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Dynamic and Static Conformational Analysis of Acylated Tetrahydrobenzazepines

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A detailed high-field NMR analysis of several acylated tetrahydrobenzazepines, supported by molecular mechanics calculations, indicates that the heterocyclic ring in these compounds exists in a chair conformation, with the carbonyl oriented *anti* to the aryl moiety in the dominant rotamer. Surprisingly, ring methylenes are typically diastereotopic at room temperature, as the barriers for the process of enantiomerization of the seven-membered ring are much higher than expected. It is shown that ring inversion is correlated (but not concerted) with rotation of the amide moiety, as the carbonyl is forced out of conjugation with the nitrogen in the transition state.

Introduction

Several years ago, we published a paper[1] noting a quite unusual feature in the ^{1}H NMR spectra of acylated tetrahydrobenzazepines such as **1**: *one* of the protons on the *N*-methylene was very deshielded (δ 4.70), appearing ca. 2 ppm downfield from the next lowest field aliphatic proton signal. This was recognized as a result of the anisotropic effect of the amide carbonyl function, which is oriented *syn* to C-2. An even more surprising consequence of this observation is that the protons on the seven-membered ring must be diastereotopic, and therefore, ring flipping to the enantiomeric structure is slow at room temperature. The activation barrier for this process is thus several kilocalories per mole higher than expected for a nonconstrained aliphatic ring (e.g., the barrier for the enantiomeriztion of benzocycloheptene[2a] is 11 kcal·mol^{-1}, vide infra). In view of the intervening great advances in NMR instrumentation, we decided to reexamine this series of compounds in more detail.

Results and Discussion

Ground-State Structure. Room temperature NMR data for compounds **1**−**11** are presented in Tables 1−3. We will describe in more detail acetamide **1**, but the similarities in the spectral features, and especially the H−H coupling constants, when measurable, indicate that, unless otherwise noted, the conclusions reached for this amide are valid also for the others.

First, the spectrum is dominated by one major acyl rotamer. There is a minor isomer, for which only the methyl singlet is clearly visible in the ^{1}H spectrum (3% relative abundance, at δ 2.30 vs δ 1.86 for the major rotamer in $CDCl_3$). Irradiation of the signal at δ 1.86 results in a 3% nuclear Overhauser enhancement of H-9 at δ 7.19, showing that, in the major rotamer, the carbonyl is oriented *syn* to C-2. Shielding by the aromatic ring current evidently contributes to the unusually high field absorption of the acetate methyl group in this conformer.

Second, we define the geometry of the seven-membered ring. For that, we must eliminate multiplet overlap and second-order effects, so that vicinal $^3J_{HH}$ values can be measured. In the case of **1**, we examined the ^{1}H NMR, at 600 MHz, in a mixture of $CDCl_3$ and C_6D_6, which provided a well-separated first-order spectrum. With the help of 2D techniques such as COSY and HMQC, we were able to fully assign the chemical shifts of all the protons in this molecule, as well as the values of the coupling constants between them (see Tables 1 and 2; ^{13}C chemical shifts are presented in Table 3). As a convention, both in the tables and in the rest of the paper, the amide moiety is considered to be α-oriented, i.e., below the plane of the seven-membered ring. We found a 2% enhancement of H-4β (δ 1.12) upon irradiation of the 2β signal (δ 2.35), indicating that these two protons are both pseudoaxial and on the same side of the molecule; this observation helps to distinguish protons on either of the two faces of the molecule.

We then determined the lowest energy conformation of **1** with molecular mechanics[3] (see the Experimental Section); as seen in Figure 1, this conformer has the carbonyl *syn* to C-2 (vide supra). Experimental and calculated coupling constants were in very good agreement (Table 4), indicating that the conformation in the ground state is indeed a chair. This is consistent with literature data for similar ring systems.[2,4−6] The next lowest energy conformation for this amide rotamer (found

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TABLE 1. ^{1}H NMR Chemical Shifts for 1−11

