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Conformational analysis of 1-acetyl-2-methylhydrazine

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Abstract

The conformational analysis of 1-acetyl-2-methylhydrazine was performed using DNMR spectroscopy and quantum chemical calculations (B3LYP/6-31+G*, AM1 and PM3). Activation barrier for interconversion of *Z* and *E* conformers was measured to be 16.1 kcal/mol by DNMR. DFT calculations indicate that there are four minima on the 1-acetyl-2-methylhydrazine potential energy surface and the most stabile is *Z* conformer with the hydrogen bond between carbonyl group oxygen and hydrogen at non-amide nitrogen. The amide nitrogen was found to be close to planar in minima but strongly pyramidalized in TS. The activation barriers calculated at B3LYP/6-31+G* level of theory were in good agreement with experimentally measured one. AM1 method with molecular mechanics correction gave potential energy surface in reasonable agreement with DFT results, but the activation energies were strongly underestimated. PM3 method was found to give unsatisfactory results for conformational analysis of 1-acetyl-2-methylhydrazine. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: 1-Acetyl-2-methylhydrazine; Rotational barriers; Transition state; DFT calculations

1. Introduction

Substituted hydrazines represent an important class of compounds due to the role these compounds play as peptidomimetics [1–3] and nonsteroidal ecdysone agonists [4,5]. Moreover, hydrazine plays a very important role in the production of pharmaceuticals, agrochemicals and dyestuffs [6–8]. The extent to which substitution affects the structure and dynamics of C–N and N–N bonds in substituted hydrazines is a critical issue both from the standpoint of a proper understanding of this functional group in its above-mentioned applications and for fundamental physical organic chemistry.

Several systematic methods have been developed recently for the synthesis of substituted hydrazines [9–12]. Extremely complex NMR spectra were obtained for pure tetrasubstituted hydrazines synthesised by such a systematic approach [11,12]. These spectra can be interpreted as those of the mixture of different conformers. In the earlier NMR studies of acyclic diacylhyrazines [13,14] very high (sometimes greater than 20 kcal/mol) barriers of rotation have been measured. It has been suggested [15] that these barriers correspond to amide bond. Some authors [14,16] have proposed that relatively high barriers to rotation around N–N bond measured for tetraalkylhydrazines are caused by severe sterical interactions between the bulky substituents.

The conformational isomerism in substituted hydrazines have been investigated by using a variety of methods such as DNMR spectroscopy [13–15],

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Table 1
^1H and ^{13}C chemical shifts of 1-acetyl-2-methylhydrazine. Values in parenthesis are ^2J(to CO) or ^3J (to CH_3) from NH proton, in Hz

	Solvent	Conformer	Acetyl methyl	Acetyl-NH or CO	Methyl-NH	Methyl
^1H	$CDCl_3$	Z	1.88	8.82	4.67	2.51
	$CDCl_3$	E	2.03	8.23	3.82	2.53
	DMSO	Z	1.74	9.25	4.75	2.39
	DMSO	E	1.88	8.29	3.38	2.41
^{13}C	$CDCl_3$	Z	20.96 (<1)	169.55 (9.0)	–	38.89
	$CDCl_3$	E	19.20 (4.6)	176.18 (3.9)	–	39.63
	DMSO	Z	20.71	168.00	–	38.62
	DMSO	E	19.44	173.51	–	39.09

molecular mechanics (MM) [17] and quantum chemical calculations [17–22]. The applied theoretical approaches for determining the rotational barriers include the transition state search and the calculation of energy profile of the rotation and are quite close to those used in the conformational analysis of amides [22–26]. The calculation of potential energy surface can be a method of choice for molecules possessing several bonds with comparable rotational barrier [27,28].

The analysis of the conformational space of the complex tetrasubstituted hydrazine molecules by high-quality quantum chemical methods like ab initio calculations can be very time consuming. In the current work we have used 1-acetyl-2-methylhydrazine as a model compound to study conformational preferences of substituted hydrazines and also to test semiempirical and DFT calculations for the conformational analysis of hydrazines.

