Theoretical Study of the Structure and Rotational Flexibility of Diacylhydrazines: Implications for the Structure of Nonsteroidal Ecdysone Agonists and Azapeptides

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Abstract: High-level ab initio calculations have been used to determine the minimum energy structures of *N*,*N*′-diformylhydrazine, *N*-methyl-*N*,*N*′-diformylhydrazine, and *N*,*N*′-dimethyl-*N*,*N*′-diformylhydrazine. These calculations show that the global minimum is a nonplanar structure in which the nitrogen lone pairs are essentially perpendicular to one another. However, the energy required for (*Z*,*Z*)-diformylhydrazine to adopt a planar structure is less than 1 kcal/mol (MP2/6-31+G**). This is due to attractive intramolecular hydrogen bonds between the *N*-hydrogens and the carbonyl oxygens in the planar geometry. When one or both amide configurations are inverted (*Z*,*E*; *E*,*E*), or when the nitrogens are substituted, with methyl for example, these hydrogen bonds are lost and the planar structure becomes much less stable relative to the twisted rotamer. Thus, we conclude from these calculations that diacylhydrazines are intrinsically nonplanar with respect to the CO−N−N−CO torsion, and that with the exception of (*Z*,*Z*)-diformylhydrazine the rotational barriers are large. The observation of a planar crystal structure for diformylhydrazine is due to additional intermolecular hydrogen bonds which are available to planar diformylhydrazine in the crystal lattice. Finally, these calculations have significant implications for the structure and dynamical properties of nonsteroidal ecdysone agonists, azapeptides, and azatides which incorporate the diacylhydrazine structure.

Introduction

The structure and rotational isomerism of diacylhydrazines have been topics of significant interest for nearly 30 years.[1−3] The extent to which acylation affects the structure and dynamics of the N−N bond is a critical issue, both from the standpoint of fundamental physical organic principles and for a proper understanding of this functional group in its numerous occurrences in medicinal and agricultural chemistry. It can be argued alternatively that the lone pairs are less repulsive because of resonance with the amide carbonyl, or that the barrier should be larger because of additional eclipsing interactions as a result of the planar amide nitrogens.[2] NMR studies[3] suggest that acyclic diacylhydrazines have twisted ground state geometries with very large, sometimes greater than 20 kcal/mol, barriers to rotation. These rotational barriers are much larger than are typical for alkyl-substituted hydrazines,[4] but virtually all of the rotational barriers measured by NMR are for highly substituted diacylhydrazines with very bulky substituents (e.g., benzyl) at both nitrogens. This has led some investigators[2b] to question whether the NMR experiments are representative of the diacylhydrazine functionality, or simply due to severe eclipsing interactions between the bulky substituents. Attempts to resolve this question by determining the lowest energy structure for the parent diformylhydrazine have met with mixed results. Most of the crystal structures obtained for diacylhydrazines[5] that are not N-substituted give a planar CO−N−N−CO dihedral angle of 180°, but at least one crystal structure[6] and one NMR experiment[7] find a twisted geometry. Thus, it is far from clear what the structure or intrinsic barrier should be for unsubstituted or monosubstituted diacylhydrazines.

There are several theoretical studies[8] of the parent diformylhydrazine which might shed light on the structure of diacylhydrazines. One[8a] is irrelevant because the experimentally observed planar structure[5] was enforced. Jeffrey et al.[8b,c] computed structures and energies for (*Z*,*Z*)-diformylhydrazine (**1**) at the HF/3-21G level, and found that the lowest energy structure has a CO−N−N−CO dihedral angle of 84°. This directly contradicts the crystal structure for **1** which is found by a variety of investigators[5] to be planar (i.e., CO−N−N−CO dihedral angle of 180°). However, the planar (180°) structure is only calculated to be 1.3 kcal/mol less stable than the twisted conformation. More recent calculations[8d] at a higher level of theory give essentially the same results. The 0° planar structure was not evaluated. One could reasonably conclude from this result and from the crystal structure that, in the absence

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of nitrogen substitution, the preferred geometry for diacylhydrazines is twisted, but that the intrinsic barrier to rotation about the N−N bond is very small (1−2 kcal/mol). In this view, the large barriers observed in the NMR experiments can be ascribed to an unfavorable repulsive interaction between the bulky substituents on nitrogen which are forced to be eclipsed in the planar geometry.

Beyond being a question of theoretical interest, the structure and dynamics of substituted diacylhydrazines have taken on increased importance in recent years. This is due to the role this functionality plays in important biological applications such as peptidomimetic azapeptides,[9] and a recently discovered class of nonsteroidal ecdysone agonists.[10] The conformation about the central N−N bond in azapeptides is uncertain, as evidenced by examples with both planar and twisted crystal structures.[11] The CO−N−N−CO dihedral angle and relative barrier are critical information if one is to rationally compare the structure of azapeptides to other peptidomimetics or peptides. This problem is illustrated by the uncertainty surrounding the conformation of novel azatides[12] recently reported by Han and Janda.[9a]

The highly specific insecticidal activity of certain dibenzoylhydrazines[10] has generated significant commercial interest because they are potent agonists of the insect molting hormone ecdysone. This underlies their unique mode of insecticidal activity and generates further interest in the conformational behavior of diacylhydrazines. It is difficult to model these compounds or formulate a meaningful pharmacophore[13] without a better knowledge of the structure and flexibility of the central N−N bond than currently exists.

