

Theoretical Study of Some Nitrososulfamide Compounds with Antitumor Activity

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Abstract: The lowest-energy conformations of four 2-chloroethylnitrososulfamides were determined using the MM+ molecular mechanics method as implemented in Hyperchem 6.0. Some of the calculated structural parameters, angles and bonds lengths were compared with the crystal structure data of N-nitroso-N-(2-chloroethyl)-N'-sulfamoyl-proline. Using MM+, AM1 and PM3 the *anti* conformation was predicted to be more stable than the *syn* conformation in each of these compounds. With these methods we found that the relative energy of the transition state (TS) was considerably higher, but with the *ab initio* method using RHF with minimal basic function STO-3G we found that the *syn* conformation is predicted to be slightly more stable. The determination of some atomic charges of a selection of atoms on the *syn*, *anti* and TS structures of the various compounds provided some details about the nature of the transition state.

Keywords: Nitrososulfamides; Molecular modelling; *syn* conformation; *anti* conformation; Transition state.

Introduction

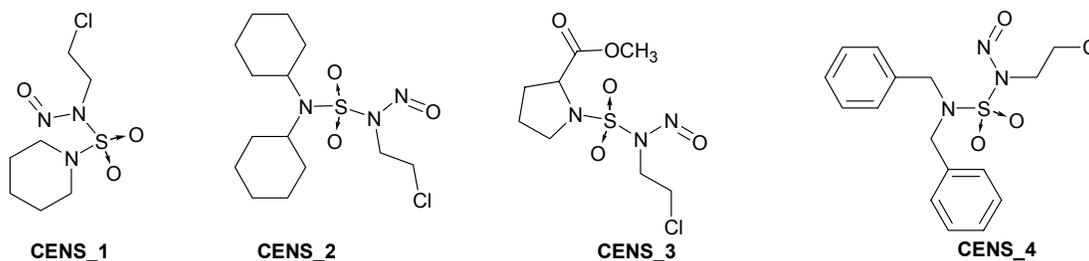
Until now, nitrosourea compounds have been considered some of the most powerful alkylating agents used in the chemotherapy, but they present the disadvantage of releasing isocyanate, a very toxic product, which limits their use [1]. It has been shown that this problem can be avoided by

synthesizing a new family of compounds in which the nitrosourea function is replaced by the sulfonyl group [2]. It has also been shown that these 2-chloroethylnitrososulfamide compounds (CENS) were very active antitumor agents and could be considered new typical mutagenic and carcinogenic compounds [3]. Molecular modeling has become a useful tool for examining different interactions in molecules [4]. As no theoretical studies had previously been done on these compounds, we became interested in applying computational methods (MM+, PM3, AM1 and *ab initio*) to some of these 2-chloroethylnitroso-sulfamides and we now report our results in this area.

Results and Discussion

The 2-chloroethylnitrososulfamide molecules used in our theoretical study have been prepared in our laboratory by Abdaoui *et al.* [2, 3]. They are shown in Figure 1. Figure 2 shows the common alkylating moiety of these molecules.

Figure 1. The structures of the four CENS.



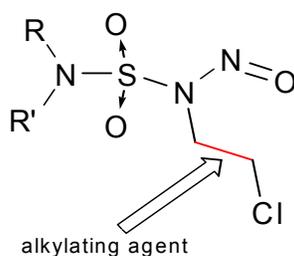
CENS_1: N-Nitroso-N-(2-chloroethyl)-N'-sulfamoylpiperidine

CENS_2: N-Nitroso-N-(2-chloroethyl)-N'-dicyclohexylsulfamide

CENS_3: N-Nitroso-N-(2-chloroethyl)-N'-sulfamoylprolinate

CENS_4: N-Nitroso-N-(2-chloroethyl)-N'-dibenzylsulfamide

Figure 2: Alkylating moiety in CENS



All the molecular mechanics calculations were carried on a Pentium 133 MHz with the MM+ force field as implemented in Hyperchem 6.0. The different 2-chloroethylnitrososulfamide compounds were

