



ORIGINAL ARTICLE

Quantum chemical investigation of the molecular structure of some 2,3-dihydro-1,4-diazepines and related molecules



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Received 19 June 2011; accepted 24 August 2011

Available online 3 September 2011

KEYWORDS

Ab-initio;
Semi-empirical;
MO calculations;
Möller-Plesset MP2;
NDDO;
AM1;
PM3;
1,4-Diazepines;
Tautomerism

Abstract Accurate ab-initio and semi-empirical molecular orbital calculations with full geometry optimization were performed on the various tautomeric forms of some 2,3-dihydro-1,4-diazepines and related molecules. The highly accurate ab-initio calculations at the HF/6–31G** level with Möller-Plesset Second-Order Perturbation Theory (MP2) refinement clearly established the higher stability of the enamine tautomer of the 1,4-diazepine ring over the di-imine form by 27.786 kJ/mol, whereas the semi-empirical calculations at the NDDO level (AM1 and PM3) predicted comparable energies within reported errors of the two methods. However, both ab-initio and semi-empirical NDDO methods predicted similar geometries in agreement with observed geometrical parameters. The AM1 calculations predicted small energy differences among the three tautomeric forms of 2,3-dihydro-5-methyl 7-phenyl 1,4-diazepine with the more polar enamine tautomer being the more stable tautomer in the half-chair conformation which is likely to predominate in polar media through stabilizing intermolecular solute-solvent interactions.

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1. Introduction

The medicinal success of 1,4-benzodiazepines I (Fig. 1) (Sternbach et al., 1963, 1964; Rudzik et al., 1973; Mattila and Larni, 1980; Tallman et al., 1980; Rall, 1990) continues to stimulate considerable interest (Cazaux et al., 1983; Seahill and

Smith, 1983; Salman et al., 1986; Gilman et al., 1990, 1993; Hamdi and Ahmed, 1993, 1996; Zycov et al., 1993; Pihlaja et al., 1997; Simeonov et al., 1997; Zahra et al., 2003; Venkatraj and Jeyaraman, 2006; Meanwell and Walker, 2008; Thakur et al., 2010) in this important class of N-heterocyclic compounds and related systems. The well-documented dependence of the biological activity of these systems on the stereochemistry of the seven-membered ring system (Fryer et al., 1986) is largely responsible for the continued interest in the study of the tautomerism of the 1,4-diazepines using a diversity of experimental and theoretical techniques such as NMR, X-ray diffraction and molecular mechanics calculations.

These studies have indicated that the chair-form of the seven-membered system has the lowest energy. However, a

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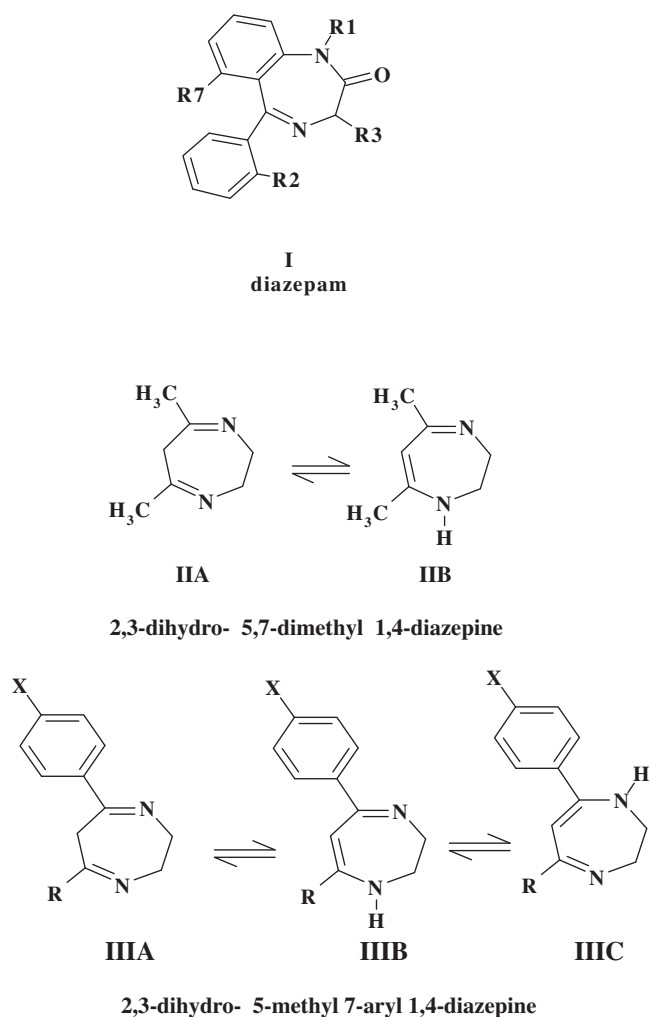


Figure 1 The structures of some 1,4-diazepines.

rapid inter-conversion involving the boat-shape conformation was also established by NMR spectroscopy for the diazepine ring in some 1,4-benzodiazepines and related 2,4-benzodiazepines (Venkatraj and Jeyaraman, 2006).