H	**1**[a]	**1**[b]	**2**[c,d]	**3**[e,f]	**3**[e,g,h]	**4**[c,i]	**5**[a]	**5**[a,g]	**6**[a]	**7**[a]	**7**[a,g]	**8**[a,l]	**9**[a]	**10**[a]	**11**[c]
2α	4.70	4.69	5.05	4.45	4.34	4.50	5.43	4.75	4.65	4.75	4.70	4.69	4.54	4.47	4.82
2*β*	2.60	2.35	2.91	2.79	2.83	2.62	3.11	2.90	2.64	2.60	2.78	2.62	2.37	2.68	3.11
3α	1.90	1.86	1.99	1.90		1.60	2.38	2.40	1.95	1.96		1.95	1.10[m]	1.98	1.80
3*β*	1.76	1.52	2.11	1.83		1.83	1.77	1.86	1.76	1.83		1.80	0.90[m]	1.32	2.25
4α	2.00	1.70	1.99	1.99		1.90	2.02	1.12	1.98	2.07		2.04	1.58	1.05[m]	2.78
4*β*	1.35	1.12	1.51	1.38		1.29	1.48	1.57	1.28	1.46		1.39	1.30	0.65[m]	2.59
5α	2.75	2.54	3.05	2.72	2.70	2.49	2.35	2.57	2.25	2.88[k]	2.62	2.80	2.97	2.81	
5*β*	2.70	2.40	2.76	2.72	2.70	2.69	2.73	2.90	3.36	2.85[k]	2.71	2.80	2.53	2.18	
6	7.23		7.26	7.20	7.20	7.18	7.23			8.17		7.94	7.23	6.80	7.88
7	7.23		7.12	7.20	7.20	7.18	7.23		6.84[k]			7.34	7.23	2.25[m]	7.64[k]
8	7.23		6.92	7.20	7.20	7.18	7.23		7.16	8.12	8.08		7.23	6.94	7.50[k]
9	7.19		6.64	7.20	7.20	7.02	7.05		6.75[k]	7.32	7.35	7.80	7.08	2.15[m]	7.26
C*H*$_3$CO	1.86						2.37[j]	2.90[j]	1.87	1.90	2.34	1.88	1.80	1.78	1.94

[a] At 297 ± 2 K in $CDCl_3$. [b] At 297 ± 2 K in 2:3 $CDCl_3/C_6D_6$. [c] At 180 ± 2 K in CD_2Cl_2. [d] Benzoate: *δ* 7.20 (*o, m*), 7.26 (*p*). [e] At 255 ± 2 K in $CDCl_3$. [f] EtO: *δ* 4.22, 4.04, 1.18. [g] Minor isomer. [h] EtO: *δ* 4.23, 1.35. [i] CHO: *δ* 8.14 (major isomer) and 8.21 (minor isomer). [j] CH_3CS. [k] Values in the same column may be interchanged. [l] 5% MeOH added for solubility. [m] Methyl groups.

TABLE 2. J_{HH} Values for 1−11[a]

J	**1**	**2**	**3**	**4**	**5**	**5**[b]	**6**	**7**	**8**	**9**	**10**	**11**
2α,2*β*	13.3	13.5	14	13.5	13	13.5	13.2	13.5	13.5	13.2	14	13.5
2α,3α	3.6		4	3	3.5		3.5	3.5	3.5		4	8.5
2α,4α	1.3		1		1	1	1.0	1		2.2		
2α,3*β*	3.6		4	3	3.5	4	3.5	3.5	3.5		4	7
2*β*,3α	12.4		14	13.5	12.5	12	12.0	12.5	12		12	0.5
2*β*,3*β*	2.2	2	2		2	3.5	2.0	2			2	7
3α,3*β*	14.1	14	15	14	14.5	3.5	14.0		14		14	16.5
3α,4α	3.6		3	3	3.5	14	3.5		3			2.5
3α,4*β*	12.5	12	12	13	12.5	12.5	12.0	12.5	12			13
3*β*,4α	3.9	3			3.5		3.5		3.5			5
3*β*,4*β*	3.3	1			3.5		3.5	3	3.5			3.5
3*β*,5*β*	1.2								2.5			
4α,4*β*	13.8	13	14	14	14		14.0	14	14	13.8		16
4α,5α	2.1	2		1.5	3.5	2	1.8	2	4	1.7		
4α,5*β*	6.2	3	6	6			6.0	6	4	6.6		
4*β*,5α	12.5	12		13	13	12.5	12.5	12.5	13	13.2		
4*β*,5*β*	1.8				3.5		1.8	2.5		1.7		
5α,5*β*	14.0	13	13.5	13	13.5	15	14.0	14		14.2	14	
6,7		7.5							8			7.5
6,8		0.5						2			0.5	1.5
7,8		7.5					8.0					7.5
7,9		1.5					0.5		1.5			1.5
8,9		7.5					8.0	8				7.5

[a] For solvent and temperature, see Table 1; data refer to the major rotamer, unless otherwise indicated. [b] Minor isomer.

