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# Structural characteristics of some mercaptoacetic acid hydrazides

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**Abstract**

NMR and molecular modeling were used to analyze the conformational states of a series of mercaptoacetic acid hydrazides. A chemical exchange phenomenon was observed in the phase-sensitive NOESY spectrum of all derivatives in both $CDCl_3$ and DMSO-*d6* solvents. Chemical shifts, temperature and solvent dependence as well as MonteCarlo conformational search suggest that two rotamers exist around the amide bond in solution in a slow, for the NMR time scale, interconversion at room temperature. The *trans* conformer is predominant in $CDCl_3$ and seems to be stabilized by the presence of hydrophobic interactions between the two aliphatic ends of the molecule. The relative population of the *cis* conformer increases tenfold in DMSO-*d6* stabilized through the formation of hydrogen bonds.


*Keywords:* $^{1}$H NMR; $^{13}$C NMR; Molecular mechanics; Conformational analysis; Hydrazides; Amide rotation

## 1. Introduction

The chemistry of hydrazones and their derivatives has been extensively investigated in recent years, since this group presents interesting chelating properties and is a common structural feature in many biologically active molecules [1,2]. More specifically some mercaptoacetic acid hydrazones and hydrazides have been reported to possess interesting antimicrobial, antifugal and anticonvulsant activity [3–5].

In the course of our research efforts towards the preparation of new compounds containing the 1,2,4-triazole ring, a well known pharmacophore, [6–10] we have described the synthesis of some 5-adamantyl-4-aryl-1,2,4-triazoles, bearing a 3-mercaptoacetic acid substitution, which exhibit antifungal and antimicrobial activity (Fig. 1, compounds **2**, **3**) [11]. The $^{1}$H NMR spectra revealed an interesting feature, since two series of signals were observed. This phenomenon was previously been described only for the $SCH_2$ protons in a series of related analogues [3–5,12], however, a controversy still exists concerning this observation. According to the authors these protons resonated as two singlets, or as a doublet and this pattern was attributed to the existence of two rotamers around the sulfur bridge or to the presence of the enolic form, or to hydrogen bond formation between NH and S atom. On the other hand it has been proposed that *N*-acyl hydrazones could undergo an *E*/*Z* conformational isomerization as far as the N=N

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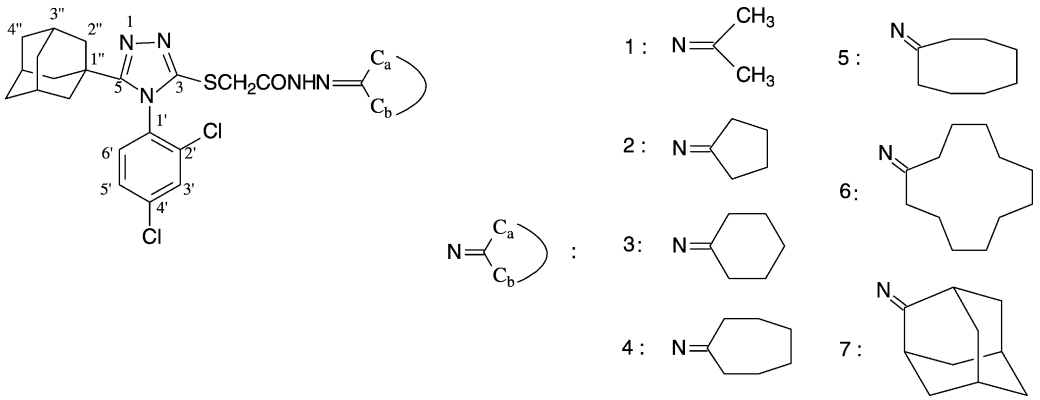



Fig. 1. Structure and numbering of compounds **1**–**7**.

bond is concerned or a *cis–trans* isomerization around the amide bond –C(O)NH– [13,14]. In an attempt to study in detail this phenomenon we present here the preparation of some new, structurally related analogues (Fig. 1, compounds **1**, **4**–**7**), which together with the previously reported derivatives were used for the comprehensive spectral study of this class of compounds on the basis of their $^{1}H$ and $^{13}C$ NMR data in $CDCl_3$ and DMSO-*d6*, EXSY spectra and molecular mechanics calculations.

## 2. Experimental

### 2.1. Synthesis

All reagents used were purchased from Aldrich Chemical Company. Melting points were taken in glass capillary tubes on a Büchi 530 apparatus and are uncorrected. Silica gel TLC was performed on $60_{F\text{-}254}$ precoated sheets and column chromatography was carried out on silica gel (60–120 mesh). The elemental analyses (C, H, N) of all compounds were performed by the Service Centrale de Microanalyses (CNRS, Vernaison, France) and are within the range of experimental error (±0.4% of the calculated values).