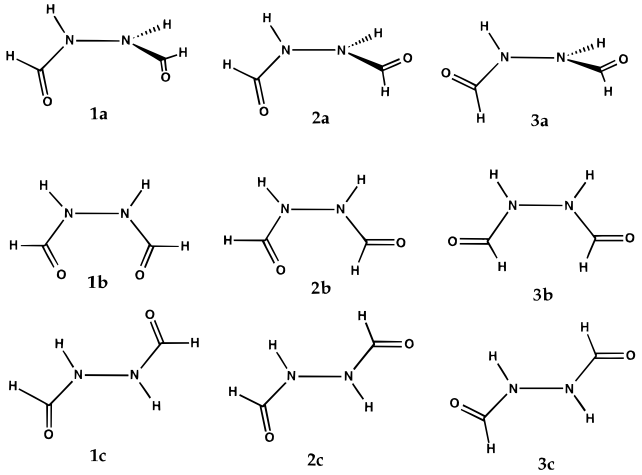
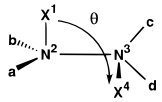


Figure 1. Rotamers of diformylhydrazine.

We have undertaken a more complete theoretical study of the diacylhydrazine structural motif at a consistently high level of theory. Whereas previous calculations[8] focused on the *Z*,*Z* and to a lesser degree *E*,*E* configurations of diformylhydrazine, we examined all of the probable mimima and maxima on the potential energy surface for all three possible configurations (i.e., *Z*,*Z* (**1**), *Z*,*E* (**2**), and *E*,*E* (**3**)). In addition, we have studied the effect of *N*-methyl and *N*,*N*′-dimethyl substitution on the structure and dynamics of diacylhydrazines. These calculations should help sort out the conflicting data for diacylhydrazine structure and dynamics, and are crucial for understanding the structure of azapeptides and the dibenzoylhydrazine-derived ecdysone agonists. The results of these calculations will also provide valuable data for the derivation of molecular mechanics parameters for diacylhydrazine torsional potentials.[14]

Procedure

The Gaussian92 program[15] was used to compute relative energies for eight dihedral angles, θ, about the N−N bond in **1**−**3** (Figure 1). Two dummy atoms (X^1, X^4) were used to define θ so that it would



correspond to the dihedral angle between the nitrogen lone pairs. This is achieved by fixing the angles $X^1-N^2-N^3$ and $X^4-N^3-N^2$ to 90°, and by defining the dihedrals of the nitrogen substituents with respect

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Table 1. Relative Energies[a] (kcal/mol) for Rotamers of **1**−**5**

structure		θ (deg)	HF/6-31G* [b]	HF/6-31+G** [b]	MP2/6-31+G** [b]
Z,Z	**1a**	min	0.0	0.0	0.0
	1b	0	19.7	20.6	17.0
	1c	180	3.2	2.3	0.8
Z,E	**2a**	min	0.0	0.0	0.0
	2b	0	12.7	12.8	10.8
	2c	180	9.7	9.4	7.3
E,E	**3a**	min	0.0	0.0	0.0
	3b	0	17.4	17.7	14.8
	3c	180	13.6	13.9	12.0
Z,Z	**4a**	min		0.0	
	4c	180		7.0	
Z,Z	**5a**	min		0.0	
	5c	180		19.1	

[a] A complete table including total energies for each rotamer is included as supporting information. [b] Energies relative to the minimum energy for **1**−**5**.

to X^1 and X^4. For example, the a−N−N−X^1 and b−N−N−X^1 dihedral angles are constrained by symmetry to have equal magnitudes and opposite signs. Rotamers in which $\theta = 0°$ or 180° have eclipsing lone pairs and are planar, except where pyramidalization at nitrogen causes deviations from planarity.

Where the nitrogens are pyramidal, the degree of pyramidaliztion ϕ is defined using the convention described by Michl.[16] The pyramidalization angle ϕ measures the deviation from planarity for the three nitrogen substituents with respect to a common plane passing through nitrogen.

Each point on the PE surface was computed using the 6-31G* or 6-31+G** basis set. All structures were completely optimized without any assumptions other than constraining the X^1−N−N−X^4 dihedral angle for selected rotamers. A large basis set with polarization functions on all atoms and diffuse functions on the heavy atoms was employed because polarization functions are often required to reproduce correct pyramidalization of nitrogen lone pairs.[17] In addition, any energetic comparisons are likely to be sensitive to interaction between the diffuse adjacent nitrogen lone pairs. The presence of diffuse and polarization functions should allow us to represent these interaction energies more accurately. The 6-31+G** basis set is large enough that it should give excellent results for conformational energies. This was followed by MP2 calculations using the 6-31+G** basis set. Correlation effects are typically small for rotational barriers,[17] but given the potential for a weak intramolecular hydrogen bond and the $\pi-\pi$ interactions in **1**, correlation effects might be significant for the N−N torsion.

