Investigation of Azoxides and Olefins [3 + 2] Cycloaddition to 1,2,3-Oxadiazolidines by a Combination of Density Functional Theory and Semiempirical Methods

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Theoretical studies of the aspects of an azoxide addition to olefins is presented. The stability of the 1,2,3-oxadiazolidine ring is discussed in regard to its capability to undergo a retro cycloaddition reaction. The structural features necessary to increase the stability of the heterocycle is proposed and evaluated. The computational results are supported with experimental observations.

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Introduction.

There are four possible five membered heterocycles with consecutive O-N-N heteroatoms (an aromatic ring, two partially reduced rings, and a fully reduced ring). The fully reduced ring, 1,2,3-oxadiazolidine, is not a known compound in either an isolated form or in combination with benzene. It is reasonable to believe that the aromatic

Scheme 1

1,2,3-oxadiazole Δ^2-1,2,3-oxadiazoline Δ^4-1,2,3-oxadiazoline 1,2,3-oxadiazolidine

form of this five membered heterocycle, 1,2,3-oxadiazole, should be considerably more stable than its fully reduced form and could be prepared, if not in its isolated form than as a fused benzo-derivative. To the best of our knowledge neither of these compounds is known [1]. It seems that the stabilization of the ring can be obtained by attaching highly charged substituents. These kinds of compounds are better known in the literature as sydnones and sydnonimines [2]. Semiempirical [3], Hückel [4] and ab initio [5] studies on these structures were performed previously, targeting the determination of their reactivity and charge distribution in the ring.

The 1,3-dipolar cycloaddition reactions are useful in the synthesis of heterocyclic compounds [6]. Many 1,3-dipoles are isoelectronic to an allyl anion. It has four electrons with at least one charge-separated resonance structure having opposite charges in a 1,3-relationship. It is this structural feature that leads to the name, a 1,3-dipolar cycloaddition reaction. Mechanistic studies have shown that the transition state for 1,3-dipolar cycloaddition is not very polar. The rate of reaction is not strongly sensitive to solvent polarity. There is a general agreement that the reaction is a concerted [$_\pi 4_s$ + $_\pi 2s$] cycloaddition [7]. The distribution of charge separation that is implied is more apparent than real, because most 1,3-dipolar compounds are not highly polar. The polarity implied by any single structure is balanced by the other contributing structures.

In regard to their synthetic application, two things are important: the regioselectivity and the stereoselectivity. Many specific examples demonstrate that the 1,3-dipolar cycloaddition is stereospecific, *syn* addition in respect to the dipolarophile. This is what one would expect for a concerted process. Here we are presenting our computational studies in combination with experimental results provided by others that explain why the majority of the 1,2,3-oxadiazolidines cannot be prepared by a cycloaddition reaction and what is the reason for their instability.

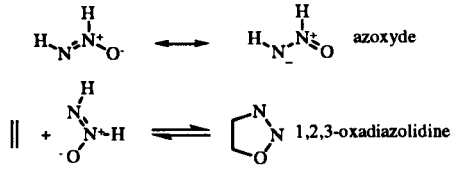
Methodology.

All semiempirical computational studies were performed on a DEC 7620 computer. Chem-3D Plus on a Macintosh was used as a graphical interface for drawing and visualizing all structures and for preparing the input files for MOPAC 6.0 [8] and these were optimized by Dewar's AM1 [9] semiempirical method. The search for the transition states and their verification [10] was performed as described previously [11]. For density functional theory calculation a GAUSSIAN 94 [12] computational package was used. Energy and, in some cases, full optimization was performed with hybrid density functional methods that is a combination of Becke's three parameter functional [13] and non-local correlation is provided by the Lee-Yang Par [14] expression.

Results and Discussion.

In principle 1,2,3-oxadiazolidines can be obtained by a 1,3-dipolar cycloaddition of azoxide to alkenes. The structure of the azoxide is isoelectronic to the allyl anion with two resonance structures that represent delocalization of the partially negative charge on the terminal oxygen and nitrogen (Scheme 2). This type of the reaction can be studied through simple frontier molecular orbital theory [15]. According to this theory the frontier orbital (HOMO-LUMO) overlap between the two reactants is responsible for formation of the chemical bond. The new forming bond is more easily formed if the two frontier orbitals are closer to their energy. Both [2 + 4] cycloaddition and [2 +3] cycloaddition are six electron involved

Scheme 2



addition reactions with an aromatic transition states structure [16]. Thus we can compare the reactivity of the azoxide-ethylene pair with the butadiene-ethylene pair. The activation barrier for the latter pair was estimated to be 27.5 kcal/mol [17]. The computed frontier orbital energy differences by AM1 with these two examples are presented in Table 1. For the butadiene-ethylene addition, the lowest energy gap is 10.77 eV and it is between the LUMO of the ethylene and the HOMO of butadiene. According to the frontier orbital theory, the azoxide addition to ethylene is an inverse, LUMO 1,3-dipoles controlled reaction. The energy gap is slightly lower (10.57 eV) and the activation energy should also be slightly lower than the 27.5 kcal/mol which was estimated for ethylene-butadiene cycloaddition reaction. Of course, by introducing a stronger dienophile or dipolarophile such as maleic anhydride both 4π electronic parts of the cycloaddition reaction, butadiene and azoxide are HOMO controlled (Table 1). In this case the cycloaddition of the butadiene-maleic anhydride is preferred over the azoxide-maleic acid cycloaddition pair (Table 1).

