ion, and the other giving only [M + 1] persisted in repeated trials. Positive ion low resolution FAB also showed $m/z = 170$. In addition to the NMR data shown in other tables, for 2: ¹³C NMR (CDCl₃) δ 179.3 (C₂), 52.2 (C₃), 25.7 (C₄), 29.5 (C₅), 29.9 (C₆), 42.0 (C₇), 32.8, 27.5 (*tert*-butyl) (tentative assignments); for 1: ¹³C NMR δ 177.2 (C₂), 36.3 (C₃), 23.3 (C₄), 29.7 (C₅), 30.4 (C₆), 62.9, and 33.5, 26.5 (*tert*-butyl) (tentative assignments).

7-Methylhexahydro-2H-azepin-2-one (3) was prepared similarly. In this case only a single isomer was isolated by crystallization: needles, mp 89.0-90.5 °C (lit.³⁰ mp 90-91 °C).

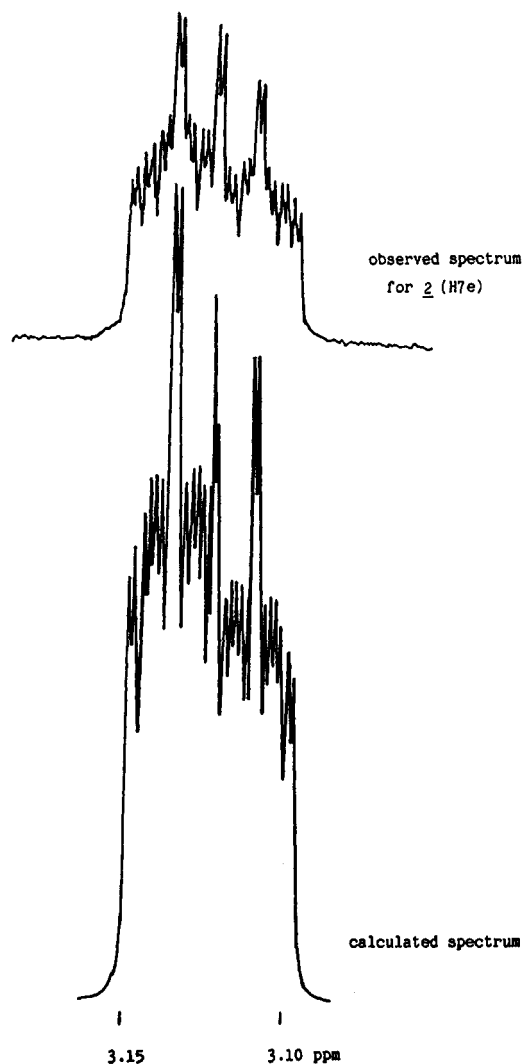


Figure 2. H7e pattern of 3-(1,1-dimethylethyl)hexahydro-2H-azepin-2-one (2), and the LAOCON simulation. Small splittings are long-range couplings to equatorial hydrogens.

Spectra. The ^1H -NMR spectra of 1–3 were run at the Colorado State University Regional NMR Center, on a Bruker 600-MHz instrument using a 32768-pt. data table for a spectral width of 6024 Hz, leading to ± 0.368 Hz as a formal error function for line position. However, modern instruments in fact do considerably better because of peak-matching characteristics. Since the Colorado facility did not provide digital peak lists, it was necessary to simulate the spectra in an analog manner. This was done using the LAOCON-based spectrum calculation program of the Nicolet EM 360 spectrometer. Parameters were varied until the calculated spectrum was superimposable on the original spectrum (suitably expanded for regions in question, cf. Figure 2). The error in line positions was less than 0.1 Hz for 1. For 2, the overlapping of resonances for axial hydrogens (not all of which could be simulated at once) necessitated fitting only the noninterfering parts of the pattern. The uncertainty is somewhat

greater for these hydrogens. For 3, particular difficulty was encountered with the resonances for H7e and H7a, as well as for two of the axial hydrogens, which overlapped. However, the error in line position is still less than 0.2 Hz for the clear parts of the spectrum for these protons. Usually the error in line position was less than 0.1 Hz. Some of the data were obtained in benzene- d_6 solution, and the data transferred with some modifications to CDCl_3 (as solvent) spectral simulations. A few of the simpler simulations were run using LAOCON-5 on a personal computer.³¹ COSY spectra, used to aid connectivity assignments, were run on a Nicolet EM 360 instrument.

Calculations. The MMX calculations (PCMODEL³² version 3.0) were the most troublesome, tending to give different results in different trials on the same molecule by sizable factors. MM+, AMBER, BIO+, and OPLS are of the HyperChem calculation package,³³ run on a 486 personal computer. There were some problems with consistency in different trials on the same molecule with the HyperChem version of AMBER, BIO+, and OPLS. These data are shown for rough comparison purposes only. However, MM+ (HyperChem) was nicely consistent. The molecular mechanics program utilized MM2(87) run on a VAX system. The following parameterization was used in addition to parameters native to the program. Torsional parameters: C–C–N–lp, C–C(O)–N–lp, O=C–N–lp, each $V_1 = 0.0$, $V_2 = 0.0$, $V_3 = 0.0$; stretching parameter, N–lp, $K_s = 6.2$, $L(\text{O}) = 0.5$; bending parameters, H–N–lp, $K(\text{B}) = 0.3$, $\theta = 105.0$; C–N–lp, 0.3, 114.0; C–C–N, 0.5, 109.5; C(O)–N–H, 0.35, 90. The MM3 calculations (1990 version), although not requiring the assumption of parameters, gave less reasonable results in our hands. Using MM2 parameters for the amide function in MM3 partially improved the fit of 3 to ax–eq energy differences by NMR. Early work using MM2(77) gave somewhat similar data as MM2(87), yielding better agreement in J for some pairs of hydrogens, but worse in others.

The AM1 and PM3 calculations^{16,34} were derived from MO-PAC6, run on a Silicon Graphics IRIS system. The AM1 (hexadecane) calculations, which attempt to emulate the effects of this solvent, were run using Spartan³⁵ on a Silicon graphics IRIS system.

In using LACA to establish predicted NMR coupling constants, the dihedral driver option of MM2 was used to rotate each bond in question 30° on either side of a predetermined conformational energy minimum in 5-deg increments. Thus, if the coupling constant between H6a and H7a were to be determined, the C6–C7 bond was rotated, etc. This was done for each major conformer, eq-chair, ax-chair, eq-boat, ax-boat. Those contributing conformations within 2 kcal of the absolute energy minimum were used in the final LACA calculations. Generally, about 20–30 contributing conformations were used in the calculations of coupling constant.

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