2. Experimental

1-Acetyl-2-methylhydrazine was synthesised by the known procedure of Condon [29]. Dynamical NMR spectroscopy experiments were carried out at 500.13 MHz from 0.7 M DMSO-d_6 solution on the Bruker AMX500 instrument.

Density functional calculations at B3LYP/6-31+G* level were performed using the Gaussian 98 program package [30]. Semiempirical AM1 and PM3 calculations were performed using MOPAC 7.0 [31].

To find minima on potential energy surface, in all cases all possible conformers obtained by rotations around amide and N–N bonds were optimized and obtained structures analyzed using frequency calculations at respective levels of theory. Transition states (TS) between all unique minima were sought using SADDLE algorithm [32] in MOPAC and QST2 algorithm [33,34] in Gaussian. Obtained candidates for TS were then further optimized and confirmed as TS by frequency calculations (number of imaginary frequencies equals 1 for TS). Further, minima connected by each found TS were sought by IRC calculations.

3. Results and discussion

3.1. DNMR measurements

At room temperature two conformers in the ratio 9/1 are observed in $CDCl_3$ as well as in DMSO solution. These two conformers result from the restricted rotation around CO–NH bonds and are assigned as *Z* and *E* conformers. More abundant is the *Z* conformer on the basis of analogy with the assigned conformers of 1-acetyl-2-phenylhydrazine [35] and our systematic study of the series of acylsubstituted hydrazines [36]. Additional confirmation to the correct assignment of conformers in the present case is obtained from the values of the ^3J coupling constant from acetyl methyl carbon to NH proton, which gives in trans orientation 4.6 Hz; and in cis orientation it is less than 1 Hz (Table 1).

For the DNMR measurements acetyl protons are the best choice, being separated at low temperature by 70 Hz. NH protons cannot be used due to the multisite exchange with the water always present in DMSO and the difference in NMe protons is too small to be useful for the exchange rate calculation. Rate constants were obtained by the comparison of experimental (Table 2)

Table 2
DNMR measurements of 1-acetyl-2-methylhydrazine

Temperature, K	Rate of interchange k
316	1
328	2.8
336	4.9
348	13.8
350	15.5
356	23
362	29
368	42

Table 3
Total energies (E) and enthalpies (H) of minima and transition states found on the potential energy surface of 1-acetyl-2-methylhydrazine at B3LYP/6-31 + G* level of theory. All values in a.u.

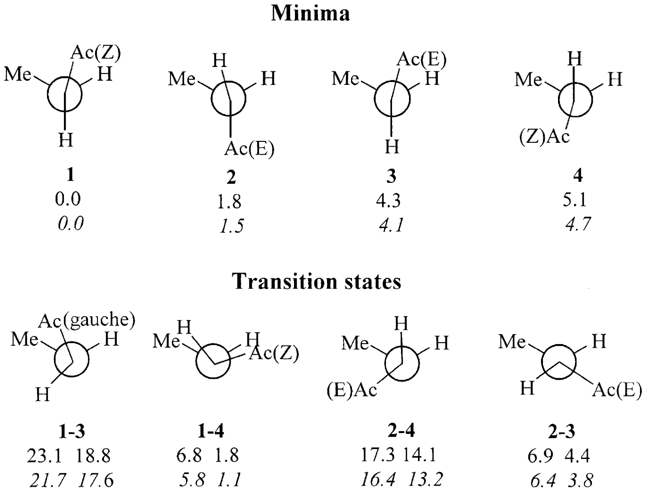
	E	H
1	−303.8568	−303.7287
2	−303.8539	−303.7263
3	−303.8499	−303.7222
4	−303.8487	−303.7212
1–3	−303.8200	−303.6941
1–4	−303.8459	−303.7194
2–3	−303.8429	−303.7161
2–4	−303.8263	−303.7002

and calculated by GNMR program (Cherwell Scientific) spectra. The dependence of $\log(k/T)$ on the T was obtained as equation $\log(k/T) = 10.32 - (\Delta H^{\#}/19.14T) + (\Delta S^{\#}/19.14)$ with the following statistical parameters $R = 0.995$, $\mathrm{SD} = 0.0394$. From that equation the thermodynamical parameters were calculated resulting in $\Delta H^{\#} = 16.1 \pm 0.4$ kcal/mol; $\Delta S^{\#} = -7.4 \pm 1.3$ cal/(K × mol).