Table 1

Frontier Orbital Energies (eV) of the Reactants and their Frontier Orbital Energy Gaps (eV)

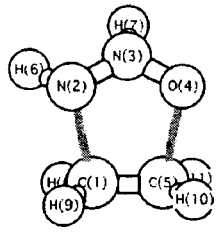
Reactant	HOMO	LUMO	A	B	C	D
ethylene	-10.55	1.44				
maleic anhydride	-12.02	-1.62				
1,3-butadiene	-9.33	0.45	11.00	10.77	12.47	7.71
azoxide	-10.66	0.02	10.57	12.10	12.05	9.04
N,N'-Dimethylazoxide	-9.90	0.20	10.75	11.33	12.22	8.38

$A = LUMO_{reactant}\text{-}HOMO_{ethylene}$; $B = LUMO_{ethylene}\text{-}HOMO_{reactant}$; $C = LUMO_{reactant}\text{-}HOMO_{anhydride}$; $D = LUMO_{anhydride}\text{-}HOMO_{reactant}$

In many of our previous studies we have used the AM1 semiempirical method for the evaluation of the reactivities of different heterocycles [18]. Although there are an enormous number of organic compounds, they all have very similar structural features. For example, there are only a few different C-C bonds (single, double triple, aromatic, *etc.*). This is the reason why empirical parametrized molecular mechanic methods are capable of producing structures for many organic molecules that are very close to the X-ray determined structures. All semiempirical methods are parametrized as well and structures for many organic molecules are also reproduced with semiempirical methods. Structural parameters are obtained for the experimental geometries determined by X-ray and electron diffraction, microwave spectroscopy, and from high level of ab initio calculations where experimental data are not available. There are no parameters for transition state structures and different computational methods usually produce diverse transition state structures. The energy of the molecular system is also hard to compute. Usually semiempirical methods, low level of ab initio, as well as density functional theory methods produce unacceptable values. The theory level that gives satisfactory energies cannot be applied to relatively large chemical systems. The solution to this problem is a compromise: computation of the geometry with semiempirical methods such as AM1 and evaluation of the energies with accurate density functional theory methods. We have demonstrated that, density functional theory method produces accurate activation energies for cycloaddition reactions [19]. We have also verified that the density functional theory energies on AM1 geometries on the hydrogen, carbon, nitrogen, and oxygen containing organic systems produces almost identical energies as a full density functional theory computational study [20]. We will again test this approach on the example of the addition of azoxide to ethylene. The AM1 and density functional theory computed transition state structures for the concerted mechanism of the cycloaddition are presented in Table 2. In many of the cycloaddition studies [21], it was demonstrated that the density functional theory calculation is necessary to accurately determine geometries and energies. Our computational studies reveal that the geometries produced by AM1 and density functional theory are very similar (Table 2).

Table 2

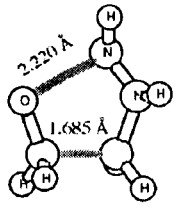
The Geometric Parameters for Azoxide Addition to Ethylene Computed with AM1 (A) and Density Functional Theory (B)



	A	B
r21/°	2.029	2.027
r32/°	1.296	1.320
r43/°	1.245	1.279
r54/°	2.012	2.040
r51/°	1.386	1.397
a321/Å	101.7	98.9
a432/Å	114.9	15.0
a543/Å	104.7	99.7
a154/Å	100.2	101.0
a215/Å	101.3	101.4

The computed activation barrier for the azoxide addition to ethylene follows the pattern of geometry similarity. The full density functional theory calculation estimated the activation barrier at 19.8 kcal/mol. In our earlier studies we have determined that the density functional theory energies on AM1 geometries were around 2 kcal/mol higher than the full optimization. Here we have this effect. The estimated activation barrier is 22.3 kcal/mol.

Considering the activation energy of the ethylene addition to 1,3-butadiene to be around 27 kcal/mol, it is conceivable that a reaction with this activation barrier should be experimentally possible. This conclusion is similar to one obtained previously on the basis of the frontier molecular orbital energy gap study. The question is, why is there no experimental evidence of the preparation of 1,2,3-oxadiazolidines in this way? The answer may be in the low stability of the 1,2,3-oxadiazolidines. The computed activation barrier for the elimination of formaldehyde from 1,2,3-oxadiazolidine through transition state structure **1** is only 7.2 kcal/mol and it prevails that the

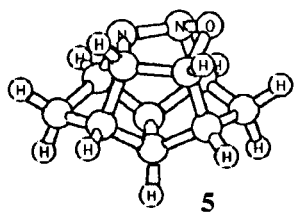


1

Figure 1. The transition state structure for the concerted mechanism of formaldehyde elimination from the 1,2,3-oxadiazolidine.