TABLE 3. ^{13}C NMR Chemical Shifts for 1−11

C	**1**[a]	**2**[b,c]	**3**[d,e]	**3**[d,f,g]	**4**[a]	**4**[a,f]	**5**[a]	**6**[a,h]	**7**[a]	**8**[a,i]	**9**[a,j]	**10**[a,k]	**11**[b]
2	42.40	47.40	48.75	48.90	44.74	49.63	54.66	47.06	47.00	47.09	55.45	42.40	45.11
3	28.91	30.14	29.55	30.11	29.17	32.79	26.72	28.86	28.65	28.65	35.59	41.23	22.81
4	26.40	26.14	26.22	26.22	26.31	25.63	26.56	25.56	25.84	25.84	40.08	31.36	39.55
5	34.34	35.12	34.63	34.58	34.72	34.67	33.78	24.03	34.55	34.55	29.98	46.60	202.86
5a	140.41	139.11	139.75	139.75	140.03	140.03	138.36	129.09	142.32	145.94	140.54	137.89	134.92
6	130.00	130.05	129.74	130.01	130.44	130.36	130.34	157.37	125.69	130.41[l]	129.29[l]	129.56	133.72
7	127.43[l]	127.02	127.99[l]	128.04[l]	126.03[l]	126.03[l]	127.48[l]	119.58	146.82	129.02[l]	127.30[l]	134.17	128.49
8	127.80[l]	126.80	126.95[l]	127.06[l]	127.87[l]	127.70[l]	128.71[l]	127.04	122.65	129.93	127.66[l]	129.80	129.63
9	127.34[l]	128.20	126.54[l]	126.85[l]	127.38[l]	127.01[l]	125.66[l]	110.02	129.68	129.66[l]	127.12	137.24	128.27
9a	143.60	143.95	142.08	142.61	141.57	141.41	145.05	144.99	149.38	143.61	143.87	139.40	141.19
R*C*ON	170.10				161.94	162.20	199.69[m]	169.69	168.62	170.10	170.18	170.05	170.66
*C*H$_3$CO	22.50						34.22[m]	22.38	22.69	22.56	22.83	21.54	21.23

[a] At 297 ± 2 K in $CDCl_3$. [b] At 255 ± 2 K in $CDCl_3$. [c] Benzoate: *δ* 135.86 (*i*), 127.87 (*o*), 127.67 (*m*), 129.56 (*p*). [d] At 276 ± 2 K in $CDCl_3$. [e] EtOCO: *δ* 14.65, 61.41, 154.92. [f] Minor isomer. [g] EtOCO: *δ* 14.73, 61.47, 155.33. [h] MeO: *δ* 55.86. [i] 5% MeOH added for solubility. CO_2H: *δ* 168.09 [j] 3-Me$_2$: *δ* 23.83, 29.37. [k] Me groups: *δ* 32.89 (4α), 24.54 (4*β*), 21.54 (7), 17.49 (9). [l] Values in the same column may be interchanged. [m] CH_3CS.

with the GMMX subroutine of PCModel, which performs a random search for low-lying conformers) is a boat, 2.7 kcal·mol^{-1} higher in energy than the chair, and therefore not significantly populated. It is important to note that, in the ground state, *the amide function and the aromatic ring are not coplanar; for* **1**, *the calculated dihedral angle between the planes containing these moieties is 74°*. The lowest energy conformer with the carbonyl *anti* to C-2 (corresponding to the minor amide rotamer) is a very similar chair. It is 1.5 kcal·mol^{-1} higher in energy than

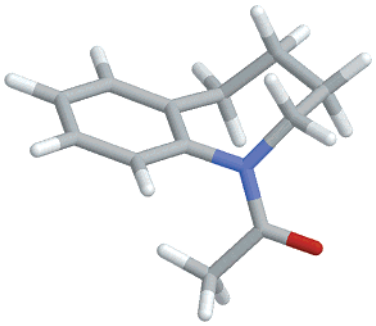
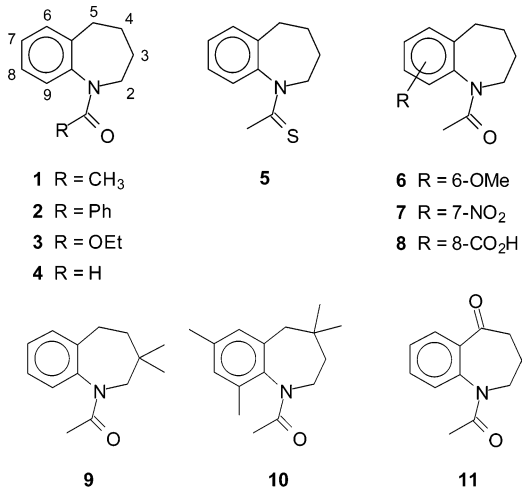


FIGURE 1. Calculated minimum conformation for acetamide **1**.