Although early theoretical investigations have used the relatively faster but inheritably less rigorous molecular mechanics (MM) methods, more recent reports have used the relatively more accurate semi-empirical methods particularly AM1 and PM3 which provide a satisfactory account of the molecular geometries and relative energies of large molecular systems (Dewar et al., 1985, 1993; Stewart, 1989; Feller and Peterson 1998). Nevertheless, even with the current advances in computational techniques and widely available fast computers, the use of the more accurate ab-initio methodologies is prohibitively restricted to small and medium sized molecular systems unless highly sophisticated and dedicated parallel computing facilities are employed.

In this work, a combination of standard semi-empirical techniques (AM1 and PM3) and accurate ab-initio MO calculations are employed for the determination of stabilities and equilibrium geometries of the various tautomeric forms of some representative 1,4-diazepines. Typical Structures are shown in Fig. 1.

Table 1 Selected bond lengths (Å), bond angles (°) and dihedral angles (°) for tautomer II(A) of the 2,3-dihydro 1,4-diazepine parent system. For key, see Fig. 1.

	Quantum chemical calculations				
	Ab-initio		Semi-empirical		
	3-21G	6-31G**	6-31G**	MP2	AM1
<i>Bond lengths (Å)</i>					
N(1)–C(2)	1.4729	1.4526	1.4646	1.4292	1.4551
C(2)–C(3)	1.5373	1.5254	1.5252	1.5369	1.5253
C(3)–N(4)	1.4727	1.4499	1.4630	1.4290	1.4549
N(4)–C(5)	1.2522	1.2496	1.2846	1.2763	1.2831
C(5)–C(6)	1.5152	1.5189	1.5184	1.4918	1.4898
C(6)–C(7)	1.5153	1.5147	1.511	1.4918	1.4898
C(7)–N(1)	1.2522	1.2495	1.2853	1.2763	1.2832
N(4)–H	–	–	–	–	–
C(6)–H	1.09	1.091	1.1025	1.128	1.111
N(1)···N(4)	3.236	3.181	3.182	3.188	3.165
<i>Bond angles (°)</i>					
N(1)–C(2)–C(3)	114.53	113.240	111.355	117.772	115.564
C(2)–C(3)–N(4)	114.622	118.201	118.680	117.875	115.631
C(3)–N(4)–C(5)	123.795	124.663	122.909	125.608	126.855
N(4)–C(5)–C(6)	131.755	131.248	130.980	133.694	131.486
C(5)–C(6)–C(7)	121.594	116.947	114.377	119.115	121.034
C(6)–C(7)–N(1)	131.637	126.720	125.725	133.635	131.392
C(5)–C(6)–H	106.862	108.576	109.304	107.089	106.751
C(7)–C(6)–H	106.918	109.045	109.511	107.085	106.751
C(5)–N(4)–H	–	–	–	–	–
H–C(2)–H	107.79	106.893	109.083	107.203	106.539
H–C(6)–H	105.152	105.592	106.015	107.002	105.532
<i>Dihedral angles (°)</i>					
C(5)–C(6)–	–13.553	–50.098	36.255	–10.891	–11.779
C(7)–N(1)–					
C(6)–C(7)–	1.9798	0.978	–57.585	0.487	0.951
N(1)–C(2)–					
C(7)–N(1)–	48.037	67.380	1.685	41.908	44.742
C(2)–C(3)–					
C(5)–N(4)–	47.113	19.923	–73.377	41.260	43.919
C(3)–C(2)–					
N(1)–C(2)–	–78.037	–72.149	71.569	–66.450	–70.112
C(3)–N(4)–					
H–C(7)–N(1)–	179.477	179.699	–178.732	178.866	179.207
C(2)					

2. Computational methods

Ab-initio calculations were performed with the Gaussian 03W package (Frisch et al., 2004). Semi-empirical calculations were performed using the original parameter set of the MOPAC 6 package (Dewar et al., 1985; Stewart, 1989). The geometries of the various tautomeric forms of 2,3-dihydro-1,4-diazepines are obtained using full geometry optimization at both the semi-empirical and ab-initio methods. Ab-initio full geometry optimization was carried out using the GDIIS method (Pulay, 1980, 1982; Csaszar and Pulay, 1984; Farkas, 1995; Farkas and Schlegel 1999) at the HF/3-21G, HF/6-31G** and HF/6-31G** MP2 levels.

The ground state molecular energies and stabilities of these systems were computed at a higher level of a basis set using extended HF/6-31G** basis set with diffuse functions and refined using Möller-Plesset Second-Order Perturbation Theory (MP2) calculations aimed at accounting for the correlation energy.

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