### 2.2. General method for the preparation of the hydrazides *1*–*7*

The appropriate ketone (1.2 mmol) was added to a solution of [5-adamantyl-4-(2,4-dichlorophenyl)-4*H*-1,2,4-triazol-3-yl]mercaptoacetic acid hydrazide (1.15 mmol) [11] in absolute ethanol (20 ml). The mixture was refluxed for 24 h and then, allowed to stand overnight. The solvent was vacuum-evaporated and the residue was purified by column chromatography (silica gel), using mixtures of dichloromethane/cyclohexane: 1/2–1/3 (v/v) as the eluent to give 68–77% yield of the target compounds. Mp: **1**: 128–130 °C (EtOH), **2**: 225–228 °C (EtOH), [11] **3**: 134–136 °C (EtOH), [11] **4**: 119–121 °C (EtOH), **5**: 123–125 °C (EtOH), **6**: 196–198 °C (EtOH), **7**: 162–164 °C (EtOH).

### 2.3. NMR methods

NMR spectra were recorded on a Bruker DRX 400 spectrometer at 400.13 and 100.6 MHz for $^{1}H$ and $^{13}C$ experiments, respectively, equipped with a direct and an inverse 5 mm broadband probe and $B_0$ gradients. All spectra were recorded using 5 mg of each product dissolved in 0.6 ml of $CDCl_3$ or DMSO-*d6* in a 5 mm tube at ambient temperature (20 °C). Standard Bruker pulse programs were used throughout.

The 2D experiments were carried out with the following parameters (a) COSY were recorded with gradient pulses for selection, spectral width 12.5 ppm in both dimensions, 16 transients for each FID; 512 $t_2$ points, 256 $t_1$ increments; recycling delay 2 s; (b) the phase-sensitive NOESY were obtained with time-proportional phase incrementation (TPPI), $t_m = 1.0$ s, a recycling delay of 2 s; spectral with of 5000 Hz in both dimensions, 256 $t_1$ increments, 2048 points in the $t_2$ dimension and 16 transients for each FID; a $\pi/2$ shifted sine-squared weighting function was applied

prior to Fourier transformation and zero filled along $f_1$ to 512 points. (c) C–H correlation spectra (HSQC) were obtained using sensitivity improvement Echo–Antiecho, phase-sensitive (TPPI) with $B_0$ gradient pulses for selection of $^1$H coupled to carbons. A sweep width of 15 ppm for $^1$H and 240 ppm for $^{13}$C was used with 128 FIDs in the $t_1$ domain and 1 K data points in the $t_2$ domain, 48 transients for each $t_1$ increment and recycling delay 1.5 s. Data were processed using a shifted sine-square bell and zero filled along $f_1$ to 1024 points. The HMBC experiments were performed using a low pass *J*-filter (3.4 ms) and a delay in order to observe the long-range couplings (65 ms). As in the HSQC experiments, $B_0$ gradient pulses were applied in order to select $^1$H coupled to $^{13}$C nuclei, 256 transients with 128 increments in the $t_1$ domain and 1 K data points in the $t_2$ domain. Data were processed using a shifted sine-square bell and zero filled along $f_1$ to 1024 points.

### 2.4. Molecular calculations

Molecular calculations were performed using Macromodel 6.5 (Schrondinger) [15] running on a Silicon Graphics O2 R5000 computer under IRIX 6.3. The MMFF force field was used [16] as implemented in the Macromodel software. The Polak–Ribiere (conjugate gradient) minimization method with an energy convergence criterion of 0.01 kJ/mol was used for geometry optimization.

A 2000 steps conformational search was performed using MonteCarlo/Low Mode (MC/LMOD) [17] mixed mode strategy involving systematic search of low frequency modes (LMOD) or torsional Monte-Carlo mode (as implemented in the MonteCarlo Multiple Minimum command in Macromodel/Batchmin). Volume of the N=C< substituent was calculated using the VOL mode implemented in Macromodel.

## 3. Results and discussion

For the preparation of the compounds 5-adamantyl-4-(2,4-dichlorophenyl)-3-mercapto-4*H*-1,2,4-triazole [10] reacted with ethyl bromoacetate in alkaline medium, to give the corresponding mercaptoacetic acid ethyl ester, which was readily converted to the hydrazide after treatment with hydrazine hydrate. This hydrazide was finally treated with a number of ketones (acetone, cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, cyclododecanone and adamantanone) to result in the substituted hydrazides **1**–**7**.