TABLE 4. Calculated vs Experimental Vicinal Coupling Constants for 1

H−C−C−H		calcd (MM3) dihedral angle/deg	$^3J_{HH}$	exptl $^3J_{HH}$
2α	3α	66	1.9	2.2
2α	3β	178	12.4	12.4
2β	3α	50	4.2	3.6
2β	3β	66	2.3	3.6
3α	4α	61	2.8	3.3
3α	4β	55	3.8	3.9
3β	4α	177	13.2	12.5
3β	4β	60	2.9	3.6
4α	5α	75	0.9	1.8
4α	5β	180	12.8	12.5
4β	5α	41	6.6	6.2
4β	5β	74	1.0	2.1



the global minimum (experimental value 2.1 kcal·mol^{-1} at rt; see Table 6).

Dynamic Transformations. We determined the barriers for the ring-flipping process that converts the seven-membered rings of **1**−**5**, **7**, **9**, and **11** to their enantiomeric forms by dynamic NMR. Specifically, we simulated the coalescence of the protons of the methylene adjacent to nitrogen (see Table 5 and the Experimental Section) in the temperature-dependent ^{1}H NMR spectra. As expected, entropies of activation are not large, and therefore, $\Delta G^{\ddagger}$ values for different compounds can be compared even though they may have been measured at different temperatures.

Since the ground-state conformations of all the acylated tetrahydrobenzazepines are quite similar (vide supra), one might have expected that the barriers for ring inversion would also be close. This is clearly not the case (see Table 5). Instead, the activation barriers, which are in the order thioacetyl (**5**) > acetyl (**1**) > benzoyl (**2**) > urethane (**3**), parallel the values for the well-known process of amide-type rotation, e.g., 24.1 (*N*,*N*-dimethylthioacetamide), 18.2 (*N*,*N*-dimethylacetamide), 15.0 (*N*,*N*-dimethylbenzamide), and 14.8 kcal·mol^{-1} (*N*,*N*,*O*-trimethylurethane) kcal·mol^{-1}.[7] It is tempting to postulate, therefore, that amide rotation and ring flip are aspects of one concerted process. To validate this proposition, one has to find if the rate of amide rotation (from the major to the minor conformer) for these compounds is the same as the rate of ring flip.

TABLE 5. Dynamic-NMR-Derived Kinetics for Ring Inversion of Tetrahydrobenzazepines

T/K	*k*/s^{-1}	Δ*G*/kcal·mol^{-1}	*T*/K	*k*/s^{-1}	Δ*G*/kcal·mol^{-1}
		1[a]			
335.9	16	18.0 ± 0.3	385.3	500	18.1 ± 0.1
352.9	90	17.7 ± 0.2	404.0	1450	18.2 ± 0.1
368.0	165	18.1 ± 0.2	422.4	4000	18.2 ± 0.3
		2[a]			
335.9	400	15.7 ± 0.4	385.3	7000	16.0 ± 0.2
352.9	1400	15.7 ± 0.4	404.0	15000	16.2 ± 0.2
368.0	2200	16.1 ± 0.3			
		3[b]			
274.6	9	14.8 ± 0.3	296.4	95	14.7 ± 0.2
283.0	29	14.6 ± 0.2	315.5	300	14.9 ± 0.1
		4[c,d]			
214.3	30	11.0 ± 0.2	250.1	800	11.3 ± 0.2
231.2	180	11.1 ± 0.2	297.5	20000	11.6 ± 0.3
		4[c,e]			
214.3	50	10.8 ± 0.2	250.1	1700	10.9 ± 0.3
231.2	350	10.8 ± 0.2	297.5	40000	11.2 ± 0.3
		5[a]			
353.0	3.5	19.9 ± 0.4	394.5	25	20.8 ± 0.2
373.5	8	20.5 ± 0.3	415.1	70	21.1 ± 0.2
		7[a]			
297.0	12	15.9 ± 0.3	353.0	900	16.0 ± 0.1
320.7	100	15.9 ± 0.2	394.5	11500	16.0 ± 0.1
337.5	350	15.9 ± 0.1	415.1	25000	16.2 ± 0.2
		9[a]			
335.9	75	16.9 ± 0.3	385.3	1500	17.1 ± 0.2
352.9	300	16.8 ± 0.2	404.0	3500	17.3 ± 0.2
368.0	500	17.2 ± 0.2	422.4	9000	17.4 ± 0.3
		11[b]			
250.1	3	14.1 ± 0.3	320.7	700	14.6 ± 0.1
297.0	150	14.4 ± 0.2	337.5	2700	14.5 ± 0.1

[a] In C_6D_5Br. [b] In $CDCl_3$. [c] In CD_2Cl_2. [d] Major amide rotamer. [e] Minor rotamer.