3.2. DFT calculations

DFT calculations yielded four minima on the potential energy surface given on Scheme 1 and Table 3, corresponding to two Z and two E conformers. It should be noted that in all cases the amide group was almost planar and the exact planar forms were only ca 0.3 kcal/mol less stable than slightly pyramidalised forms.

The most stable Z conformer **1** is stabilized by the hydrogen bonding between the carbonyl group oxygen and neighbouring N–H hydrogen as evidenced by the relatively short N…H distance (2.4 Angstroms). Similar hydrogen bonding has earlier been reported for 1,2-diacylhydrazines [19–22]. The next stable E conformer **2** has both carbonyl and acyl groups rotated by almost 180° and is less stable by 1.5 kcal/mol. The two remaining E and Z conformers (**3**, 4.1 kcal/mol less stable than **1** and **4**, 4.7 kcal/mol less stable than **1**) have energies too high to be observed experimentally. At the same time



Scheme 1. Minima and transition states found on the potential energy surface of 1-acetyl-2-methylhydrazine at B3LYP/6-31 + G* level of theory. Roman numbers give relative energies and italics relative enthalpies (for minima relative to most stable conformer, for TS relative to respective minima) in kcal/mol.

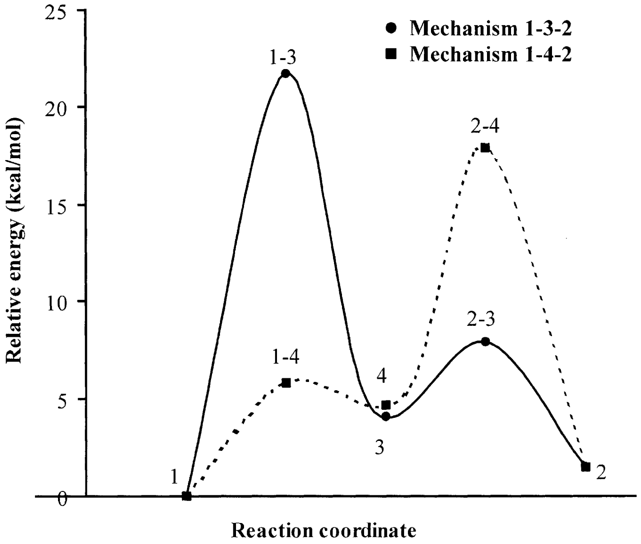


Fig. 1. The energy pathways for interconversion of most stable *Z* and *E* conformers (1, 2) calculated at B3LYP/631 + G* level of theory.

calculated energies of the most stable *Z* and *E* conformers **1** and **2** reproduce quite well the observed conformational equilibrium (1.5 kcal/mol energy difference corresponds to 93:7 ratio of *Z* and *E* conformers).

Transition states on the B3LYP/6-31+G* potential energy surface are presented in Scheme 1. First it should be noted that the amide nitrogen is clearly pyramidal in all TS, while in the minima it is close to planar. All TS found correspond to the rotation around either the N–N or amide bond, so that we do not have a direct pathway between most stable conformers **1** and **2**. The conversion of **1** to **2** must thus involve either conformer **3** or **4** as an intermediate. The energy pathways for both mechanisms are given on Fig. 1. Both of them involve one low barrier (5.8 and 6.4 kcal/mol for mechanisms **142** and **123**, respectively) rotation around the NN bond and one high barrier (21.7 and 16.4 kcal/mol for mechanisms **142** and **123**, respectively) rotation around the amide bond. The **142** mechanism is the energetically favourable interconversion pathway due to lower (by 5.3 kcal/mol) calculated energy barrier. The calculated activation enthalpy for the high barrier rotation of **1-4-2** mechanism (16.4 kcal/mol) is also in very good agreement with the experimentally observed value (16.1 kcal/mol).