Comparison of *Z,Z*; *Z,E*; and *E,E* Minima

Relative energies for selected rotamers of each diformylhydrazine configuration, *Z,Z* (**1**), *Z,E* (**2**), and *E,E* (**3**), are given in Table 1. Associated potential energy surfaces appear in Figures 2, 5, and 6. The relative energies and selected geometrical values for the minima of each configuration, **1a**, **2a**, and **3a**, are given in Table 2. At the HF/6-31+G** level the minima for all three combinations of amide configurations are very close in energy. Structures **1a** and **3a** differ by only 0.1 kcal/mol. The highest energy configuration **2a** is a mere 0.5 kcal/mol less stable than the most stable configuration **1a**. However, inclusion of electron correlation at the MP2/6-31+G** level changes the ordering and magnitudes significantly. At the post-Hartree−Fock level, **1a** is still most stable, but **2a** and **3a** are 1.0 and 1.3 kcal/mol higher in energy than **1a**, respectively. The relative energies for **1a**, **2a**, and **3a** calculated at the MP2/6-31+G** level are in good agreement with experiment.[7,18]

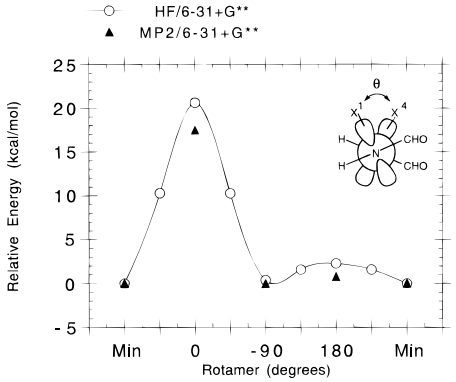

Figure 2. Calculated potential energy surface for the *Z,Z* configuration.

The minimum energy structures of **1**−**3** are all nonplanar and approach orthogonality with respect to the lone pairs. Values of θ range from 90° to 101° (Table 2). This is consistent with previous ab initio calculations[8b−d] for **1** which also gave a nonplanar minimum. Thus, all computational methods attempted so far find that the preferred torsion of the N−N bond approaches 90° with respect to the lone pairs. Furthermore, the *Z,Z* configuration is computed to be more stable than either the *Z,E* or *E,E* configuration at the HF/6-31+G** and MP2/6-31+G** levels.

***Z,Z* Configuration.** The energies of selected points on the torsional potential for **1** (*Z,Z*) are reported in Table 1 and depicted in Figure 2. The curve is highly asymmetric, with a minimum near 90°, a high barrier at 0°, and an extremely low barrier at 180°. This latter barrier varies from 3.2 kcal/mol at the HF/6-31G* level down to only 0.8 kcal/mol at the MP2/6-31+G** level. The result is a broad and extremely flat potential surface. We confirmed that the 180° structure is a true transition state for rotation about the N−N bond by calculating force constants. One imaginary frequency is found as expected, but the magnitude of this imaginary mode is small. This is a direct consequence of the flat potential at 180°, and is consistent with our observation of essentially unrestricted rotation through the 180° structure.

The low barrier for the 180° rotamer **1c** is most likely due to favorable intramolecular interactions between the N−H hydrogens and the carbonyl oxygens. It has been suggested on the basis of the crystal structure[5] and previous MO calculations[8] that there are two significant intramolecular hydrogen bonds in the planar 180° structure (Figure 3, Table 3). At the HF/6-31+G** and MP2/6-31+G** levels the H···O distance is 2.27 and 2.32 Å, respectively. This is consistent with the H···O distance of 2.39 Å observed[8b] experimentally. The fact that this structure is still slightly less stable than the twisted conformation indicates that the favorable electrostatic interactions of **1c** are overcome by the repulsive interaction between the nitrogen lone pairs.

