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An Account of the Regioselectivity of β-Substituted Nitroalkenes in Nitrone [2+3] Cycloaddition by FMO Theory*

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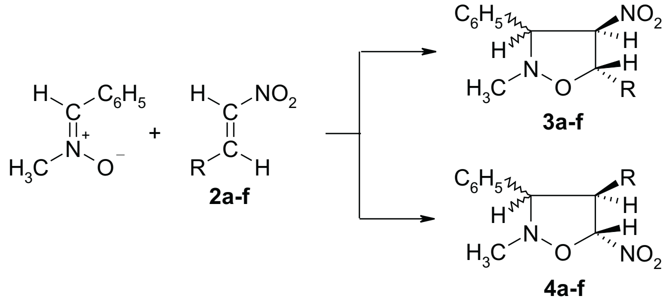
The regioselectivity of β-R-substituted nitroethylenes in nitrone [2+3]cycloaddition may seem to be difficult for regiochemical control, since the presence of substituents on α and β carbon atoms of vinylidene moiety can work at cross-purposes [2,3]. In practice, however, these nitroalkenes usually exhibit high degree of regioselectivity independently on the Hammett σ_p constants of substituent R. For example, the cycloaddition of C-phenyl-N-methylnitrone **1** with nitroalkenes **2a**–**e** yields 2-methyl-3-phenyl-4-nitro-5-R-isoxazolidines **3a**–**e** as mixture of suitable 3,4-*cis* and 3,4-*trans* stereoisomers [4–6]. The regioisomers **4a**–**e** were not detected in reaction mixtures. Only in the case of *trans*-carbomethoxynitroethylene **2f** both theoretically possible regioisomers, *i.e.* **3f** and **4f**, were obtained in *ca* 1:1 molar ratio [5] (Scheme).

Scheme



R=CH_3 (**a**), H (**b**), Cl (**c**), CN (**d**), CF_3 (**e**), $COOCH_3$ (**f**)

In order to provide a better understanding of the nature of these reactions, in this contribution we performed quantum-chemical calculations of the stationary structures of nitrone **1** and nitroalkenes **2a**–**f** (Table). The calculations were carried out us-

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[*] Part 47 in the series *Synthesis and properties of azoles and their derivatives*. Part 46 see [1].

ing MOPAC-93 program package of Steward [7]. The standard AM1 Hamiltonian was chosen since this one gave the essential structural features of nitroalkenes and nitrones in better agreement with the experimental data than did the MNDO or PM3 methods [8]. We try to address the following questions: (i) what is the electronic structure of the reactants **1** and **2a**–**f**, and (ii) can the experimentally observed regioselectivity be explained in terms of FMO considerations [9].

Table. Essential molecular properties of C-phenyl-N-methylnitrone **1** and nitroalkenes **2a**–**f**.

Nr	R	$\sigma_p(R)^a$	$r_{C=C}$ [Å]	Eigenvectors of the LUMO		E_{LUMO} [eV]	Eigenvectors of the HOMO		E_{HOMO} [eV]	Charges on the reaction sites [e]	
				O/C_α	C/C_β		O/C_α	C/C_β		O/C_α	C/C_β
1	–	–	–	0.350	0.390	–0.30	0.513	–0.480	–8.45	–0.225	–0.445
2a	CH_3	–0.17	1.343	0.432	–0.628	–0.87	0.694	0.551	–11.27	–0.223	–0.052
2b	H	0.00	1.335	0.435	–0.625	–0.90	0.684	0.628	–11.95	–0.197	–0.121
2c	Cl	0.23	1.343	0.463	–0.639	–1.27	0.652	0.474	–11.38	–0.212	–0.068
2d	CN	0.71	1.344	0.513	–0.589	–1.81	0.653	0.558	–12.01	–0.155	0.007
2e	CF_3	0.53	1.336	0.523	–0.622	–1.79	0.677	0.672	–12.75	0.128	–0.155
2f	$COOCH_3$	0.44	1.340	0.522	–0.562	–1.74	0.487	0.463	–12.20	–0.124	–0.088

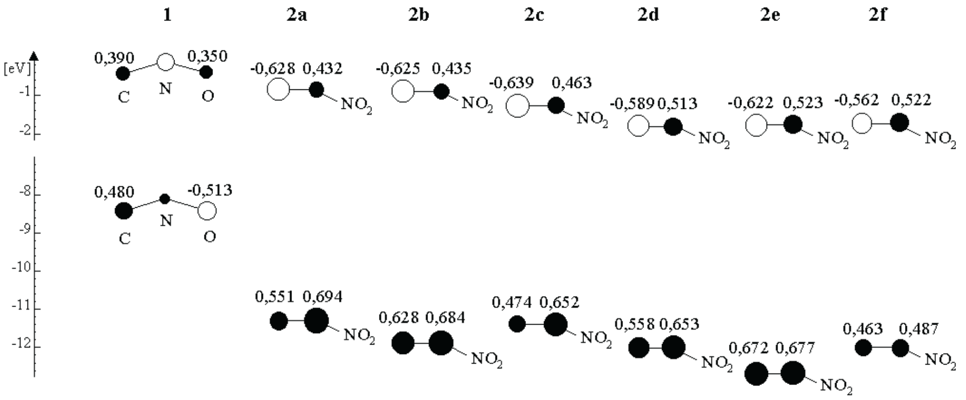
[a] Data taken from [14].