The rotation rate was, therefore, measured by NMR for compounds **1**, **3**−**5**, and **10**; the kinetic data obtained are presented in Table 6. The main technical difficulty was the small relative population of the rotamer with the carbonyl *anti* to C-2.

Among these compounds, the minor isomer is present in the highest proportion for urethane **3**. We followed the rotation process through the line shape analysis of the coalescence of the C-3 signal. As the data in Table 6 indicate, the rotation of the carbamate moiety is significantly slower than the ring flip, with a difference in barriers of 1 kcal·mol^{-1} or more. For acetamide **1**, where

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TABLE 6. Dynamic-NMR-Derived Kinetics for Amide Rotation of Tetrahydrobenzazepines[a]

T/K	K	ΔG_0/kcal·mol^{-1}	k/s^{-1}	ΔG/kcal·mol^{-1}
		1[b,c]		
299.2	0.029	2.09	0.016[d]	20.0 ± 0.1
335.9	0.028	2.40	1.5	19.5 ± 0.5
352.9	*0.028*	*2.49*	17	18.8 ± 0.4
368.0	*0.027*	*2.64*	40	19.0 ± 0.3
385.3	*0.027*	*2.76*	50	19.8 ± 0.3
404.0	*0.026*	*2.93*	100	20.1 ± 0.4
422.4	*0.025*	*3.08*	200	20.6 ± 0.4
		3[e,f]		
283.0	0.39	0.53	7.5	15.5 ± 0.4
296.4	0.42	0.52	14	15.9 ± 0.3
315.5	0.43	0.52	47	16.2 ± 0.2
332.5	*0.47*	*0.49*	157	16.3 ± 0.2
		4[b,g]		
353.0	0.13	1.47	1	21.3 ± 0.4
373.5	0.14	1.45	3	21.4 ± 0.3
394.5	*0.17*	*1.41*	14	21.4 ± 0.2
415.1	*0.18*	*1.40*	49	21.5 ± 0.2
		5[e,h]		
367.0	0.031	2.53	0.064	23.6 ± 0.1
		10[b,i]		
352.5	0.076	1.79	0.2	22.0 ± 0.5
385.3	0.080	1.93	1.2	22.7 ± 0.4
404.0	*0.088*	*1.95*	7	22.5 ± 0.3
422.4	*0.095*	*1.97*	38	22.1 ± 0.4

[a] Unless otherwise indicated, obtained by line shape analysis (see the Experimental Section); values of K and ΔG_0 in italics are extrapolated. [b] In C_6D_5Br. [c] Coalescence of the acetate ^{1}H signals. [d] Obtained by EXSY;[8] mixing time 1.5 s. [e] In $CDCl_3$. [f] Coalescence of the C-3 signals. [g] Coalescence of the formate ^{1}H signals. [h] Obtained by EXSY using the thioacetate ^{1}H signals; mixing time 0.5 s. [i] Coalescence of the H-8 signals.

the minor isomer constitutes only 3% of the mixture, such a measurement is technically more demanding, but we were still able to follow the coalescence of the acetate singlets in the ^{1}H spectrum. Since the error margins were larger than we would like, we also obtained the acetyl rotation barrier, at rt, by the two-dimensional EXSY technique.[8] The latter experiment was likewise performed for thioacetamide **5**. Unambiguously, for **1**, **3**, and **5**, the rate of amide rotation is significantly slower than that of the seven-membered ring inversion, with energy barriers higher by 1.3−2.9 kcal.mol^{-1}.

The two processes cannot, therefore, be concerted, since their kinetic parameters are different. But, as shown above, they also cannot be totally unrelated. The best way to understand these results is to postulate that the processes are correlated but distinct. An examination of molecular structures shows that if the aliphatic ring were to simply invert, at some point of the reaction pathway the amide moiety would have to become coplanar with the aromatic ring, with high steric congestion between the carbonyl and H-9. This potential strain may be relieved by rotating the amide carbonyl partially out of the C-2/N/C-9a plane, but without quite reaching the transition state for full amide rotation.

