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Beyond benzene sulfides and thiepins: Tautomerizations and thiepins inversions at theoretical levels

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Abstract

Geometries, enthalpies and energy barriers for tautomerization of X–benzene sulfides (X–B) to their corresponding X–thiepins (X–T), as well as thiepins ring inversions, are calculated at HF, MP2, and B3LYP levels of theory, using 6-311G* basis set (X = F, Cl, Br, CH_3, OCH_3, CF_3, CN and NH_2). The gas phase change of enthalpy of activation for tautomerization of H–B to H–T is 18.90 kcal mol^{-1}, while that for the reversed reaction (H–T to H–B) is 12.04 kcal mol^{-1}, at B3LYP level. These calculations appear in clear contrast to those calculated by MNDO [R. Gleiter, G. Krennrich, D. Cremer, K. Yamamoto, I. Muratas, J. Am. Chem. Soc. 107 (1985) 6874], although successfully reproduce the previous estimations of Pye et al. [C.C. Pye, J.D. Xidos, R.A. Poirier, D.J. Burnell, J. Phys. Chem. A, 101 (1997) 3371] concerning the prevailed thermodynamic data in favor of benzene sulfides. Substituents are found to have small effects on (X–B)–(X–T) equilibria as well as conformational inversions of X–T. In any case, locking H–T or H–B may not be the real challenge, in the gas phase, compared to the intrinsic tendency of either compound for losing sulfur and producing benzene. The aromatic characters of X–T and planar transition states for their inversions are estimated using magnetic (NICS) and structural criteria (bond length localizations) indicating the moderate aromaticity of the former and extreme antiaromaticity of the latter. A rather good consistency is found between results of B3LYP calculations and those of the more time consuming MP2 method.

Keywords: Thiepin; Benzene sulfide; Tautomerization; Electronic effects; *Ab initio*; DFT; NICS

1. Introduction

The rearrangement of bicyclo[4.1.0]hepta-2,4-diene (norcaradiene, **1**), to 1,3,5-cycloheptatriene (tropilidene, **2**), is a subject of long-standing experimental [1–6] and theoretical [7,8] interest. In contrast, less attention has been paid to the tautomerizations between benzene imine-azaepine (**3**–**4**), benzene oxide-oxepin (**5**–**6**), and benzene sulfide (X–B)–thiepin (X–T) (**7**–**8**). This is despite their usefulness as synthetic intermediates and therapeutic agents [9–13] (Scheme 1).

Rzepa suggested an interesting issue in the area of heteropines, where planar perimeter of p_π AOs, occupied by $4n$ electrons, can be twisted into Möbius forms with the gain of π resonance energy [14]. These may reduce or eliminate anti-aromaticity in symmetrically substituted tub or boat shaped conformations of heteropines with C_s symmetry. Möbius aromatic forms of 8π electron heteropines of O-, NF-, S-, and PF-substituted seven-membered rings, with an axis of symmetry, are investigated through DFT calculations [15]. Among heteropines, several thiepin derivatives exhibit diverse biological activities mainly in the central nervous system [16–18]. Alternatively, a comparison of the thermal stability of the three systems azepine **4**, oxepin **6**, and thiepin **8** reveal that the latter is the most puzzling

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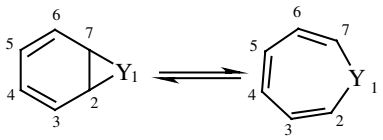

1 Y= CH_2 **2** Y= CH_2
3 Y= NH **4** Y= NH
5 Y= O **6** Y= O
7 (T) Y= S **8** (B) Y= S

Scheme 1. Valance tautomerization between norcaradiene **1** and 1,3,5-cycloheptatriene **2** and the related pairs of heterocyclic compounds **3**–**8**.

[19]. Since a number of annulated thiepins are known to thermally undergo a facile sulfur extrusion reaction. Thus, unlike oxepin **6**, equilibrium between thiepin **8** and its valence isomer **7** does not seem likely [20]. Nevertheless, in a primary theoretical study, resonance energies of 430 substituted thiepins are calculated using a simple Hückel method. The results predict thiepins substituted with electron-withdrawing groups (methoxy, carbonyl, and fluorine) are less antiaromatic than the parent thiepin [21].

