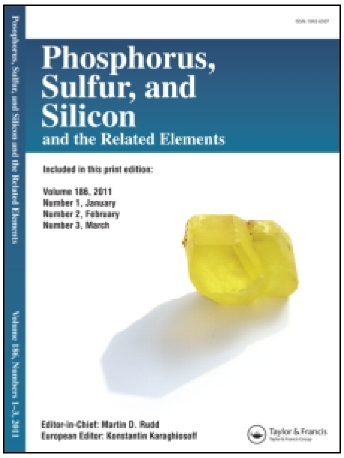

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INTERMOLECULAR PROTON TRANSFER PROCESS IN SULFUR TAUTOMERIC HETEROCYCLES. I. A QUANTUM CHEMICAL APPROACH

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Molecular structures of two tautomeric aromatic heterocycles, 2-mercaptobenzoxazole and 2-mercaptobenzothiazole, were analyzed from a quantum chemical approach by means of AM1 semiempirical molecular orbital calculations. Thiones are the preferential tautomeric structures of these compounds in solid phase and solutions, and the AM1 profiles of potential wells agree the experimental evidences.

In spite of the good description of the thione and thiol structures by the AM1 approach, the experimental tautomerism observed at room temperature can not be explained by means of an *intramolecular protonic transfer* mechanism. The potential barrier AM1 calculations of both tautomers range from 40 to 50 kcal/mol, approximately.

Therefore, we have postulated a tautomeric process through a geometrical model of co-planar dimers in these heterocyclic compounds. These dimers are more stable than the respective monomers and this model permit to assume a simultaneous *intermolecular proton transfer* process between sulfur and nitrogen centers in the thiocyanate (NCS) syntonic units. Our results give a coherent mechanistic explanation to several experimental observations in chemical reactions and spectroscopic data.

Keywords: 2-mercaptobenzoxazole; 2-mercaptobenzothiazole; AM1 calculations; tautomeric equilibrium; sulfur heterocyclic dimers

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INTRODUCTION

Recently, Adelaere et al.[1] have found a novel synthetic route of *o*-amino-benzenethiol, an important synthetic intermediate for pharmaceutical, rubber and dye industries, by heating of 2-mercaptobenzothiazole in an excess of hydrazine, ethylenediamine or propylenediamine, under milder conditions than "alkaline fusion". This new synthetic route can be well understood assuming a nucleophilic attack to the thione tautomer on the carbon of the NCS syntonic unit. However in spite of several other experimental evidences about the tautomeric equilibrium that these sulfur heterocyclic species such as 2-mercaptobenzoxazole (MBO) and 2-mercapto-benzothiazole (MBS), present in solution of polar and non-polar solvents,[2] from a commercial point of view, mistakes in the sales of these compounds as thiols have disconcert to many experimentalists.

During the last time we have been interested in the electronic properties of the NCS syntonic unit [3–5] and the resonance and inductive effects that substituents induce on the sulfur atom through the carbon and nitrogen centers. Particularly we have been interested in the proton transfer (PT) process between sulfur and nitrogen centers. Therefore we have decide to study MBO and MBS as two particular molecular species involving a tautomeric process due to the proton transfer in the thiocyanate NCS syntonic unit (see Fig. 1).

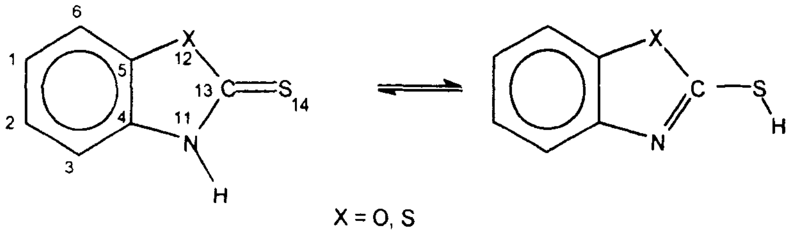

FIGURE 1 Tautomeric equilibrium of MBO and MBS systemsGJ

In the present work we analyze the nature of the electronic and molecular structure of these two tautomeric aromatic heterocycles, MBO and MBS. and the PT migration on the NCS syntonic unit from a semiempirical quantum chemical approach. Up to date, *ab initio* calculations are not reliable enough in order to understand these complexes molecular dynamic process in the NCS syntonic unit, mainly due to the M.O. basis set dependence of these sulfur compounds.[3] In order to understand the thermodynamical stabilities of these molecular structures, as well as the potential barriers for the PT process, we have used several semiempirical methods such as: MNDO, PM3 and AM1, and *ab initio* calculations in the 3–21 G* and 6–31 G* basis sets, however, after compare from a thermodynamical and geometrical point of view the molecular structures of the monomers under study, we have found the most reliable results in the AM1 approach.