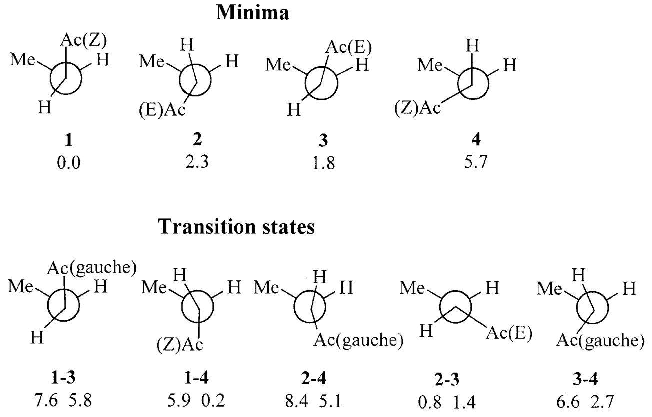
Table 4
Heats of formation (ΔH_f) of minima and transition states found on the potential energy surface of 1-acetyl-2-methylhydrazine at AM1 level of theory. All values in kcal/mol

	ΔH_f (NOMM)	ΔH_f (MMOK)
1	−20.41	−20.04
2	−18.12	−17.63
3	−18.65	−18.36
4	−14.76	−13.92
1–3	−12.85	−7.88
1–4	−14.54	−13.82
2–3	−17.28	−16.36
2–4	−9.69	−6.92
3–4	−12.07	

It should be noted that despite the fact that TS connect two minima corresponding to rotation around single bond the TS (except for **1-5**) do not correspond to the eclipsed but rather to the gauche conformers. The rotations around the single bond are always accompanied by considerable changes in the pyramidalization of amide nitrogen and also rotations around the other bonds, thus making eclipsed conformations correspond to the higher order saddle points.

3.3. Semiempirical methods

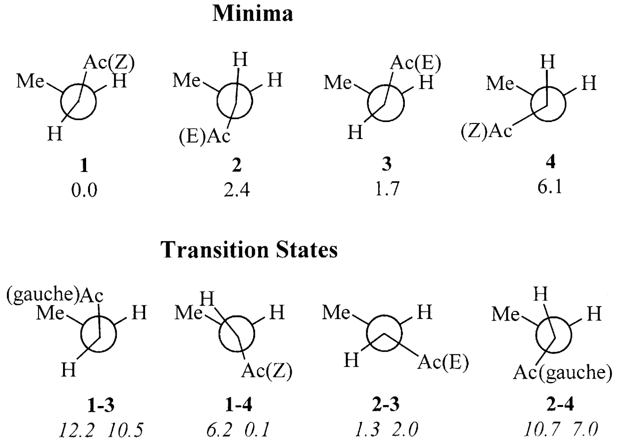
A known deficiency [37] of all semiempirical



Scheme 2. Minima and transition states found on the potential energy surface of 1-acetyl-2-methylhydrazine at AM1(NOMM) level of theory. Roman numbers give relative heats of formation (for minima relative to most stable conformer, for TS relative to respective minima) in kcal/mol.

methods of MNDO family (MNDO, AM1, PM3) are significantly lower predicted rotational barriers around amide bonds compared to experimentally observed ones and the tendency to overestimate the stability of pyramidal nitrogens compared to planar ones. To correct this molecular mechanics correction has been proposed [38], which consists of adding a torsional potential to the *X*-N-C-O angle ($X = \mathrm{R}$ or H). In the current work we have tested both purely quantum mechanical approach (NOMM) and molecular mechanically corrected method (MMOK) as implemented in MOPAC 7 program package.