Whereas **1c** benefits from favorable intramolecular electrostatic and hydrogen bonding interactions, **1b** suffers from highly destabilizing nonbonded interactions. Structure **1b** lies 19.7 kcal/mol higher in energy than **1a** at the HF/6-31G* level. At the MP2/6-31+G** level, this difference is smaller, but remains quite large at 17.0 kcal/mol (Figure 2). Rotation between the +90° and −90° conformations would be extremely rapid

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Table 2. Relative Energies (kcal/mol), θ (X−N−N−X Dihedral) (deg), and ϕ (Nitrogen Pyramidalization) (deg) for **1a**, **2a**, and **3a**

	HF/3-21-G			HF/6-31G*			HF/6-31+G**			MP2/6-31+G**		
structure	rel *E*	θ	ϕ	rel *E*	θ	ϕ	rel *E*	θ	ϕ	rel *E*	θ	ϕ
1a (*Z*,*Z*)	0.0	98.8	4.5	0.0	101.3	8.8	0.0	101.4	8.2	0.0	99.2	10.2
2a (*Z*,*E*)	0.1	90.4	2.3, 4.9[a]	0.3	90.7	5.6, 10.5[a]	0.5	91.2	4.7, 9.2[a]	1.0	90.8	4.7, 11.0[a]
3a (*E*,*E*)	−1.0	90.1	2.4	0.0	90.6	6.0	0.1	90.5	5.0	1.3	90.4	4.3

[a] *Z* and *E* configurations, respectively.

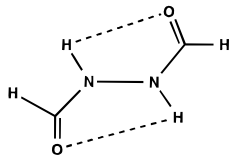


Figure 3. Intramolecular hydrogen bonds in **1c**.

Table 3. Comparison of Calculated and Crystal Structure Geometries (Å, deg)

geometrical parameter	MP2/6-31+G**		crystal structure[a]	crystal structure (cocrystal)[b]
	1a	**1c**		
N−N	1.387	1.388	1.381	1.399
N−H	1.011	1.014	1.038	0.893, 0.860[c]
N−C	1.384	1.360	1.332	1.317, 1.335[c]
C=O	1.223	1.234	1.239	1.223, 1.199[c]
N−N−H	114.48	113.79	118.52	113.14, 113.95[c]
N−N−C	118.39	117.51	119.34	122.17, 121.12[c]
N−C=O	124.05	122.79	123.65	124.95, 124.83[c]
O=C−H	124.13	124.42	123.24	117.96, 118.74[c]
X−N−N−X (θ)	99.22	180.00	0.00	102.8
N−N−C=O	16.12	7.20	0.030	3.4, 2.1[c]
H···O	2.948	2.268	2.387	2.930, 2.942[c]
ϕ	8.2	7.0	0.0	1.3, 0.3[c]

[a] Diformylhydrazine crystallized neat.[8b] [b] Diformylhydrazine co-crystallized with 18-crown-6-ether.[20] [c] With respect to 18-crown-6 ether, proximal and distal amides, respectively.

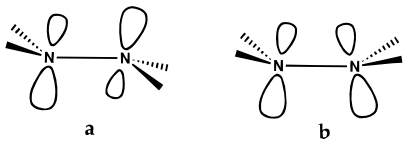


Figure 4. Pyramidalization of nitrogens occurs as shown; i.e., the p-orbitals have C_2 symmetry (a), except for **1c** in which pyramidalization is C_s (b) in order to preserve the intramolecular hydrogen bonds.

through the 180° maximum but would meet a large wall at 0°. The high energy required for crossing through the 0° structure is due to strong repulsion between the carbonyl oxygens, and between the eclipsed nitrogen lone pairs. The nitrogens in the 0° conformation (**1b**) are both significantly pyramidal at the HF/6-31+G** and MP2/6-31+G** levels (ϕ = 17.4° and 17.8°, respectively). Nitrogen pyramidalization reduces the unfavorable eclipsing lone pair repulsion (Figure 4a). This also means that **1b** is not the true transition state for rotation about the N−N bond, although it is probably reasonably close. The 0° transition state is difficult to locate unambiguously because rotation and pyramidalization are coupled, and pyramidalization requires very little energy. Nevertheless, we were able to locate the transition state at the HF/6-31+G** level, and it is 3.5 kcal/mol higher in energy than structure **1b**. This represents the worst case since the carbonyl oxygens are eclipsing in **1b**, and the pyramidalization angle is large. The energy difference between the 0° and 180° conformations and the true transition states for rotation should be smaller for the other configurations.

It is interesting to note that the nitrogens in **1c** are planar at the HF/6-31G* and HF/6-31+G** levels, but are slightly pyramidal (ϕ = 7.0°) at the MP2/6-31+G** level. Unlike the

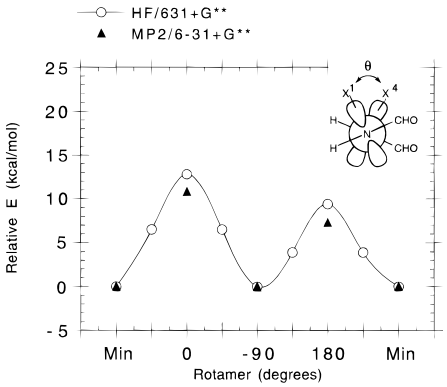


Figure 5. Calculated potential energy surface for the *Z*,*E* configuration.

0° structure (**1b**), pyramidalization of the 180° structure (**1c**) maintains C_s symmetry (Figure 4b). This is less effective at reducing the lone pair repulsions, but maintains the intramolecular hydrogen bonds more effectively than a C_2 distortion (Figure 4a).