COMPUTATIONAL DETAILS

Calculations were carried out in an Apollo 10000 computational work station, at the University of Chile. Molecular geometries were optimized under total relaxation energy by using the MNDO,[6]AM1,[7] and PM3[8] procedures. *Ab initio* calculations in the 3-21 G* and 6-31 G* basis sets were done for the monomeric compounds. The molecular parameters for dimers and the potential profiles of the intermolecular proton transfer process developed in the AM approach are presented in this work.

RESULTS AND DISCUSSIONS

It is a well known fact that under normal conditions of temperature and pressure, solutions of protic or nonprotic solvents of MBS are currently found as thione-thiol forms,[2] where the thio-ketone is the predominant species at room temperature. The same conclusion was obtained by Koch[10] through electronic absorption spectroscopy of MBS in benzene, chloroform and ethanol solutions, where the greater stability of the thiocarbonyl over the thiol form appears to be independent of the nature of the solvent.

Monomers and intramolecular proton transfer

In order to explain these tautomeric experimental observations, we have analyzed the relative stabilities of the MBO and MBS molecular tautomers by means MNDO, AM1 and PM3 semiempirical M.O. calculations and *ab initio* calculations in the 3-21 G* and 6-31 G* basis sets. The semiempirical calculations were discordant, since PM3 contrary to AM1 calculations determine the thiol structure as the main stable tautomer instead the thione structure, in disagreement with the experimental data [2,10] and the *ab initio* calculations, and the MNDO results are dependent on the parametrization used.[11] Thus we have worked in the AM1 approach because this method describes well the experimental and *ab initio* calculation trends, where, according to our calculations, thione monomers are slightly more stable than the corresponding thiol structures (3.0 and 0.5 kcal/mole for MBO and MBS, respectively). Therefore, we have discarded the MNDO and PM3 methods in the study of the PT mechanism of the tautomeric process.

TABLE I AM1 Optimized Molecular Geometry of 2-Mercaptobenzoxazole (MBO) and 2-Mercaptobenzothiazole (MBS) Tautomers[a,b]

Bond Length	*Thione(MBO)*	*Thione(MBS)*	*Thiol (MBO)*	*Thiol (MBS)*
S-H			1.329	1.327
N-H	0.988	0.993		
C-S			1.682	1.679
C-S	1.557	1.558		
N-CS	1.397	1.387	1.333	1.328
N-C_{ar}	1.404	1.401	1.412	1.401
C_{ar}-S		1.696		1.689
C_{ar}-O	1.401		1.397	
C_4-C_5	1.433	1.428	1.438	1.436
Angles	*Thione(MBO)*	*Thione(MBS)*	*Thiol (MBO)*	*Thiol (MBS)*
HSC			98.3	101.4
CNH	124.4	122.8		
NCS	130.6	127.8	131.2	126.6
CNC_{ar}	109.8	114.3	105.7	109.8
$NC_{ar}C_{ar}$	107.4	112.5	108.4	114.3
$SC_{ar}C_{ar}$		110.0		109.5
$OC_{ar}C_{ar}$	108.8		108.0	

a. To see Figure 1 for numeration indexes. b. Bond lengths in Å.

The main AM1 optimized geometrical parameters for this series under study are presented in Table I. From these data, the main changes observed in the thione and thiol tautomers for MBO and MBS compounds occur in the NCS syntonic unit. Heat of formation, ionization potential and dipole moments of these tautomeric structures are shown in Table II. Furthermore, in Table III we present the *ab initio* calculations under the same AM1 geometry optimization for the same monomeric compounds.