The details of this process are illustrated in Figure 2. In the ground-state structure, shown at the top left, the methyl group blocks the ring flip. If the acetyl group rotates partially out of the way, however, the ring flip may occur (vertical arrows). Note that this step does not involve amide rotation, as the carbonyl moiety remains pointing to the right-hand side of the molecule. At this stage, the carbonyl can relax back to the ground-state enantiomeric structure. A second, higher energy, process, which results in full amide rotation, is depicted by the horizontal arrows. This explanation rationalizes the parallelism, but not the identity, of the barriers for ring flip and amide rotation.

A nitro substituent, as in **7**, demonstrates the subtlety of the interaction of the two processes. The NO_2 group, in position 7, cannot possibly sterically affect ring enantiomerization. It does, however, reduce the ring-flip barrier by 2 kcal·mol^{-1}. The effect must be electronic: the NO_2 reduces electron density on the amide nitrogen, reducing conjugation with the carbonyl. As explained above, lowering of the amide rotation barrier also reduces the barrier for ring flip.

The situation is different for formamide **4**. In the room temperature ^{13}C spectrum, we can readily identify sharp peaks corresponding to the two rotamers. Their interconversion barrier, ca. 21 kcal·mol^{-1} (Table 6), is typical for formamides (e.g., 20.9 kcal·mol^{-1} for dimethylformamide[7]). In the ^{1}H spectrum, at low temperatures, we can follow the two similar ring-flipping processes. These are very fast (ca. 11 kcal·mol^{-1}), as compared to the other benzazepines in this study, but correspond closely to the barrier reported for benzocycloheptene.[2a] The formamide moiety, with only a hydrogen atom connected to the carbonyl, does not significantly interfere with ring enantiomerization.

Another exception is tetramethyl-substituted **10**, where we can measure amide rotation ($\Delta G^{\ddagger} = 22.4$ kcal·mol^{-1}; see Table 6), but we cannot achieve ring enantiomerization. At 422 K, the proton signals of the geminal methyl groups do not show any broadening, indicating a ring-flip barrier of more than 25 kcal·mol^{-1}. Evidently, the 9-methyl substituent effectively blocks coplanarity of the aromatic ring and amide moieties, and therefore, the ring-flipping process is drastically slowed. Further proof of this is provided, in a preliminary experiment, by the analytical separation of the enantiomers of **10**, achieved on triacetylcellulose by Prof. Albrecht Mannschreck (University of Regensburg). We are grateful for his contribution.

Finally, in the case of keto derivative **11,** the sp^2 carbon in position 5 significantly changes the stereochemistry of the seven-membered ring, as is obvious from the coupling constants shown in Table 2. Compared to that of parent compound **1**, the amide rotation barrier is relatively unchanged, but the barrier for ring inversion is significantly decreased, indicating that the seven-membered ring has become more flexible.

For molecules of even a moderate degree of complexity, several dynamic conformational processes must per force coexist. The natural tendency has been to classify their relationship simplistically: either they are seen to be concerted, i.e., two or more aspects of a single pathway, or they are described as completely independent. It is obvious that these two possibilities are extreme cases of a continuum, and that instances as shown in this work, in which processes are correlated without being concerted, must be more frequent than is generally recognized. Another paper, concerning the eight-membered

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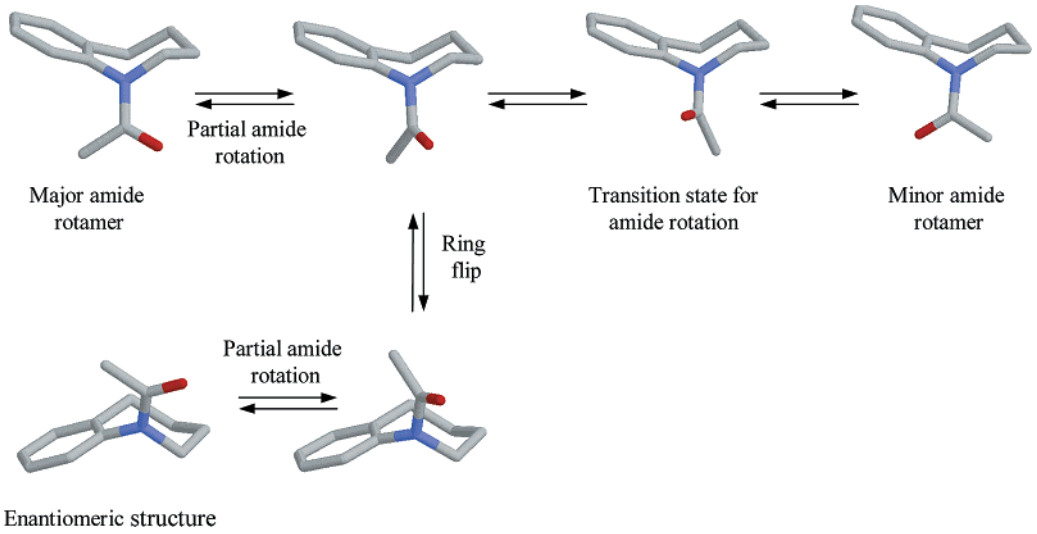