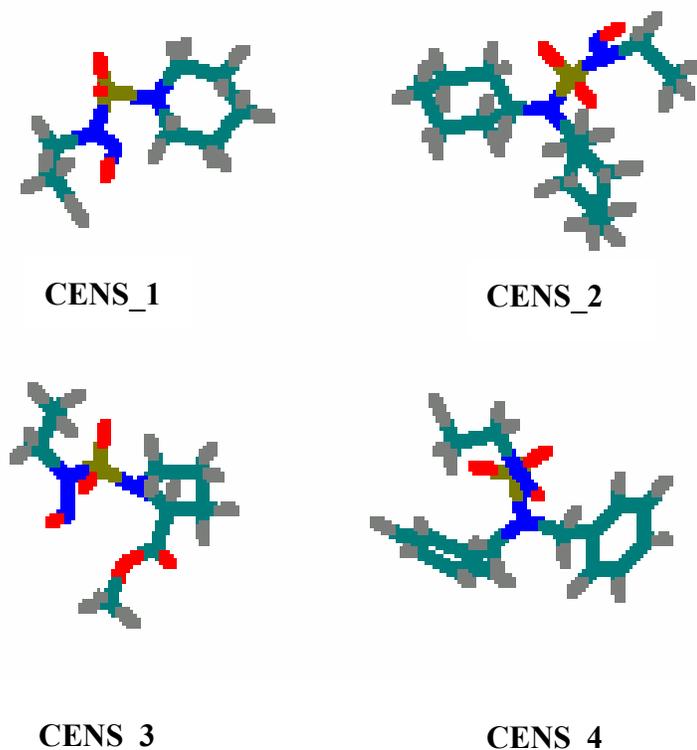
built using Hyperchem. The search of the lowest energy conformation was performed with Allinger's software including a Metropolis Monte Carlo (MMC) approach for generation of the new conformations using random variations of the randomly selected torsional angles [5]. This search was performed with a range for ring acyclic or ring torsion variation of ± 10 - 120° . The Random Walk, and Metropolis Criterion use $T = 300$ K, switching to 400 K. The structures which were found by MMC were re-minimized by Polack-Ribiere optimization using MM+.

The neutral form of compounds has been used, with a dielectric constant of 1.5 applied in the calculations of the electrostatic interaction [6]. Energy minimization was terminated when the gradient root mean square was below 0.01 kcal/mol. After the energy minimization, acceptance was determined by the following two criteria: 1) execution of a conformational search by the simulated annealing method [heat time: 0.1ps, run time: 0.5 ps, starting temperature: 100 K, simulation temperature: 300K, temperature step: 30K] which is described by Choe *et al.* [7]; 2) the structure obtained was minimized with a semi-empirical method (PM3) and we verified that there were no negative frequencies in the vibration spectrum. Table 1 gives the detailed energy data for the most favored conformations of the four CENS, which are shown in Figure 3.

Table 1: The detailed energies of the most favored conformations of the four CENS

Parameter	Compound			
	CENS 1	CENS 2	CENS 3	CENS 4
Bond	0.7717	1.8569	0.8473	0.8245
Angle	4.1127	6.0393	10.0222	4.2251
Dihedral	-2.9549	2.5646	-0.8142	-14.4350
Stretch-bend	0.1267	0.3744	-0.1083	0.1374
Vdw	6.2340	7.7230	4.6044	5.3712
Electrostatic	-14.3593	-13.9257	-13.2188	-14.4369
E steric	-6.0740	6.2890	1.3825	-18.3134

Table 1 contains some significant information: 1) the primary contribution to the energy is the electrostatic energy for CENS_1, CENS_2 and CENS_3, but for the CENS_4 compound the strongest contribution to the energy are the dihedral and electrostatic energies; 2) the bond and stretch-bend energies are relatively unimportant in the total energy; 3) the angle energy and Vdw interaction have a big influence of the energy.

Figure 3: The most favored conformations of the four CENS

During the global minimum conformational research for CENS_4, two methods were used for energy optimization: MM+ and a semi empirical method (PM3) [8]. The CENS_4 geometry was optimized with MM+, and the obtained structure was used as initial structure for the PM3 calculation. Once the minimal energy of the structure was given using the semi empirical method, we used it as the basic structure for a new calculation with molecular mechanics.

From PM3 method, as implemented in Hyperchem 6.0, a large volume of data can be produced. The values for heat of formation, electric dipole and binding energy, for the lowest-energy conformation of the four CENS are summarized in Table 2.

Table 2: Bonding energy, heat of formation (kcal/mol) and electric dipoles (Debye) for the four CENS as calculated by the PM3 semi-empirical method.

Parameter	CENS_1 (kcal/mol)	CENS_2 (kcal/mol)	CENS_3 (kcal/mol)	CENS_4 (kcal/mol)
Binding energy	-2610.314	-4455.257	-2972.178	-4291.6479
Heat of formation	-71.58632	-96.26391	-143.470	-6.504729
Dipole (D)	3.013	3.232	4.273	3.712

According to the bonding energy, quantitatively the order of the stability of the four CENS can be established as: CENS_2 > CENS_4 > CENS_3 > CENS_1.