TABLE II Heat of Formation (ΔH_f), Ionization Potential (IP) and Dipole Moment (μ) of MBO and MBS tautomers and anions by AM1 calculations

Physical Parameters	*MBO Thione*	*MBS Thione*	*MBO Thiol*	*MBS Thiol*	*MBO Anion*	*MBS Anion*
ΔH_f kcal/mol	35.11	53.81	38.17	54.31	-6.794	12.09
IP, eV	8.898	8.446	8.829	8.694	3.791	3.781
μ, D	5.00	4.60	0.48	0.92	7.89	7.54

TABLE III Ab initio calculations of MBO and MBS tautomers and anions

Structure	*3–21 G* basis set*		*6–31 G* basis set*	
	Energy (A.U.)	*Relative energy (kcal/mol)*	*Energy (A.U.)*	*Relative energy (kca/mol)*
MBO(thione)	- 790.746616	0	- 794.799186	0
MBO (thiol)	- 790.716848	16.68	- 794.785135	8.81
MBO (anion)	- 790.642167	65.54	- 794. 700899	61.68
MBS (thione)	-1111.978245	0	-1117.459077	0
MBS (thiol)	-1111.949837	17.82	-1117.445932	8.25
MBS (anion)	-1111.883842	59.24	-1117.367587	57.41

Heat of formation values determined by the AM1 calculations agree with the experimental trends observed from bond heats for thiol-thione tautomers at room temperature. [12] On the other hand, the different dipole moment expected for the thione (4.60 D) with respect to the thiol structure

(0.92 D) in MBS, as well as in MBO (see Table II), is a decisive factor in the comprehension of the thione as the preferential structure in solution according to the experimental data in polar and non polar solvents. [4,10]

Notwithstanding, the thione species is the main structure in the tautomeric equilibrium, the thiol species can be found in two main conformers. In Fig. 2 we present the C-SH rotational potential profiles of the monomeric MBO and MBS thiol structures. These AM1 calculations have been done every 5 degrees for a NC-SH rotational dihedral angle, under complete relaxation of the molecular system. From this figure we can see that the *cis*-NC-SH structure of the MBS heterocycle is the stable conformer (4 to 5 kcal/mol over the *trans*-isomer), while in the MBO both conformers present a very similar energy.

In order to analyze the PT process between N and S centers in the syntonic unit of MBO and MBS, we determined the intramolecular path of minimum potential energy through the potential-energy surface. In these calculations we used a systematic elongation of the N-H bond length in a bi-dimensional surface determined by NCS and optimizing the molecular structure at every point of the minimum energy pathway. We have made use of the TS option under the FORCE routine for the transition state calculations and we have obtained a single negative Hessian' coefficient. The AM1 calculated energies in this transition state respect to the thioketone tautomers are 50.3 and 45.1 kcal/mol for MBO and MBS, respectively. In addition, we have resorted a CI procedure involving the 100 configurations of lowest energy, improving the transition state energies, from 50.3 to 44.6 kcal/mol for MBO and from 45.1 to 42.3 kcal/mol for MBS. However, according to these theoretical calculations, this *intramolecular* PT process would not occur by thermal activation, since this route yields an extremely high *intramolecular* PT tautomeric energy.

Dimers and intermolecular proton transfer

Since the intramolecular PT process can not describe the low energy barrier observed in the experimental studies, we postulated a dimeric co-planar association between two monomers as an appropriate structural model for an *intermolecular* PT process (see Fig. 3). Our AM1 calculations in Table IV show the same trends observed in the monomers, where thiones as well as thiols present stable co-planar dimers. This new molecular array has permitted us to calculate the PT barriers for thione and thiol dimers of