The assignment of $^1$H and $^{13}$C signals in the NMR spectra was achieved by the concerted application of COSY, NOESY, HSQC and HMBC experiments. $^1$H and $^{13}$C NMR spectra of all compounds in both solvents show two series of signals.

The $^1$H NMR data for compounds **1**–**7** in DMSO-*d6* and $CDCl_3$ are provided, for the most relevant protons, in Table 1 and for the rest Section 4. The alkylidene protons of the N=C< substituent appear upfield and are severely overlapped, consequently they are not mentioned, except of the deshielded $H_a$ and $H_b$ neighboring to the imine bond. $^{13}$C chemical shifts are summarized in Table 2 for the most relevant carbons, other assignments are given in Section 4 (Table S1).

In the $^1$H spectra in DMSO-*d6* solution the chemical shift difference between the corresponding resonances in the two series of signals concerning the $CH_2$ and NH protons are $\sim$0.3 and $<$0.1 ppm, respectively.

In the majority of the compounds the two $SCH_2$ protons are almost equivalent and their resonances exhibit a second order AB system for both series of signals with the $\Delta\nu/J$ ratio ranging from 0.9 to 0.0 (Table 1).

In the phase-sensitive NOESY spectrum cross-peaks appear, relating the two AB second order systems of the two different series of signals attributed to the $SCH_2$ protons (Fig. 2). These cross-peaks exhibit the same phase as the diagonal peaks characteristic for a chemical exchange phenomenon. The same type cross-peaks are observed connecting the two NH peaks. These signals also present 'chemical exchange' cross-peaks with the residual water resonance signal existing in the DMSO solution.

Moreover, in DMSO-*d6* two additional resonances appear in the spectra at 4.03 and 3.31 ppm when the samples were prepared in relatively anhydrous conditions. These signals should originate from mobile hydrogens as they exhibit chemical exchange cross-peaks in the EXSY spectrum with the NH and the residual water peak. They are also shifted together with the water residual peak when the temperature increases and vanish when the spectra are recorded in solutions with more residual water.

Table 1
$^1$H-NMR data of compounds **1**–**7**. Chemical shifts (ppm) of the mercaptoacetic acid hydrazide moiety in $CDCl_3$ and DMSO-*d6* for both conformers together with the $\Delta\nu/J$ ratio concerning the AB second order system of two geminal $SCH_2$ protons. $I_I/I_{II}$ is the integral ratio presenting the population ratio of the two conformers. *V* is the volume of the N=C< substituent in Å$^3$

| Compound | Conformer I | | | | | Conformer II | | | | | $I_I/I_{II}$ | *V* (Å$^3$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\delta$ (ppm) | | | | $\Delta\nu/J$ | $\delta$ (ppm) | | | | $\Delta\nu/J$ | | |
| | NH | $H_a$ | $H_b$ | $SCH_2$ | | NH | $H_a$ | $H_b$ | $SCH_2$ | | | |
| | *$CDCl_3$* | | | | | | | | | | | |
| **1** | 11.13 | 2.04 | 2.00 | 3.88, 3.74 | 3.9 | 8.27 | 2.10 | 1.81 | 4.59, 4.70 | 4.5 | 1/0.07 | |
| **2** | 10.94 | 2.44 | 2.52 | 3.86, 3.72 | 3.8 | 8.05 | 2.40 | 2.17 | 4.57, 4.37 | 4.6 | 1/0.07 | 90 |
| **3** | 11.16 | 2.41 | 2.47 | 3.88, 3.75 | 3.4 | 8.02 | 2.28 | 2.18 | 4.60, 4.42 | 4.4 | 1/0.08 | 106 |
| **4** | 10.94 | 2.49 | 2.58 | 3.87, 3.80 | 1.8 | 8.30 | 2.45 | 2.26 | 4.60, 4.42 | 4.1 | 1/0.11 | 123 |
| **5** | 11.02 | 2.41 | 2.49 | 3.88, 3.84 | 0.7 | 8.39 | 2.35 | 2.27 | 4.57, 4.45 | 2.9 | 1/0.10 | 140 |
| **6** | 11.13 | 2.38 | 2.38 | 3.86, 3.82 | 0.7 | 8.52 | 2.31 | 2.16 | 4.54, 4.43 | 2.5 | 1/0.25 | 210 |
| **7** | 11.12 | 2.80 | 3.31 | 3.87, 3.79 | 2.0 | 8.38 | 2.60 | 2.79 | 4.63, 4.46 | 3.8 | 1/0.07 | 153 |
| | *DMSO* | | | | | | | | | | | |
| **1** | 10.41 | 1.90 | 1.83 | 3.99, 3.95 | 0.8 | 10.48 | 1.92 | 1.85 | 4.32, 4.26 | 0.8 | 1/1.12 | |
| **2** | 10.29 | 2.30 | 2.24 | 3.98, 3.93 | 0.9 | 10.38 | 2.3 | 2.24 | 4.30, 4.25 | 0.7 | 1/1.12 | |
| **3** | 10.53 | 2.33 | 2.20 | 3.95, 3.95 | 0.0 | 10.62 | 2.33 | 2.20 | 4.31, 4.26 | 0.6 | 1/1.08 | |
| **4** | 10.28 | 2.38 | 2.34 | 3.97, 3.97 | 0.0 | 10.37 | 2.38 | 2.34 | 4.29, 4.25 | 0.5 | 1/1.20 | |
| **5** | 10.41 | 2.37 | 2.37 | 3.98 | 0.0 | 10.50 | 2.28 | 2.23 | 4.23 | 0.0 | 1/1.20 | |
| **6** | 10.53 | 2.29 | 2.24 | 4.00, 3.96 | 0.0 | 10.69 | 2.29 | 2.24 | 4.26, 4.22 | 0.4 | 1/2.60 | |
| **7** | 10.52 | 3.28 | 3.21 | 2.95 | 0.0 | 10.59 | 2.45 | 2.50 | 4.31, 4.27 | 0.4 | 1/0.80 | |