The bond lengths and bond angles of the common fragment of the four CENS (Figure 4) calculated by molecular mechanics (Tables 3 and 4) was compared with those obtained using X-ray crystallography for N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline [2b] derived from CENS_3 (Figure 5).

Figure 4: Common fragment of the four CENS.

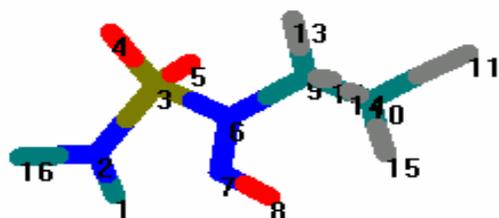


Figure 5: N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline

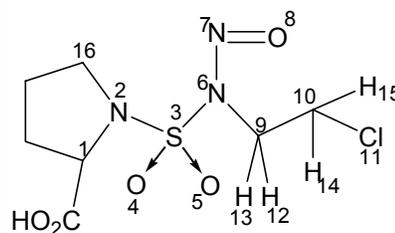


Table 3: Comparison of bond length (Å) parameters obtained by X-ray crystallography for the common fragment of the N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline and that with those obtained by molecular mechanics calculations.

Bond	Crystallographic data drawn from N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline	MM+ calculations for			
		CENS_1	CENS_2	CENS_3	CENS_4
C(1)-N(2)	1.48	1.45	1.47	1.44	1.45
C(16)-N(2)	1.45	1.45	1.46	1.45	1.45
N(2)-S(3)	1.57	1.65	1.65	1.64	1.65
S(3)-O(4)	1.44	1.44	1.44	1.44	1.44
S(3)-O(5)	1.40	1.44	1.44	1.44	1.44
S(3)-N(6)	1.68	1.65	1.65	1.65	1.65
N(6)-N(7)	1.37	1.35	1.36	1.35	1.35
N(7)-O(8)	1.20	1.17	1.17	1.17	1.17
N(6)-C(9)	1.47	1.45	1.46	1.45	1.45
C(9)-C(10)	1.50	1.54	1.53	1.54	1.53
C(10)-Cl(11)	1.73	1.79	1.80	1.79	1.79

Table 4: Comparison of bond angle ($^{\circ}$) parameters obtained by X-ray crystallography for the common fragment of the N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline and that with those obtained by molecular mechanics calculations.

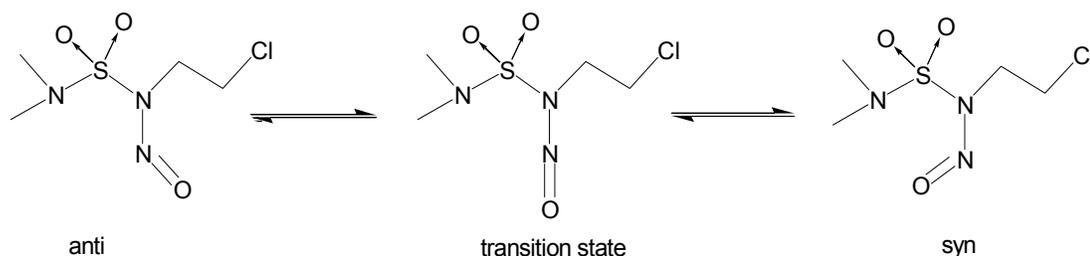
Bond	Crystallographic data drawn from N-nitroso-N-(2-chloroethyl)-N'-sulfamoylproline	MM+ calculations for			
		CENS_1	CENS_2	CENS_3	CENS_4
N(6)N(7)O(8)	113.5	123.2	124.1	123.3	123.1
N(2)S(3)O(4)	109.7	110.3	110.4	109.2	108.5
N(6)S(3)O(5)	103.0	109.7	108.9	108.7	110.0
N(6)S(3)N(2)	105.1	98.4	97.4	97.2	100.7
O(4)S(3)O(5)	121.7	118.8	120.3	120.3	117.2

According to the results of Tables 3 and 4 it should be noted that the differences between the calculated and experimental values for the bond lengths are all less than 0.05 Å except for the N2-S3 bond length; the difference then reaches 0.08 Å. In the same way, the differences between the calculated and experimental values for the bond angles does not exceed 8° except in the case of the N6-N7-O8 bond angle; the difference in this case being 10.8°. By taking into account the difference between the various structures of the CENS and the structure of the carboxylic acid of the CENS_3 (Figure 5) with which we made the comparison, concerning the common part of the CENS we can conclude that the calculated parameters show good agreement with experimental results and this opens the possibility of using detailed molecular information obtained by molecular mechanics (MM+) for analysis of the characteristics of CENS.