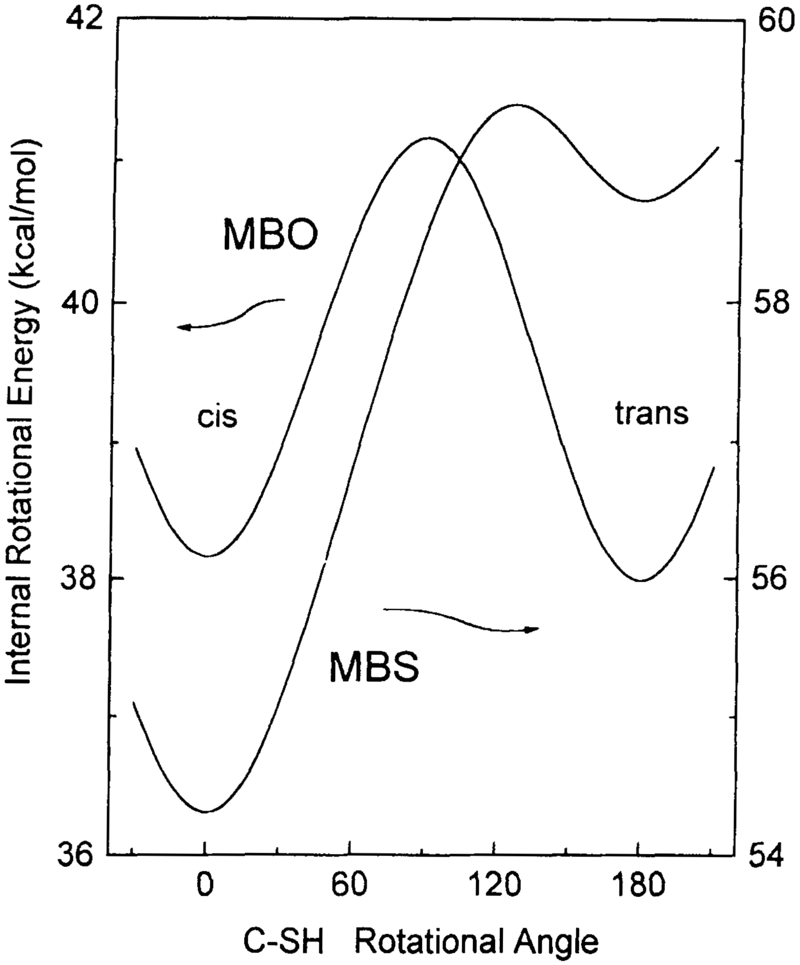

FIGURE 2 *cis-trans* Potential surface of the MBO and MBS thiols

2-mercapto-benzoxazole (MBOD) and 2-mercaptobenzothiazole (MBSD) (see Fig. 4). Both dimeric structures were calculated under complete relaxation conditions and symmetry restriction for simultaneous PT interchange between sulfur and nitrogen centers every 0.05Å, for every geometrical elongation of both hydrogen atoms.

Thione dimers are stabilized at least by 10 kcal/mol with respect to thiol dimers, with these dimeric molecular structures more stable than mono-

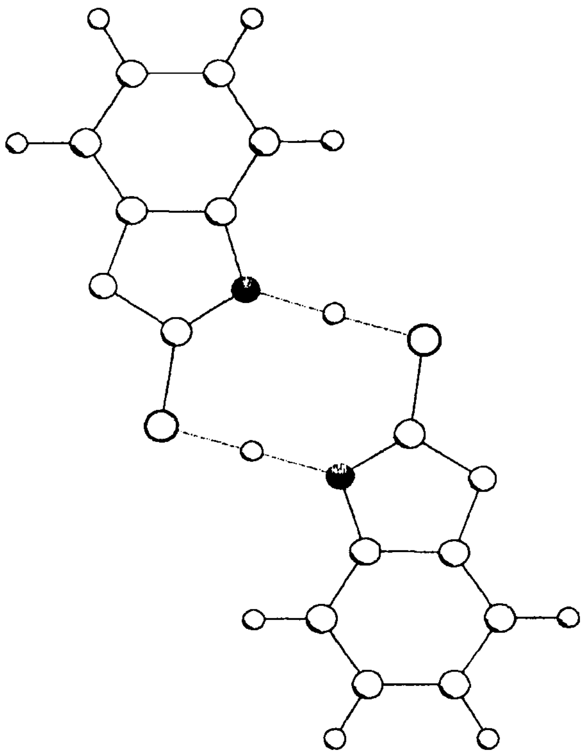

FIGURE 3 Transition state of the co-planar dimers

meric structures, in accordance with experimental data.[10] The AM1 PT potential barriers of MBOD and MBSD reach 24.3 and 21.5 kcal/mol, respectively, while thiol dimers require a lower transition energy than thione dimers. Thus, the PT potential barriers of thiol dimers reach 9.6 and 10.8 kcal/mol in MBOD and MBSD, respectively. In both cases two protons are simultaneously being interchanged in the tautomeric PT process of the thione and thiol dimers. Of the same way, our calculations have shown that the C-N distance decrease and the C-S increase in a monotonic functional dependence of the N-H bond elongation.