1,2,3-oxadiazolidine will accumulate in the reaction mixture. There is experimental evidence that fully supports our computational findings. Huisgen and Palacios Gambra's attempts to isolate 1,2,3-oxadiazole derivatives failed [22]. The reaction between the aromatic *N,N'*-diarylazoxide and highly strained *trans*-cyclooctene occurred at 85° yielding **4**. This unsuspected product is generated *via* the corresponding 1,2,3-oxadiazolidine **2** as an intermediate, which undergoes cycloreversion leading to **3** followed by a hydrogen shift affording **4** (Scheme 3).

rings in fullerene [23]. It can be postulated that this approach can also stabilize the structure of 1,2,3-oxadiazolidine.



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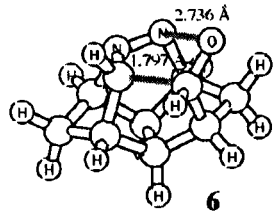

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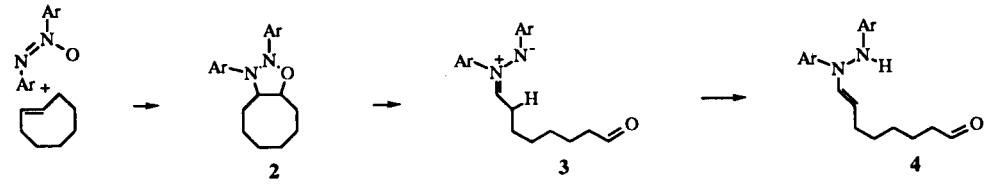
The structure **5** that is based on the five and six-membered rings that are common in fullerene series has been chosen for study because of its stability. The computed activation barrier of the ring opening of **5** through transition state **6** is 55.2 kcal/mol, considerably higher than the 7.2 kcal/mol computed for a simple 1,2,3-oxadiazolidine. It is quite obvious that these structures must be stable and can be easily synthesized. Confirmation that our computational studies are correct comes from Hünig group [24]. They were able to isolate stable cage derivatives of 1,2,3-oxadiazolidines (Scheme 4). It is interesting to point out that the cycloaddition is found to be much more facile in the presence of acid. The reaction is carried out at 0°. The only part of the **7** molecule that can be protonated is azoxide group and reaction should be azoxide-LUMO controlled as was predicted on the basis of the frontier molecular energy gap. Another interesting point is the selectivity of the cycloaddition reaction towards the formation of **9**. The difference between **8** and **9** is actually the preference to have a five over a six-membered ring in the cage. Our computational approach estimates that the activation energy for the formation of product **9** is 3.5 kcal/mol lower than the activation barrier for the formation of **8**. With an acid catalyzed reaction, this preference is 1.8 kcal/mol, one half of the uncatalyzed preference. One would argue that this must be reflected in the ratio of the products. That should be true if reaction is carried out at the same temperature. It is well known to the synthetic organic chemist that with decreasing reaction tem-

Scheme 3

Transformation of *N,N'*-Diarylazoxide and *trans*-Cyclooctene into **4**



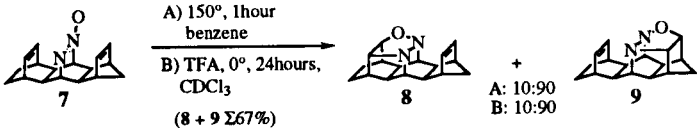
2 **3** **4**

By modifying the environment around the unstable structure, chemists were able to prepare many different compounds. One of the compounds that attracted attention due to its stability in its cage form is the combination of the phenyl

perature, selectivity is increased. It seems obvious that these two effects (increased selectivity due to temperature lowering and decreased selectivity due to acid catalyzation) cancel each other. If we now consider that the

Scheme 4

Transformation of azoxide 7 into stable cage 1,2,3-oxadiazolidines 8 and 9



ring opening of **9** is in the same manner as that of **1**, then the corresponding transition state structure is 14.3 kcal/mol above the transition state that leads to the formation of **9**, thus predicting a high stability for the cage 1,2,3-oxadiazolidines.

Conclusion.

Our computational results predict that the addition of azoxides to olefins is an experimentally feasible procedure. The estimated activation barriers are in the range usually found for cycloaddition reactions (~ 20 kcal/mol). Nevertheless simple 1,2,3-oxadiazolidines cannot be prepared with this cycloaddition reaction due to their thermal instability. This instability is reflected by the retrocycloaddition reaction followed by a hydrogen shift. If the 1,2,3-oxadiazolidine is a part of a cage molecule, the retrocycloaddition barrier becomes too high and the cycloaddition reaction becomes practical. All of the computed results are fully supported by the experimental results.

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