In the $^{13}$C spectra in DMSO-*d6* solution two series of signals are clearly observed for all carbon atoms. Quaternary carbon assignment for both series of signals was derived unambiguously from HMBC experiments. The three- and two-bond connectivity with the NH proton provides the assignment of N=C and C=O carbon atoms in all cases, verified by the connectivities with the $CH_{a(b)}$ and $SCH_2$ protons, respectively. The assignment of the carbon atoms $C_a$ and $C_b$ attached to

Table 2
$^{13}$C-NMR data of compounds **1**–**7**

| Compound | Conformer I | | | | | | Conformer II | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $SCH_2$ | C=O | N=C | C-3 | N=C–$C_a$ | N=C–$C_b$ | $SCH_2$ | C=O | N=C | C-3 | N=C–$C_a$ | N=C–$C_b$ |
| | *$CDCl_3$* | | | | | | | | | | | |
| **1** | 33.87 | 164.90 | 156.10 | 153.50 | 25.46 | 17.97 | 35.94 | 168.70 | 149.95 | 151.70 | 25.60 | 15.75 |
| **2** | 33.99 | 164.83 | 168.66 | 153.63 | 33.62 | 27.83 | 36.15 | 168.92 | 163.12 | 151.95 | 33.19 | 26.92 |
| **3** | 33.59 | 165.13 | 162.40 | 153.92 | 35.56 | 28.00 | 36.18 | 169.09 | | 152.22 | 35.39 | 25.28 |
| **4** | 33.75 | 165.03 | 164.50 | 153.63 | 36.88 | 31.14 | 36.13 | 168.97 | 158.74 | 151.79 | 35.98 | 29.96 |
| **5** | 33.65 | 165.05 | 164.82 | 153.81 | 36.54 | 28.42 | 36.09 | 169.11 | 159.21 | 151.81 | 36.35 | 27.12 |
| **6** | 33.76 | 164.95 | 162.30 | 153.89 | 32.94 | 27.59 | 36.05 | 169.35 | 155.65 | 152.00 | 31.87 | 27.99 |
| **7** | 33.67 | 165.18 | 168.78 | 153.55 | 39.25 | 32.14 | 36.24 | 168.93 | 163.19 | 151.86 | 39.34 | 30.05 |
| | *DMSO* | | | | | | | | | | | |
| **1** | 35.07 | 163.50 | 156.30 | 151.50 | 25.51 | 17.60 | 36.04 | 169.00 | 152.00 | | 25.30 | 17.90 |
| **2** | 35.06 | 162.91 | 167.10 | 151.03 | 32.98 | 28.40 | 35.90 | 168.66 | 163.83 | 151.05 | 32.76 | 28.29 |
| **3** | 34.92 | 164.22 | 163.21 | 151.15 | 35.12 | 27.24 | 36.03 | 168.69 | | 151.07 | 35.10 | 26.90 |
| **4** | 35.08 | 163.08 | 163.28 | 151.15 | 36.56 | 30.19 | 36.01 | 168.71 | 159.72 | 151.12 | 36.34 | 30.51 |
| **5** | 35.07 | 163.25 | 163.30 | 151.24 | 35.85 | 27.67 | 36.04 | 168.82 | 159.84 | 151.32 | 35.80 | |
| **6** | 35.18 | 163.51 | 163.75 | 151.64 | 31.14 | 28.37 | 35.77 | 169.41 | 155.76 | 151.77 | 31.97 | 28.00 |
| **7** | 36.11 | 163.76 | 167.59 | 151.11 | 38.81 | 38.57 | 35.10 | 168.69 | 163.34 | 151.19 | 38.96 | 38.60 |