Finally a simple chemical reactivity analysis on the NCS syntonic unit from the AM1 calculation could determine the appropriateness of this molecular model with respect to the expected reaction way of both molecular tautomers. Thus, from an experimental point of view, a nucleophilic

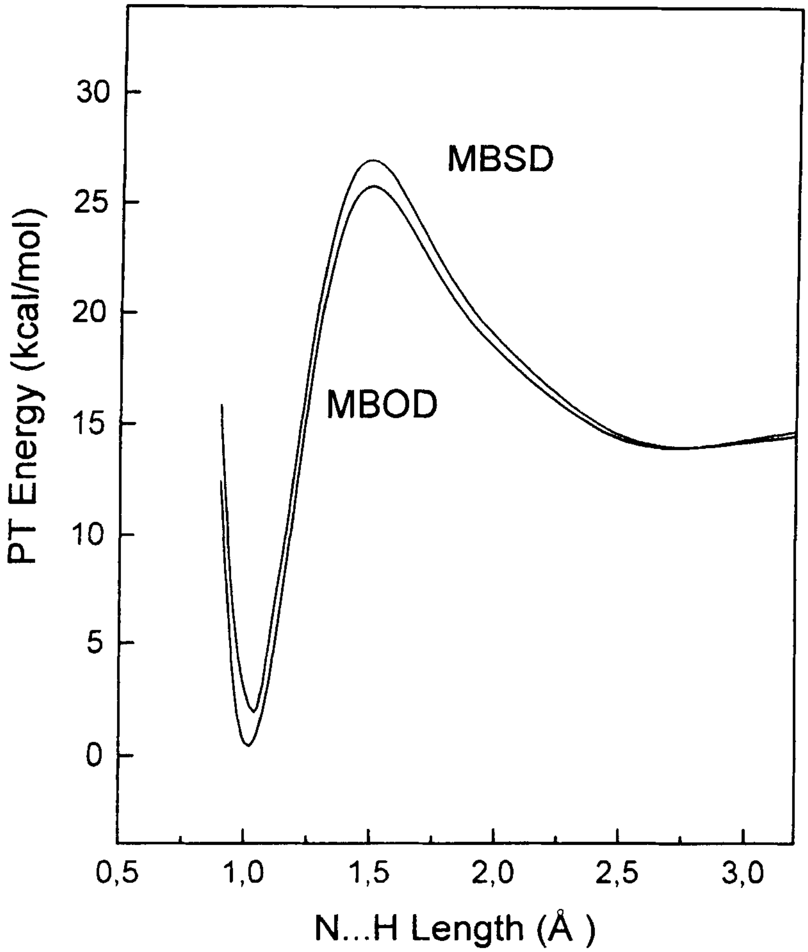

FIGURE 4 Potential surface of the MBO and MBS dimers

attack must be expected on the carbon center of the NCS syntonic unit. We have compared the nature of the HOMO and LUMO coefficients on the N, C, and S atomic centers in Table V. The molecular orbital coefficients of the before mentioned atomic centers of the thione, thiol and the anionic structures of the MBS heterocycle follow well the expected trend. It is amazing to observe that the negative charge is mainly localized on the carbon center of the MBS anion, while the thione tautomer show the best nucleophilic availability on the same carbon center at the LUMO, i.e., 30% higher than the thiol form. The same behavior is found in the MBO, MBOD and MBSD structures.

TABLE IV Heat of Formation (ΔH_f), Ionization Potential (IP) and Dipole Moment (μ) of MBOD and MBSD dimers and transition states by AM1 calculations

Physical Parameters	*MBOD Thione*	*Transition State*	*MBOD Thiol*	*MBSD Thione*	*Transition State*	*MBSD Thiol*
ΔH_f, kcal/mol (with CI)	59.15	85.58 (83.48)	73.90	96.14	120.15 (117.69)	106.86
IP, eV	8.953	8.854	8.821	8.500	8.591	8.652
μ, D	0.008	0.026	0.010	0.004	0.061	0.003

TABLE V HOMO (°) and LUMO (*) Square Coefficients of the NCS syntonic unit atomic centers of MBS tautomers and MBS anion

Atomic Center	*MBS Thione*	*MBS Thiol*	*MBS Anion*
N° (p_z)	0.0680	0.0409	0.1485
C° (p_z)	0.0002	0.0738	0.0102
S° (p_z)	0.3391	0.4331	0.4929
N* (p_z)	0.0387	0.0936	0.0043
C* (p_z)	0.4005	0.2877	0. 1938
S* (p_z)	0.2114	0.0367	0.0714

Thus, these results present a congruent mechanism with the experimental synthetic route recently developed by Adelaere et al.[1] in the MBS reaction with amines, where a favorable orbital controlled process can be expected for nucleophilic reactions on the thione form.[13]

We think that the present co-planar dimeric configuration, according to these AM1 calculations, emerges as an appropriate model for tautomeric systems where a PT process occur under low energy conditions.

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