Anti and syn calculations

The relative stabilities of the *anti* and *syn* conformers and the interconversion between them are very important to understand reactivity [9]. We have calculated the lowest-energy of the *anti* and *syn* conformers of the four CENS and the transition state (TS) for the *anti-syn* conformer using MM+, AM1, PM3 and *ab initio* methods.

Figure 6: Anti, syn and transition state structures



The *syn* conformation was built starting from the most stable conformation obtained previously, by making a 180° rotation of the N=O bond around the N-N bond. The obtained structure is optimized with MM+ by using the Polack-Ribiere algorithm to a maximum energy gradient of 0.01 kcal/(Å.mole).

Table 5: The values of the steric energy (kcal/mol) of the *anti* and *syn* structures and the difference between these two energies as calculated by MM+.

	CENS_1	CENS_2	CENS_3	CENS_4
<i>anti</i>	-6.074	1.382	6.289	-18.313
<i>syn</i>	-5.435	2.338	6.436	-14.553
ΔE (<i>syn-anti</i>)	0.638	0.955	0.147	3.760

The MM+ calculations (Table 5) show that *anti* conformation is the most stable one for the four CENS molecules studied. This difference varies from 0.147 (CENS_3) to 3.760 kcal/mole (CENS_4). Using the molecular mechanics results we can say that quantitatively the *anti* and *syn* conformations should exist in similar amounts ($\Delta E < 1$) for CENS_1, CENS_2 and CENS_3, whereas for CENS_4, only the *anti* conformation is possible because $\Delta E > 2$ [10-12].

Semi – empirical methods

The *anti* and *syn* conformations obtained for the four CENS with MM+ were re-optimized with PM3 and AM1 by using the Polack-Ribiere algorithm to a maximum energy gradient of 0.01 kcal/(Å.mole). The structure of the transition state was obtained by imposing a geometrical constraint making the N-N=O bond angle equal to 180°. The search for the transition state (TS) and vibrational calculations are done using the Eigenvector following Algorithm. The confirmation of its localization was done by checking in the vibration spectrum for the presence of only one imaginary frequency [13]. The results obtained are given in Table 6:

Table 6: The relative energy (kcal/mol) of the *anti*, *syn* and TS structures of the four CENS calculated by PM3 and AM1 semi empirical methods.

		CENS_1	CENS_2	CENS_3	CENS_4
PM3	<i>anti</i>	-2611.166	-2972.178	-4455.257	-4291.156
	<i>syn</i>	-2609.039	-2971.424	-4453.520	-4288.289
	TS	-2551.511	-2912.350	-4396.771	-4231.334
	$ \Delta E$ (<i>anti-syn</i>)	2.127	0.754	1.737	2.867
	$ \Delta E$ (TS- <i>anti</i>)	59.655	59.828	58.486	59.822

Table 6. Cont.

		CENS_1	CENS_2	CENS_3	CENS_4
AM1	<i>anti</i>	-2626.291	-2983.727	-4475.774	-4300.583
	<i>syn</i>	-2620.866	-2977.450	-4471.331	-4295.431
	TS	-2544.697	-2900.914	-----	-4231.334
	ΔE (<i>anti-syn</i>)	5.425	6.277	4.443	5.152
	ΔE (TS- <i>anti</i>)	81.594	82.813	-----	69.249

According to the results (Table 6) we can note:

1. The two methods AM1 and PM3 give the same most stable conformation (*anti*).
2. The energy difference between the *syn* and *anti* conformations is higher in the PM3 than with the AM1 method.
3. In the PM3 method, the energy difference between the *anti* conformation and the transition state is almost constant for the four CENS (around 59.kcal/mole). But in the AM1 method it varies from 69.249 to 82.813kcal/mole. According to the magnitude of this difference the transition between the *anti* to *syn* conformation is difficult.
4. One notices in our search for the transition state of CENS_3 that the imposed constraint N-N=0 equal to 180° is not respected because at the beginning of each optimization this parameter changes considerably. Consequently, we could not locate a transition state for this structure.