***Z*,*E* Configuration.** The potential energy surface for rotation about the central N−N bond in the *Z*,*E*-configuration **2** is much more symmetric (Figure 5). At the MP2/6-31+G** level, **2b** is 10.8 and **2c** is 7.3 kcal/mol higher in energy than the lowest energy conformation **2a**. The difference in **2c** is much larger than was seen in **1c**. Rotation of one amide in diformylhydrazine from *Z* to *E* precludes one of the intramolecular N−H···O hydrogen bonds which are found in the planar conformation **1c.** Thus, the barrier is significantly larger for going through **2c** relative to **1c**. This 6.5 kcal/mol difference provides a rough estimate for the stabilization due to one of the intramolecular hydrogen bonds in **1c**. The 0° barrier for **2** is somewhat smaller than in **1** because the *Z*,*E* configuration relieves the very unfavorable oxygen−oxygen interaction which is present in **1b**. Once again, structures **2b** and **2c** are not the true transition states for rotation about the N−N bond in **2**, but they should provide a reasonable estimate of the rotational barrier. In each case the nitrogens are slightly pyramidal. For **2c** the two ϕ angles are 8.7° and 9.8°. Not surprisingly, the ϕ angles in **2b** are a little larger at 11.6° and 13.0°. This distortion relieves some of the strain due to eclipsing substituents on the nitrogens and reduces the repulsion between nitrogen lone pairs.

***E*,*E* Configuration.** The 180° barrier on the *E*,*E* (**3**) potential surface (Figure 6) is also much larger than that for **1**. In **3c** both of the intramolecular hydrogen bonds found in **1c** are missing. Rotation of both amides into *E* configurations makes these favorable interactions impossible. The energy barrier for crossing **3c** (12.0 kcal/mol) is almost twice the difference between **2c** and **1c** (6.5 kcal/mol). This is reasonable, given that two intramolecular hydrogen bonds are lost going from **1c** to **3c** compared to one hydrogen bond when going from **1c** to **2c**. In the case of **3**, the hydrogen bonds are estimated to be worth 6 kcal/mol, consistent with the estimate of 6.5 kcal/mol for **2**. The relative barrier for **3b** is approximately 4 kcal/mol larger than that for **2b**, but still smaller than that for **1b.** Structure **3b** is less favorable than **2b** because the *E*,*E* configuration leads to collision of two formyl hydrogens rather

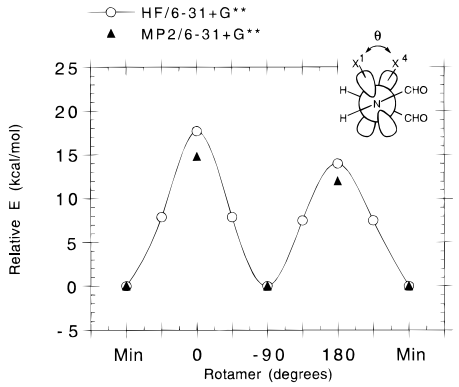


Figure 6. Calculated potential energy surface for the *E,E* configuration.

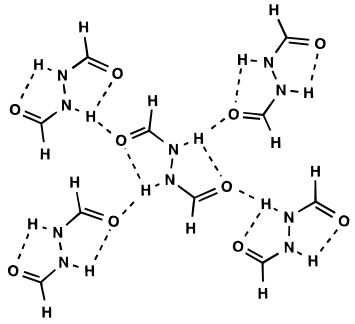


Figure 7. Hydrogen bond network in the diformylhydrazine crystal lattice, adapted from ref 8b.

than the more electrostatically favorable situation in **2b** where one formyl hydrogen is eclipsed with the other formyl oxygen.

Calculation of the 0° and 180° structures for **2** and **3** supports the view that diacylhydrazines have an inherently twisted geometry with respect to the N−N torsional angle. This is probably due to strong repulsion between the nitrogen lone pairs. The small energy difference between the twisted and planar **1c** geometries in the *Z,Z* configuration is due to the presence of two favorable N−H···O intramolecular interactions in this particular diacylhydrazine. Thus, the parent compound is an exception, and is not very representative of the series as a whole.

Comparison with Diformylhydrazine Crystal Structure

Several crystal structures have been determined for the *Z,Z* configuration of diformylhydrazine[5] **1** (Table 3). All give a planar structure analogous to **1c**. It has been proposed[8b,d] that **1** is planar because of a pair of intramolecular N−H···O hydrogen bonds. We invoke the same argument to explain the low energy barrier for **1** at 180° relative to the other configurations **2** and **3**. It should be pointed out that while dipole−dipole interactions also favor the 180° conformation in **1**, cancellation of dipoles is likely to be a small effect relative to the intramolecular hydrogen bonds. This is supported by the fact that structures such as **3b** and **3c** where the dipoles also cancel do not exhibit stability comparable to that of **1c**.