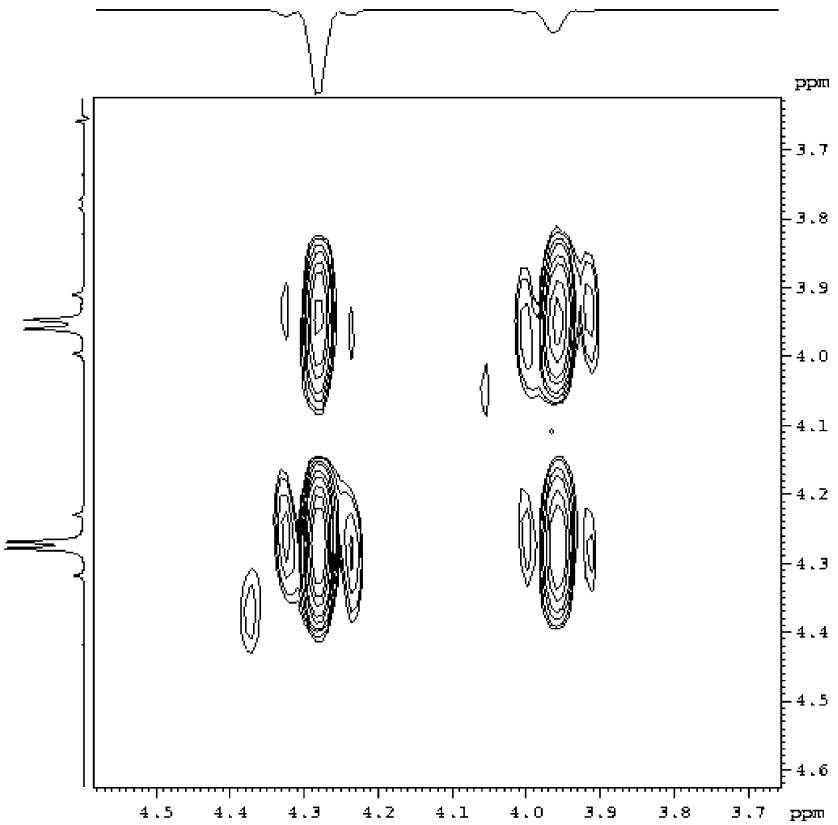



Fig. 2. Part of the phase-sensitive NOESY spectrum of derivative **2** in DMSO-*d6* containing the $SCH_2$ resonances of the two rotamers. In $f_1$ direction is presented the corresponding part of the 1D $^1$H NMR spectrum showing the two second-order AB system resonances. In $f_2$ direction is presented the row extracted from the spectrum showing the relative phase of the cross and diagonal peaks demonstrating the chemical exchange phenomenon existing between these protons.

the N=C bond is effectively accomplished from the HSQC spectra as the associated protons are downfield shifted. Differences between the chemical shifts of the corresponding carbon atoms in the two series of signals are more pronounced in the case of S–C, C=O and N=C carbon atoms being ~1, ~5 and ~6 ppm, respectively. Concerning the other carbon atoms these differences, when they exist, are of maximum 0.2 ppm (Section 4).

The two series of proton and carbon atom resonances, as well as the chemical exchange cross-peaks in the NOESY spectra reveal the existence of two structures in equilibrium slowly interconverting to each other in the NMR time scale. Chemical shift differences between the two series of signals suggest that the isomerization should concern the C=N bond or the amide bond. Giving the existing symmetry around the N=C bond for compounds **1**–**7** the inversion of the nitrogen atom or N=C rotation, will not affect the spectra. Thus, these differences can be explained only by the existence of two rotameric structures around the C(O)–N amide bond. This is in agreement with the results of the NMR study of 2,4-dichlorophenoxyacetyl hydrazide derivatives [18], where the authors observed the existence of rotamers resulting only from the amide bond rotation, although an *E*/*Z*-isomerism relative to the N=C bond is also possible [18,19].

Temperature dependence of the spectra supports also the existence of two isomers in equilibrium. Spectra recorded in a temperature range between 290 and 370 K, in DMSO-*d6* solution, showed that increasing the temperature the two series of peaks broadens

and finally, each couple of corresponding signals, coalesces to one resonance. From the separation of the $SCH_2$ signals and their coalescence temperature ($T_c$ = 360 K), the free energy of activation of this interconversion was found to be $\Delta G^{\neq}_{(360)} = 17.1$ kcal/mol [20], which is in agreement with the amide rotation barrier described in Refs. [20,21].