FIGURE 2. Dynamic processes for acetamide **1**. The methyl group of the acetyl moiety blocks direct flipping of the ring. Partial rotation, however, allows the ring to interconvert with its enantiomeric form without reaching the transition state of the full amide rotation.

ring analogues, i.e., hexahydrobenzazocines, is currently in preparation.

Experimental Section

Molecular Mechanics Calculations. Initial ground-state conformations were obtained with PCModel;[3] the structures were optimized with the MMX force field included in this package, which is based on Allinger's MM2 force field. More accurate calculations were then performed with the MM3 force field (versions 1994 and 1996).

NMR Spectroscopy. NMR spectra were run at 600.1 (^{1}H) and 150.9 (^{13}C) MHz. Probe temperatures were measured with a calibrated digital thermometer. Peak assignments in Tables 1 and 3 were unambiguously determined with the aid of two-dimensional techniques such as COSY, HMQC, and HMBC (for example, see pp S1−S5 of the Supporting Information). NMR line shape analyses were performed using computer programs based on the equations of Sutherland[9] (for two coalescing singlets) or of Alexander[10] (for the case of two spin-coupled exchanging protons). For details on EXSY (2D NMR exchange spectroscopy), see ref 8.

Synthesis of Tetrahydrobenzazepines. Compounds **1**,[11,12] **2**,[13] **3**,[14] **8**,[11] and **11**[13,15] have been reported in the literature. For this study, most of these compounds were prepared from the corresponding tetralones either via a Beckmann rearrangement of their oximes or via a Schmidt rearrangement followed by LAH reduction and acylation.

1-Formyl-2,3,4,5-tetrahydro-1H-1-benzazepine (4). A solution of 2,3,4,5-tetrahydro-1*H*-1-benzazepine (5 g, 34 mmol) in 30 mL of 80% formic acid was refluxed for 19 h. The solvent was then evaporated, and the residue, dissolved in 100 mL of ether, was successively washed with 5% $NaHCO_3$, saturated NaCl, 1 N HCl, and saturated NaCl. Evaporation of the ether left the crude formamide as an oil which was distilled (82−85 °C/0.05 Torr) to a low-melting-point solid (3.5 g, 59%). This was purified by double recrystallization from ether/petroleum ether (cooling with dry ice/acetone): mp 32 °C. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.46; H, 7.53.

1-Thioacetyl-2,3,4,5-tetrahydro-1H-1-benzazepine (5) was prepared by the reaction of **1** (1 g, 5.3 mmol) with an equivalent amount of 2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide (Lawesson's reagent) in 7 mL of HMPA, for 2.5 h at 100 °C, according to the established procedure.[16] **5** (0.78 g, 72%) was obtained as pale yellow crystals: mp 75 °C; IR 1460 cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{15}NS$ 205.0925, found 205.0911.

1-Acetyl-6-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepine (6). To a mechanically stirred mixture of 5-methoxytetralone (25 g, 142 mmol) and 400 g of polyphosphoric acid was added NaN_3 (10.5 g, 162 mmol) in small portions during 15 min. The temperature of the mixture was slowly raised to 55 °C and the stirring continued for 19 h. At this point, the mass was poured into an excess of ice−water; the precipitated solid was collected by filtration, washed with H_2O until neutral, dried, and recrystallized from MeOH. The product obtained was 6-methoxy-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (19 g, 70%): mp 162−163 °C.

The lactam (12 g, 63 mmol) was added in small portions to a slurry of $LiAlH_4$ (7.5 g, 197 mmol) in 500 mL of dry ether, and the solution was refluxed for 44 h. Excess hydride was destroyed by portionwise addition of $Na_2SO_4 \cdot 10H_2O$, and the solids were filtered and extracted with 2 × 300 mL of boiling EtOAc. The combined organic solvents were evaporated, and the residue was distilled (73−74 °C/0.03 Torr) to yield 6-methoxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11 g, 98%).