Given the calculated potential for rotating about the N−N bond in **1**, it is not surprising that the crystal structure is planar. Crystal packing should be more efficient for the planar structure. In addition, a planar geometry allows for stacked sheets of hydrogen-bonded networks with a favorable alignment of dipoles between sheets (Figure 7).[8b,d] The energetic advantage of this planar packed crystal can easily be expected to compensate the less than 1 kcal/mol cost of a planar conformation. For example, it is well known that the structure of biphenyl is sensitive to crystal packing effects. The dihedral angle between phenyl rings in biphenyl is observed to be near 0° in the crystalline state as compared to 44° in the gas phase.[19] The planar geometry is observed in the crystal structure in spite of an estimated 1.4 kcal/mol[19b] energy maximum for the planar rotamer. Beyond the effect of intermolecular forces on the geometry of **1**, the small barrier for adopting a planar structure would lead to rapid equilibration and observation of a dynamically averaged planar structure except at very low temperatures.

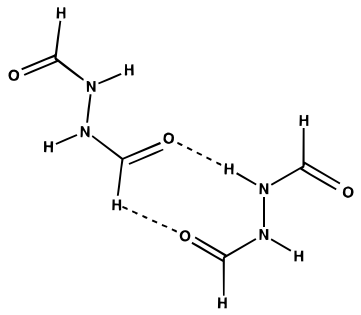


Figure 8. Diformylhydrazine dimer.

Ramondo and Bencivenni[8d] have modeled diformylhydrazine in the crystal lattice by placing hydrogen bond donors and acceptors in an arrangement which replicates the crystal field. They find that **1** will adopt a planar geometry under the influence of these external hydrogen bonds. In order to evaluate the magnitude of the intermolecular hydrogen bonds generated in the crystal structure, we computed the hydrogen bond strength for the planar dimer of (*Z,Z*)-diformylhydrazine **1** at the HF/6-31G* level (Figure 8). Although this is not the most stable van der Waals complex for the dimer, it was chosen because it is representative of one of the intermolecular interactions present in the crystal structure. Planarity was enforced in this calculation, but all other geometric parameters were optimized completely. Comparison of the planar dimer to the nonplanar monomer gave a relative energy of −3.8 kcal/mol for the dimer. Thus, the van der Waals complex is considerably more stable than the isolated molecules in spite of the energetic penalty incurred to adopt a planar conformation. It should also be remembered that each molecule in the crystal lattice participates in four of these intermolecular hydrogen bonds, and there is likely to be some cooperativity.

There is experimental evidence that crystal packing plays a significant role in the planar crystal structure of **1**. Caira et al.[20] have crystallized **1** in the presence of 18-crown-6 ether (Figure 9). In this complex two guest molecules (**1**) are trapped between two host molecules (18-crown-6). Interestingly the guest molecules in this crystal structure (**1**) adopt a twisted, not planar, conformation about the central N−N bond. One explanation is that the large crown ether disturbs the intermolecular hydrogen bonds responsible for the planar crystal structure in neat **1**. Of course, one could also argue that the twisted conformation in the inclusion complex is due to hydrogen bonds between **1** and the crown ether. In either case, comparison of the two crystal structures (Table 3) gives clear experimental evidence that intermolecular forces can play a major role in determining the N−N torsional angle in the solid state.

Effect of N-Substitution

The intramolecular hydrogen bonds which are implicated in stabilizing the 180° rotamer of **1** can be disrupted by substitution at nitrogen. The minimum energy structure for (*Z,Z*)-*N*-methyl-

(19) (a) Brock, C. P.; Minton, R. P. *J. Am. Chem. Soc.* **1989**, *111*, 4586. (b) Bastiansen, O.; Samdal, S. *J. Mol. Struct.* **1985**, *128*, 115.

(20) Caira, M. R.; Watson, W. H.; Vögtle, F.; Müller, W. *Acta Crystallogr.* **1984**, *C40*, 136.

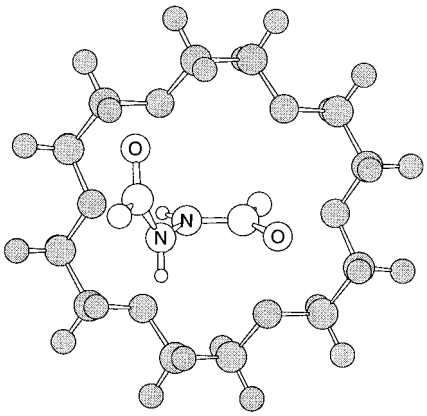
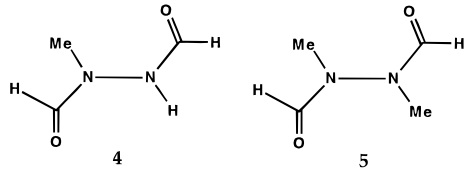


Figure 9. Crystal structure of diformylhydrazine cocrystallized with 18-crown-6 ether.