The integral ratio of the corresponding $CH_2$ signals show that the two rotamers are of almost equal populations with one of them being somehow predominant in compounds **1**–**5** and **7**. An increase of the major rotamer's population as the volume of the N=C< substituent increases is also observed (Table 1). In the case of compound **6**, where the volume of the cyclododecyl substituent is clearly bigger, the population of the major rotamer is more than 2-fold higher. The same trend is observed for the $\Delta\nu/J$ ratio concerning the two $SCH_2$ signals, which tend to be equivalent as the volume of the substituent increases.

In order to identify the two conformers the NOEs observed between the NH and the neighboring protons were used. In *trans* amide orientation a NOE exists between NH and $CH_2$, while in the *cis* amide orientation this NOE is very weak when it exists. A verification of this assignment could be done using the criteria proposed by Himmelreich et al. [17], based on the heteronuclear coupling constant between the $CH_2$ carbon and the NH proton. They proposed that this vicinal coupling constant is close to zero for the *trans* conformation. Indeed the proton coupled $^{13}C$ spectrum showed that heteronuclear $^3J_{CH2-NH}$ was found to be 3.5 Hz for $CH_2$ of Conformer II, while it was too weak to be measured for $CH_2$ carbon of Conformer I. Using both criteria resonances attributed to Conformer II (Tables 1 and 2) were assigned to the *cis* orientation and resonances assigned to Conformer I to the *trans* orientation correspondingly. Furthermore, the heteronuclear geminal coupling constant between the carbonyl carbon and NH was also found to be 7.4 Hz in the *trans* rotamers and 3.0 Hz in the *cis* rotamers, in agreement with the corresponding coupling constants proposed by Himmelreich et al. [19].

Interestingly the spectra of the compounds in $CDCl_3$ exhibit differences comparing to those in DMSO-*d6* solutions concerning mainly the rotamer's population ratio and NH chemical shifts.

Spectra recorded in DMSO–$CDCl_3$ mixture at different solvent ratio's (1/1, 1/2, 1/4, 1/5 v/v DMSO/$CDCl_3$, respectively) reveal that the rotamer II which predominates in DMSO-*d6* becomes, by 10-fold, the minor rotamer in $CDCl_3$ solution. In analogy to the observations made in DMSO solution, the relative population of rotamer I decreases as the volume of the N=C< substituent increases and the population ratio in $CDCl_3$ changes from 1/0.07 in compound **1** to 1/0.25 in compound **6** (Table 1). Moreover, the NH proton of this rotamer exhibits an upfield shift of ~2.2 ppm in $CDCl_3$.

In order to better understand the rotameric equilibrium proposed from the NMR data a theoretical study has been undertaken using molecular mechanics calculations. The conformational space of compound **2** was explored by applying a MonteCarlo–Low Mode search. All single bonds were allowed to rotate resulting in several low energy conformers. The two lower energy conformer are presented in Fig. 3, since the relative energy of all other conformers showed to be more than 2 kcal/mol suggesting that those structures are less probable in solution.

As expected from the experimental data the two most probable structures resulted from the calculations, differ mainly in the relative conformation of

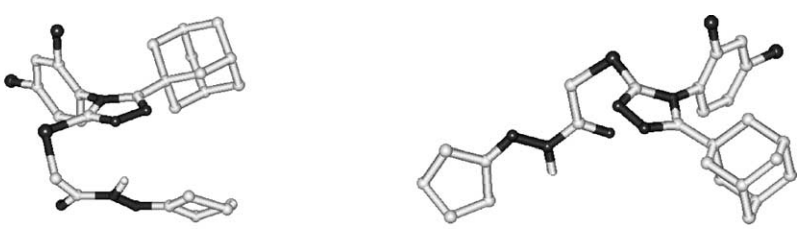



Fig. 3. Representation of the low-energy conformations for derivative **2** derived from MonteCarlo–Low Mode conformational search along with their relative energies (kcal/mol).

the amide bond. Conformer I is the global minimum and the NH bond is *trans* relatively to the C=O carbonyl bond. In Conformer II the NH bond has a *cis* orientation and exhibits a relative energy of 1 kcal/-mol. The energy difference between conformers I and II predicted from the calculations, is quite important and can explain the concentration ratio observed between the two rotameric structures in $CDCl_3$.

It is interesting to notice that Conformer I seems to be stabilized through the intramolecular hydrophobic interaction between the adamantyl moiety attached to the triazole ring and the cycloalkyl N=C< substituent, forcing the $S-CH_2$ bond to a 90° conformation. This interaction is not easy to be investigated because of the severe overlap between adamantyl and cycloalkyl proton signals in the NMR spectrum, but could explain the observed population decrease of Conformer I as the bulk of the cycloalkyl substituent increases and the steric hindrance augments.