The amine (15 g, 85 mmol) was added to 100 mL of cooled (0 °C) Ac_2O. After 2 h, the solution was allowed to warm to rt and left overnight. Evaporation of the anhydride left crude solid **6**, which was crystallized from hexane/benzene (13.3 g, 72%): mp 124 °C; HRMS *m*/*z* calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1242. Anal. Calcd: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.24; H, 7.88; N, 6.34.

1-Acetyl-7-nitro-2,3,4,5-tetrahydro-1H-1-benzazepine (7) was prepared by nitration of **1** according to the procedure of Meth-Cohn and Suschitzky;[17] the crystalline material obtained had the essentially same melting point (130 °C) as reported (131 °C).[17] However, these authors identify their product as the 9-nitro derivative of **1**. Our analysis of the aromatic ^{1}H coupling pattern shows conclusively that we obtained the

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7-nitro isomer (see Tables 1 and 2 and p S2 of the Supporting Information): HRMS *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.1044, found 234.1030.

1-Acetyl-3,3-dimethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (9). 3,3-Dimethyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one[18] (8 g, 42 mmol) was added in portions to a slurry of $LiAlH_4$ (5 g, 132 mmol) in 250 mL of dry ether, and the solution was refluxed for 41 h. The reaction mixture was treated as described above (cf. **6**), leaving crude 3,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine, which was distilled (70−74 °C/0.03 Torr) to yield a low-melting-point solid which was recrystallized from a minimal amount of petroleum ether (cooling with dry ice/acetone) (6.5 g, 88%): mp 48−49 °C. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.77; N, 7.99. Found: C, 82.04; H, 9.78; N, 7.97.

The amine was acetylated as described above (cf. **6**) to produce an oil which solidified upon trituration with petroleum ether: mp 88−89 °C; HRMS *m*/*z* calcd for $C_{14}H_{19}NO$ 217.1266, found 217.1242. Anal. Calcd: C, 77.38; H, 8.81. Found: C, 77.36; H, 8.83.

1-Acetyl-4,4,7,9-tetramethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (10). A mixture of 3,3,6,8-tetramethyltetralone (16.16 g, 80 mmol), $NH_2OH{\cdot}HCl$ (6.11 g, 88 mmol), 60 mL of pyridine, and 100 mL of EtOH was refluxed for 29 h. The crude solid oxime derivative, obtained by evaporation of the solvents, was dissolved in 400 mL of ether; the organic phase was washed with 200 mL of water and then dilute citric acid. Evaporation of the solvent yielded almost pure oxime, which was recrystallized from MeOH (16 g, 92%). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.22; H, 8.87.

3,3,6,8-Tetramethyltetralone oxime (16 g, 74 mmol) in 250 g of polyphosphoric acid was mechanically stirred while being heated slowly to 130 °C and then left at this temperature for 6 min. The mixture was cooled to 60 °C and poured into ice−water. The crystalline precipitate was extracted with $CHCl_3$ (2 × 250 mL). The organic layer was washed with H_2O and dried, giving almost pure 4,4,7,9-tetramethyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one, which was recrystallized from $CHCl_3$/MeOH to yield pure lactam (14 g, 88%). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.29; H, 8.85.

The lactam (12 g, 55 mmol) was added, in portions, to a slurry of $LiAlH_4$ (7 g, 184 mmol) in 250 mL of dry ether, and the solution was refluxed for 39 h. The reaction mixture was treated as described above (cf. **6**), leaving crude 4,4,7,9-tetramethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine, which was distilled (73−76 °C/0.07 Torr) to yield an oil (10 g, 89%). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.40. Found: C, 82.55; H, 10.39.

The amine (7 g, 34 mmol) was acetylated as described above (cf. **6**) to give an oil that was recrystallized from petroleum ether (cooling with dry ice/acetone). The product obtained was **10** (7 g, 84%): mp 63 °C; HRMS *m*/*z* calcd for $C_{16}H_{23}NO$ 245.1779, found 245.1780. Anal. Calcd: C, 78.32; H, 9.45; N, 5.70. Found: C, 78.29; H, 9.44; N, 5.72.

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Supporting Information Available: ^1H NMR spectra for **5** and **7** (some of the peaks due to the minor amide rotamer are clearly visible) and ^{13}C 1D and several 2D NMR spectra for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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