N,*N*′-diformylhydrazine (**4**) is similar to that of **1** in that the nitrogen lone pairs are almost perpendicular to one another. The barrier for **4** going through the 180° conformation is almost 5 kcal/mol higher in energy than for **1** at the HF/6-31+G** level (Table 1). Only a small part of this difference can be attributed to the larger size of the methyl group. Most of this difference is undoubtedly due to the loss of one N−H···O hydrogen bond. The barrier for the *N*,*N*′-dimethyl-*N*,*N*′-diformylhydrazine (**5**), in which hydrogen bonding is not possible, is even larger at 19 kcal/mol.



4 **5**

The large nonadditivity between **4** and **5** appears to be due to two factors. First, in the monosubstituted case, **4**, the Me−N−N and CO−N−N bond angles can open slightly in order to minimize steric crowding in the 180° rotamer. Second, the intramolecular hydrogen bond withdraws electron density from the nitrogen lone pair and reduces the repulsive interaction between the nitrogens. In the N,N′-disubstituted case, **5**, both of these effects are lost. In **5**, angle deformations which improve one methyl−carbonyl interaction make the other worse, and no intramolecular hydrogen bonds remain to pull electron density out of either nitrogen lone pair. The twisted structures calculated for **4** and **5** are consistent with the crystal structures of relevant N-substituted diacylhydrazines.[5,11,21] In all cases the CO−N−N−CO dihedral is near 90°.

Comparison of Diacylhydrazines with Hydrazine

Acyl substitution on hydrazine may actually increase the observed N−N rotational barrier due to more severe lone pair repulsions and nonbonded interactions, a consequence of decreased nitrogen pyramidalization. It has been proposed that this reduction in pyramidalization creates an unavoidable increase in steric repulsion between nitrogen substituents. More significantly, there is a strict requirement for lone pair eclipse in acylhydrazines, whereas for the corresponding hydrazines an alternative lower energy pathway involving lone pair/substitutent eclipse is possible.[2] Perhaps the most relevant comparison of the diacylhydrazine rotational barrier is with the major hydrazine barrier in which lone pairs are eclipsed.

Diformylhydrazine rotamers **2b** and **3c** present such an opportunity for meaningful comparison since these structures experience neither obfuscating hydrogen bonds nor serious formyl/formyl nonbonded repulsions. At the MP2/6-31+G** level, **2b** lies 10.8 kcal/mol above the global minimum for this hydrazine configuration. Likewise, **3c** lies 12.0 kcal/mol above the minimum at **3a**. Both values are comparable to that of the hydrazine rotamer in which lone pairs are eclipsed, 11.9 kcal/mol.[4]

Therefore, assuming that formyl/formyl and hydrogen/hydrogen nonbonded interactions are relatively small and comparable in magnitude in **2b**, **3c**, and the eclipsed conformer of hydrazine, it appears that participation of the nitrogen lone pairs in amide bonds causes neither substantial stabilization nor destabilization relative to hydrazine. However, additional alkyl substitution on nitrogen should substantially increase this rotational barrier (**4**, **5**) due to closer eclipsing interactions brought about by the flatter nitrogens. The pyramidalization angle in **2b** and **3c** ranges from 11.6° to 13.0° as compared to 20° for hydrazine.[4] This is consistent with experimental results and the explanation proposed by Dewar et al.[2a] These results are also consistent with the barrier observed by Nelsen et al.[2b] for an interesting diacylhydrazine in which each acyl substituent is tied back to form a pyrrolidinone. This conformationally restricted model gave a rotational barrier of 11.4 kcal/mol.

Implications for Azapeptides and Ecdysone Agonists

The propensity of diacylhydrazines toward twisted structures has important implications for the structure of diacylhydrazine-derived ecdysone agonists, azapeptides, and azatides. It is difficult to model[13] the ecdysone agonists without a good understanding of their structure with regard to the central N−N bond. Indeed it is impossible to even speculate rationally about the pharmacophore for these systems, or how they might mimic the natural steroidal ligand without this information. These calculations show that virtually any N-substituted dibenzoylhydrazine will have a twisted structure with regard to the central N−N bond, and that the barrier to rotation is likely to be large. Furthermore, if other structural factors cause the *Z*,*E* or *E*,*E* configurations to predominate, then nonplanar ground states with barriers of 7−15 kcal/mol can be expected even without substitution at nitrogen.

With regard to the azapeptides and azatides, substitution of nitrogen for the α-carbon leads to significant changes in the structure and dynamics of the peptide backbone. The most obvious changes are replacing a tetrahedral center with a planar nitrogen, and loss of one easily rotatable $C^{\alpha}-C$ bond. These changes have led to the general expectation that azapeptides should be more rigid[9a,b,11e] than their conventional peptide counterparts. Our calculations indicate that this substitution also introduces a strong preference for a twisted conformation about the resulting N−N bond in which the CO−N−N−CO dihedral angle approaches 90°. The only α-azaamino acid which is likely to have other easily accessible conformations is the glycine analog.