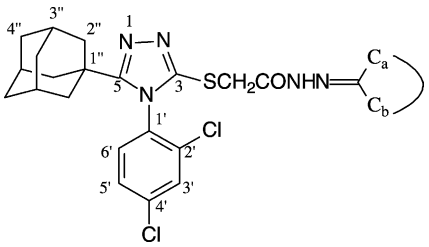
An interesting feature concerning the differences between DMSO and $CDCl_3$ is the dramatic influence of the solvent on the *cis*/*trans* equilibrium. In early studies on the conformational behavior of *N*-acylhydrazones it has been observed that the *cis* isomer is predominant in $CDCl_3$, probably stabilized as dimmer through the formation of pairs of hydrogen bonds [13,14]. More recent studies showed that the *trans* isomer is predominant in $CDCl_3$ and the *cis*/*trans* ratio is inversed in DMSO, in agreement to our results [19,22].

The stabilization of the *cis* conformer together with the downfield shift of the NH resonance in DMSO-*d6* should be explained by the formation of a hydrogen bond with the surrounding solvent. Furthermore, the existence of the two additional resonances in DMSO-*d6* could provide evidence that this hydrogen bond is probably formed with the residual water molecules existing in solution. The possibility of a hydrogen bond with water molecules is supported by recent crystallographic studies of aroylhydrazones derived from the nicotinic acid hydrazide [23,24] and crystallized from alcohol. In both cases the amide bond was found to adopt a *trans* orientation linked with water molecules via the carbonyl oxygen and/or the NH hydrogen.

In conclusion, experimental NMR data and molecular mechanics calculations consent that the mercaptoacetic acid hydrazides under study exist in two rotameric conformations around the amide bond. The *trans* conformer is predominant in $CDCl_3$ and seems to be stabilized by the presence of hydrophobic interactions between the two aliphatic ends of the molecule. The *cis* conformer is stabilized in DMSO solution probably through the formation of hydrogen bonds.

## 4. Supporting material

$^1$H-NMR chemical shifts (ppm) of compounds **1**–**7** in (**A**) $CDCl_3$ and (**B**) DMSO-*d6*. Chemical shifts in parentheses concern Conformer II.




Protons of the 4-(2,4-dichlorophenyl) and 5-adamantyl groups were resonated in almost the same frequency (±0.02 ppm) for all compounds. The chemical shift values of these protons (in ppm) are as follows:

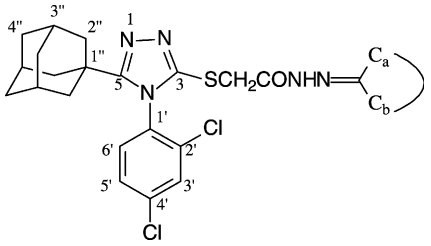
**A**.

Phenyl 3′-H: 7.62 (7.59),
Phenyl 5′-H: 7.46 (7.42),
Phenyl 6′-H: 7.34 (7.36),
Adamantyl 2″-H: 1.98, 1.82,
Adamantyl 3″-H: 1.98,
Adamantyl 4″-H: 1.70, 1.59, and concerning DMSO-*d6*.

**B**.

Phenyl 3′-H: 8.02 (7.99),
Phenyl 5′-H: 7.68 (7.70),
Phenyl 6′-H: 7.76 (7.78),
Adamantyl 2″-H: 1.89, 1.75,
Adamantyl 3″-H: 1.88,
Adamantyl 4″-H: 1.62, 1.51.

Table S1
$^{13}$C-NMR chemical shifts (ppm) of compounds **1**–**7**. (**A**) in $CDCl_3$, (**B**) in DMSO. Chemical shifts in parentheses concern Conformer II