Many highly substituted thiepins containing a cyclic 8π-electron system are prepared [22,23]. Novel synthesis and X-ray crystallography of an unsubstituted monoannulated thieno [3,4-*d*]thiepin system with remarkable thermal stability appears very interesting [24–26]. In addition, thiepin 1,1-dioxide [27] and thiepins which form complexes with transition-metals enhance stabilization of parent thiepine structures [28].

An enthalpy of 7.00 kcal mol^{-1} is encountered for the valence tautomerization between H–B (7) and H–T (8), at QCISD(T)/6-31G*//MP2/6-31G* [29]. The structure of the transition state for the conformational inversion of H–T is shown to be planar with the QCISD(T) inversion enthalpy of 7.29 kcal mol^{-1}. Barrier of tautomerization for H–B is estimated to be 20.50 kcal mol^{-1}. Following our studies on heteropines [30,31], we wondered how electronic effects influence such tautomerizations, and thiepins inversions and also became interested to gain more insights into structures and reactivities of X-substituted H–B and H–T. In this manuscript the valence tautomerization (Fig. 1) and ring inversion (Fig. 2) of two series of X–B and X–T are studied using quantum chemical methods: HF, MP2, and B3LYP (X = H, F, Cl, Br, CH_3, OCH_3, CF_3, CN, and NH_2).

2. Computational methods

All structures are optimized at the HF [32], MP2 [33], and B3LYP [34] levels of theory with the 6-311G* basis set [35]. For HF and B3LYP the frequency calculations are done at the same level to determine the nature of the optimized structures (i.e., number of imaginary frequencies: 0 for minima, 1 for transition states, etc.) and to obtain zero-point energies (un-scaled) and thermo-chemical corrections. As anticipated, for most cases the frequency calculations at the expensive MP2 level do not converge as easily as the B3LYP. Nucleus independent chemical shift NICS calculations [36] are performed using the gauge independent atomic orbitals method (GIAO/B3LYP/6-311G*) [37]. The ghost atom (Bq) is placed at the ring center. Evidently, the geometrical center of the ring's heavy atoms serve as the most easily defined reference point. This is the standard NICS location, NICS(0), and is used along with that of 1 Å above the plane of the ring, NICS(1). The NICS(1) is recommended to be a better measure of the π electron delocalization, compared to NICS(0), due to the lack of local σ shieldings [38].

The reliability of various density functional theory (DFT) models is already evaluated for the study of bond dissociation energies, heats of formation, and geometrical parameters [39–41]. Among all DFT methods, B3LYP often gives geometries and vibrational frequencies which are closest to those obtained from the MP2 method [42]. Thus, B3LYP with the 6-311G* basis set is employed, in this work, as the method of choice. The NBO population analysis on optimized structures are also accomplished at

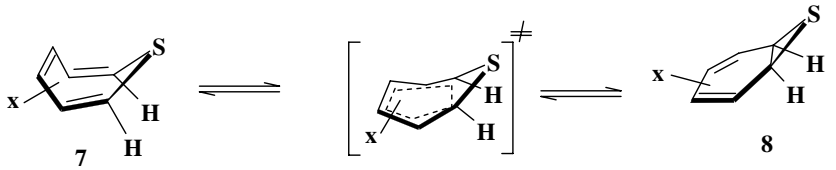

Fig. 1. Binary valence tautomerizations between 3- and 4-(X)substituted thiepins (**7**, X–T), and their corresponding 3- and 4-(X)substituted benzene sulfides (**8**, X–B), where X = H, F, Cl, Br, CH_3, OCH_3, CF_3, CN, and NH_2.

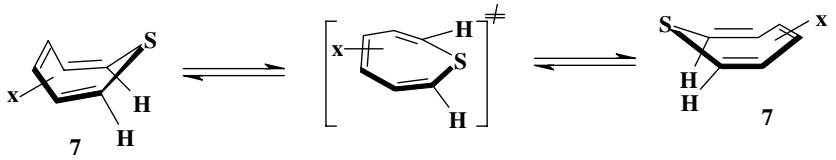

Fig. 2. Conformational ring inversions in 3- and 4-(X)substituted thiepins (X–T), where X = H, F, Cl, Br, CH_3, OCH_3, CF_3, CN, and NH_2.