In addition to structural changes imparted by substitution of nitrogen for the α-carbon, these calculations also imply that the rotational barriers for azapeptides are likely to be significantly greater than they are for the corresponding peptides.[22] This is

(21) (a) Ranganathan, D.; Bamezai, S.; Cun-heng, H.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 5739. (b) Glowka, M. L.; Iwanicha, I.; Najman, L. *Acta Crystallogr.* **1991**, *C47*, 618. (f) Otterson, T. *Acta Chem. Scand., Ser. A* **1978**, *32*, 127. (c) Bruno, G.; Bombieri, G.; Del Pra, A.; Previtera, T.; Vigorita, M. G.; Basile, M. *Acta Crystallogr.* **1984**, *C40*, 671. (d) Otterson, T. *Acta Chem. Scand.* **1978**, *A32*, 127.

(22) (a) Stryer, L. *Biochemistry*; W. H. Freeman and Co.: New York, 1995. (b) Creighton, T. E. *Proteins: Structures and Molecular Principles*; W. H. Freeman and Co.: New York, 1984.

due to two effects. First, the azapeptides introduce a repulsive interaction between nitrogen lone pairs which is not present in the N−C$^{\alpha}$ bond of conventional peptides, and which must be overcome in order to rotate about the azapeptide N−N bond. Second, the change from α-carbon to nitrogen subsitutes a planar, or near planar, center for a tetrahedral carbon. Substitution of nitrogen for the α-carbon not only destroys chirality at that center but also forces the lone pairs and the substituents on both nitrogens to be eclipsed in the planar geometry. This, as has been pointed out by others,[2] has the effect of raising the rotational barrier. These differences are likely to have significant consequences for the overall structure and flexibility of azapeptides, and particularly azatides, as compared to their conventional peptide counterparts. Azapeptides and azatides warrant additional calculations which are designed to more specifically address their structure and dynamics, but such calculations are beyond the scope of this paper.

Conclusion

On the basis of our calculations, the structure and rotational barriers for diacylhydrazines can be summarized as follows. In the *Z,Z* configuration of the parent **1**, the twisted and planar geometries are comparable, with the 180° geometry being less than 1 kcal/mol higher in energy than the twisted minimum. This is a direct result of the presence of two intramolecular hydrogen bonds in the planar geometry. These energetically favorable hydrogen bonds significantly mitigate the repulsive interaction between eclipsing nitrogen lone pairs in the 180° structure. If, however, the nitrogens are substituted or the configuration about the amides is altered, one or both of the hydrogen bonds in the planar geometry are lost and the planar geometry becomes much less stable. This leads to the observation of twisted ground states for substituted diacylhydrazines as well as large rotational barriers. For example, the 180° barrier for the *E,E* configuration **3** where both intramolecular hydrogen bonds are lost is comparable to that of alkyl-substituted hydrazines at 12.0 kcal/mol.

The planar crystal structure observed for the *Z,Z* configuration of the parent diformylhydrazine **1** is a consequence of the unusually small 180° barrier, and formation of an intermolecular network of hydrogen bonds in the crystalline state which favors a planar or near planar geometry. Calculations for dimers of **1** which are representative of the intermolecular interactions in the crystal structure give interaction energies of −3.8 kcal/mol. This represents a significant driving force for a planar crystal structure. As described above, substitution at either nitrogen has an enormous effect on the rotational barrier because it eliminates one or both of the stabilizing hydrogen bonds present in the planar geometry of the parent. Substitution also interrupts the intermolecular hydrogen bonds which are available in the crystal lattice of **1**. For example, *N*,*N*′-dimethyl-*N*,*N*′-diformylhydrazine (**5**) has a very large maximum at the eclipsed geometry (19 kcal/mol, HF/6-31+G**), and the crystal structure is consistent with this calculated result. The observed CO−N−N−CO dihedral angle in crystalline **5** approaches 90°.[21d]

These results show that the low barrier for attaining a planar 180° structure found previously for diformylhydrazine is an exception brought about by the presence of two intramolecular hydrogen bonds in the planar conformation. The intrinsic barrier for the eclipsing lone pairs appears to be comparable, where a fair comparison can be made, to the intrinsic barrier which results from eclipsing lone pairs in hydrazine. Extrapolation from the low rotational barrier found in (*Z,Z*)-diformylhydrazine to other diacylhydrazines leads to an inaccurate picture of the N−N torsional potential. On the contrary, we find that any N-substituted diacylhydrazine can be expected to be nonplanar with a large barrier for adopting a planar conformation.

These calculations also help to clarify the structure of diacylhydrazine-derived ecdysone agonists and azapeptides. A better understanding of the essential features of this structural motif is fundamental to rationalizing the structure and rotational flexibility of these biologically important classes of compounds.

Supporting Information Available: Table giving the total energies for rotamers of **1**−**5** (2 pages). See any current masthead page for ordering and Internet access instructions.

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