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| **A**. *$CDCl_3$* | | | | | | | |
| C-5 | 162.28 | 162.2 | 162.34 | 162.2 | 162.15 | 161.68 | 162.0 |
| C-1″ | 35.74 | 35.73 | 35.82 | 35.74 | 35.74 | 35.81 | 35.72 |
| C-2″ | 40.09 | 40.01 | 40.20 | 40.11 | 40.11 | 40.16 (40.13) | 40.11 |
| C-3″ | 27.76 | 27.75 | 27.84 | 27.75 | 27.74 | 27.82 (27.91) | 27.74 |
| C-4″ | 36.03 | 36.02 | 36.12 | 36.03 | 36.03 | 36.11 (36.20) | 36.03 |
| C-1′ | 130.7 | 130.78 | 130.84 | 130.75 | 130.73 | 130.78 | 130.71 |
| C-2′ | 134.14 | 134.32 (134.6) | 134.34 | 134.22 | 134.21 (134.38) | 134.35 (134.62) | 134.26 |
| C-3′ | 131.0 | 130.97 (130.71) | 131.07 | 130.98 (130.70) | 131.00 (130.68) | 131.08 (130.74) | 130.97 (128.65) |
| C-4′ | 137.70 | 137.8 (137.0) | 137.79 | 137.7 (137.04) | 137.71 (137.02) | 137.83 (137.20) | 137.68 |
| C-5′ | 128.34 | 128.39 (128.10) | 128.48 | 128.41 (128.06) | 128.42 (128.04) | 128.54 (128.11) | 128.40 |
| C-6′ | 131.12 | 131.11 (131.53) | 131.19 | 131.10 (131.53) | 131.08 (131.36) | 131.16 (131.70) | 131.08 (131.56) |
| N=C< substituent | – | 25.0 (24.71) | 27.10 | 29.98 (30.11) | 27.37 (27.05) | 22.17 (22.10) | 38.83 (37.60) |
| | | 24.77 (24.57) | 26.21 | 24.51 (24.21) | 25.18 (25.11) | 22.27 (22.58) | 37.89 (37.49) |
| | | | 25.68 | 27.20 (27.36) | 23.98 (24.23) | 22.71 (22.87) | 37.64 (37.46) |
| | | | | 30.22 (30.08) | 24.72 (24.38) | 22.95 (23.10) | 36.27 (33.04) |
| | | | | | 26.06 (26.12) | 23.22 (23.16) | 27.62 (29.60) |
| | | | | | | 23.48 (24.21) | 27.62 (27.58) |
| | | | | | | 24.64 (24.45) | 39.04 (38.87) |
| | | | | | | 24.81 (25.69) | |
| | | | | | | 24.88 (25.75) | |
| **B**. *DMSO* | | | | | | | |
| C-5 | 161.0 (161.2) | 160.64 (160.83) | 160.83 (160.55) | 160.63 (160.84) | 160.86 (160.64) | 161.08 (160.93) | 160.82 (160.63) |
| C-1″ | 35.12 | 35.11 | | 35.11 | 35.12 | 35.52 | 35.13 |
| C-2″ | | 39.78 | 39.78 | 39.77 | 39.77 | 40.17 | 39.78 |
| C-3″ | | 27.28 | 27.32 | 27.30 | 27.31 | 27.70 | 27.33 |
| C-4″ | | 35.7 | 35.73 | 35.71 | 35.72 | 36.11 | 35.74 |
| C-1′ | | 131.46 (131.28) | 131.48 (131.31) | 131.47 (131.26) | 131.45 (131.22) | 131.78 (131.57) | 131.30 (131.50) |
| C-2′ | | 133.50 (133.41) | 133.55 (133.47) | 133.53 (133.43) | 133.52 (133.42) | 133.79 (133.77) | 133.48 (133.56) |
| C-3′ | | 130.21 | 130.28 (130.26) | 130.24 (130.28) | 130.21 (130.30) | 130.56 (130.66) | 130.29 (130.25) |
| C-4′ | | 136.23 (136.14) | 136.28 (136.20) | 136.28 (136.17) | 136.17 (136.33) | 136.51 (136.72) | 136.30 (136.21) |
| C-5′ | | 128.78 (128.76) | 128.84 (128.80) | 128.78 (128.84) | 128.74 (128.86) | 129.07 (129.22) | 128.84 (128.79) |
| C-6′ | | 132.54 | 132.59 (132.59) | 132.57 | 132.55 (132.55) | 132.90 (132.84) | 132.56 (132.56) |
| N=C< substituent | | 24.43 (24.36) | 26.88 (26.67) | 29.55 (29.61) | 26.88 (26.88) | 23.71 (25.29) | 38.56 (38.48) |
| | | 24.29 (24.21) | 25.71 (25.61) | 26.98 (26.94) | 25.99 (26.02) | 23.59 (25.08) | 37.21 (37.17) |
| | | | 25.07 (25.07) | 23.90 (23.69) | 24.70 (24.79) | 23.37 (24.25) | 37.10 |
| | | | | 29.74 (29.88) | 24.31 (24.31) | 28.95 (23.00) | 31.06 (30.55) |
| | | | | | 23.94 (23.81) | 22.81 (22.81) | 27.11 (27.09) |
| | | | | | | 22.77 | 27.11 (27.09) |
| | | | | | | 22.50 | |
| | | | | | | 22.05 (22.20) | |
| | | | | | | 25.96 (25.96) | |

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