Results of AM1 calculations are presented in Table 4. Purely quantum chemical approach (NOMM) yields 6 minima on the AM1 potential energy surface. However, as two of them were energetically well above the minima **1** and **3**, respectively, and separated from these minima by the activation barriers less than 0.1 kcal/mol, we did not consider them as individual entities. The remaining four minima are presented in Scheme 2.



Scheme 3. Minima and transition states found on the potential energy surface of 1-acetyl-2-methylhydrazine at AM1(MMOK) level of theory. Roman numbers give relative heats of formation (for minima relative to most stable conformer, for TS relative to respective minima) in kcal/mol.

The geometries of obtained minima are somewhat different from the DFT ones—in all cases the amide nitrogens were clearly pyramidal (dihedral angles C-N(-N)-H were 120–130°). Also, the ordering of conformations **2** and **3** is reversed. It seems that AM1 overestimates the stability of conformer **3** by ca 2 kcal/mol.

Transition states obtained with AM1/NOMM are also somewhat different from those obtained with DFT method. The geometries of TS between minima **2** and **3**, and **1** and **3** are quite similar to those obtained at B3LYP/6-31+G* level, while the other two are quite different from their DFT counterparts—in both cases the amide nitrogen is inverted and in the case of TS between minima **2** and **4** also the carbonyl group has gauche rather than trans orientation relative N–N bond. There is also additional TS between minima **3** and **4**. The barriers for rotations are clearly underestimated compared to DFT results.

Application of the force field correction to the AM1 method yields 4 minima on the potential energy surface (Scheme 3). The geometries of these minima are quite close to DFT results. However, the ordering of minima **2** and **3** is still opposite to that of the B3LYP/6-31+G* results as was the case with AM1/NOMM results.

Four transition states were obtained with the AM1/MMOK method. The geometries of these TS were reasonably close to the DFT ones. However, the corresponding activation energies were still underestimated as was the case with the AM1/NOMM method.

Similar to AM1, the PM3 method can also be used either without or with force field correction to the amide linkage. The approach without molecular mechanic corrections (PM3/NOMM) gave us unexpectedly 8 minima on potential energy surface. Two of them, the most and least stable ones, were energetically clearly separate from others, which differed in energy scale only by less than 0.5 kcal/mol and were separated from each other by the barriers less than 0.2 kcal/mol high. The application of force field correction did not improve the situation—there were now 10 minima, which were spread over 1 kcal/mol range in energy scale and had rather low interconversion barriers between them. We concluded that PM3 method was not suitable for conformational analysis of 1,2-substituted hydrazines due to the unreasonably high number of minima on the potential energy surface.

4. Conclusions

Dynamical NMR measurements of acetyl protons interchange were carried out in DMSO solution. The enthalpy of activation for the reaction of conformational change was calculated to be $\Delta H^{\#} = -16.1 \pm 0.4$ kcal/mol. Comparison of this value with calculated rotational barriers of 1-acetyl-2-methylhydrazine indicates that results of DFT calculations at B3LYP/6-31+G* level were in good agreement with DNMR experiment. Predicted relative populations of *Z* and *E* conformers are very close to the experimental result. Semiempirical methods AM1 and PM3 overestimate the number of minima and underestimate the rotational barriers. However, the force field correction remarkably improves the quality of AM1 results. Thus, AM1 with MM correction can be considered a suitable method for the conformational analysis of hydrazines with large substituents where the DFT or ab initio calculations are too time-consuming.

DFT calculations indicate that there are four minima on the 1-acetyl-2-methylhydrazine potential energy surface and the most stabile conformer **1** has hydrogen bond between carbonyl group oxygen and hydrogen at non-amide nitrogen. The amide nitrogen was found to be close to planar in minima but strongly pyramidalized in TS.

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