Ab Initio method

In order to confirm this result we used an *ab initio* method. For this purpose we optimized the *syn* and *anti* conformations by the same procedure used in PM3 and AM1 calculations using the RHF method with a minimal basic function STO-3G. In the simplest case of the CENS_1 molecule the system is formed with 97 basis functions and 291 Gaussian primitives and this represents a great challenge for calculation with an IBM Pentium III 133 MHz personal computer (in terms of computational time). The transition state was obtained with the same procedure as that used in AM1 and PM3 methods. The calculation of the transition state was given with the same method RHF/ STO-3G). The results obtained are shown in Table 7:

Table 7: The relative energy (kcal/mol) of the *anti*, *syn* and TS structures of the four CENS calculated by the RHF method with a minimal STO- 3G basis function.

	CENS_1	CENS_2	CENS_3	CENS_4
E <i>anti</i>	-941384.75	-1057519.50	-1110126.50	-1154040.75
E <i>syn</i>	-941386.78	-1057521.00	-1110126.67	-1154045.37
E (TS)	-941300.25	-1057434.37	-1110041.50	-1153959.62
ΔE (<i>anti-syn</i>)	2.03	1.50	0.17	4.62
ΔE (TS- <i>syn</i>)	84.53	86.63	85.17	85.74

These results allow the following observations:

1. We obtain a completely contrary order of stability to that obtained by the other methods (molecular mechanics and semi empirical). Thus, the *syn* conformation is now slightly more stable than the *anti* conformation.
2. The energy barrier between the *syn* conformation and the transition state is around 85 kcal/mole.
3. Since the energetic barrier between the *syn* conformation and the transition state is very important (85 kcal/mol) we can say that the transition between the *syn* to *anti* conformations is very difficult.

From the results of Table 8 some important information can be observed. On the one hand, the N center atoms of CENS_1, CENS_2 and CENS_3 undergo a reduction of 2/3 of their electronic density (obtained by the PM3 method) in the various transition states but for CENS_4 it loses only a half of its electronic density. On the other hand, the electronic density in the SO₂ group in CENS_1, CENS_2 and CENS_3 varies considerably, but in CENS_4 it remains almost constant. We thus note that in the CENS_1, CENS_2 and CENS_3 the SO₂ group plays a significant role in the formation of transition state but in CENS_4 it does not appear to participate in the structure of the transition state.

Table 8: The charge of selected atoms obtained by PM3 calculations (four CENS in *syn*, *anti* and transition form).

	N (center)	N (nitroso)	O (nitroso)	S (nitroso)	O4, O5
CENS_1					
<i>anti</i>	-0.584	0.338	-0.279	2.264	-0.813, -0.796
<i>syn</i>	-0.561	0.360	-0.286	2.232	-0.798, -0.825
TS	-0.186	-0.044	-0.103	0.774	-0.322, -0.340
CENS_2					
<i>anti</i>	-0.572	0.332	-0.280	2.279	-0.826, -0.800
<i>syn</i>	-0.560	0.359	-0.295	2.211	-0.811, -0.797
TS	-0.167	-0.044	-0.091	0.786	-0.341, -0.349

Table 8. Cont.

	N (center)	N (nitroso)	O (nitroso)	S (nitroso)	O4, O5
CENS_3					
<i>anti</i>	-0.562	0.349	-0.269	2.273	-0.832, -0.793
<i>syn</i>	-0.564	0.363	-0.270	2.231	-0.791, -0.828
TS	-0.173	-0.024	-0.092	0.788	-0.352, -0.341
CENS_4					
<i>anti</i>	-0.545	0.335	-0.290	2.253	-0.822, -0.810
<i>syn</i>	-0.548	0.348	-0.276	2.0204	-0.805, -0.821
TS	-0.257	0.191	-0.330	2.140	-0.810, -0.797

Conclusions

First, the comparison between the computational results and the crystallographic data shows that molecular mechanics is a powerful tool to study CENS derivatives. Second, according to the MM+, PM3 and AM1 calculations, the *anti* conformation is more stable than the *syn* conformation but the transition between the *anti* and *syn* conformations is not favorable because the relative energy of the transition state is higher. Third, the *ab initio* calculations (RHF/STO-3G) give contradictory results. Thus, the *syn* conformation became slightly more stable. To clarify these discrepancies further studies using other more powerful computational methods with superior basis sets or the DFT method are necessary. We also note that the presence of the two aromatic systems in the CENS_4 molecule confers it a particular behavior. With MM+ calculations we observe only the *anti* conformation and with PM3 charge calculations the SO₂ group in the transition state do not undergo charge modification.

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Sample availability: Available from the authors.

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