We began our investigations with the study on electronic structure of parent nitroethene **2b**. The frontier orbitals of the optimized structure of **2b**, which have the appropriate symmetry for an interaction with the frontier orbitals of nitrone **1**, are presented in perturbational diagram (Fig.). As it can be seen, the LUMO of **2b** is the $\pi^*_{C=C}$ orbital located perpendicular to the plane of the molecule. The energy of this one is calculated to be –0.90 eV and has the largest amplitude at the β-carbon atom with the coefficient of –0.625, compared with 0.432 at the α-carbon atom. The atomic charges at the α- and β-carbon atoms are –0.197 and –0.121 e, respectively. These results indicate that the α-carbon atom is most susceptible for electrophilic attack. The HOMO and HOMO-1 of **2b** are degenerated. They are found at –11.89 eV and are distributed mainly at the oxygen atoms of nitro group and are not of interest for the reaction of the alkene part of molecule. The HOMO-2 is a $\pi_{C=C}$ orbital and it is the bonding counterpart to the LUMO. The energy of this orbital is calculated to be –11.95 eV and it has slightly larger amplitude at the α-carbon atom (0.684), compared with the β-carbon atom (0.628).

An electronic structure of **2b** is changed significantly when the substituent R is introduced into β-position of nitrovinyl moiety. In particular, the substituents with negative value of Hammett σ_p-constant make nitroalkene much better electron acceptor, while for the substituent with negative value of σ_p the one becomes a less electron acceptor. Substituent R influences the HOMO level in similar manner as the LUMO level. It is worth of mentioning that the C=C double bond length of nitroalkenes remains relatively constant irrespectively on the nature of the R substituent.

The frontier orbitals of the nitrone **1** are presented in the left of the Figure. The LUMO of **1** is calculated to be –0.30 eV, while the HOMO is at –8.45 eV. Their symmetry is appropriate for an interaction with the HOMO and LUMO of **2a**–**f**, respectively. The LUMO of **2** has the largest amplitude at the carbon atom with the coefficient of 0.390, compared with 0.350 at the oxygen atom of >C=N(O)- moiety, while the HOMO of **2** has the largest amplitude on the oxygen atom with the coefficient of –0.513, compared with 0.480 at the carbon atom.

From perturbation interaction diagram, it is evident that the interactions between the HOMO of 1,3-dipole and LUMO of dipolarophiles are predominant in all studied cases ($\Delta E_1 < \Delta E_2$). The reversal interactions cannot be considered because the differences between both frontier interactions ($\Delta\Delta E$) are much higher than 1 eV (Fig.). Such an orbital arrangement is indicative of normal type reaction according to Sustmann classification of cycloaddition reaction [10,11]. According to Fukui considerations, the preferred regioisomeric transition state will be that in which orbitals of larger atomic coefficients are overlapped [9,12]. Because for the reactions of nitroalkenes **2a**–**e** the larger atomic orbital coefficient within 1,3-dipole molecule is found in the HOMO at oxygen and in the nitroalkenes **2a**–**e** LUMO at the β-carbon atom, the regioselectivity of the reactions studied should be in agreement with the structures of 2-methyl-3-phenyl-4-nitro-5-R-isoxazolidines **3**. In the case of nitroalkene **2f** the atomic orbital coefficients for α- and β-carbon atoms are very close. Therefore, two theoretically possible regioisomers should be formed in comparable ratio. Thus the regioselectivity of the reactions studied is well reproduced by AM1 calculations of reactant's FMO energies and atomic coefficients on the reaction sites.



$\Delta E_1 = \lvert E_{HOMO\ nitron} - E_{LUMO\ alken} \rvert$	7,58	7,55	7,18	6,64	6,66	6,71
$\Delta E_2 = \lvert E_{HOMO\ alken} - E_{LUMO\ nitron} \rvert$	10,97	11,65	11,08	11,71	12,45	11,90
$\Delta\Delta E = E_2 - E_1$	3,39	4,10	3,90	5,07	5,79	5,19

Figure. Interaction diagram for the [2+3]cycloaddition of C-phenyl-N-methylnitrone (**1**) and nitroalkenes (**2a**–**f**). Data taken from the Table.

Summarizing, the results obtained one can state that the reaction under study is governed by charge-transfer control. In spite of highly polarized structures of dipolarophiles **2a**–**f** there is no evidence that coulombic interactions play a dominant role in determining of their regioselectivity. These conclusions are in agreement with the results of quantum-chemical study of the critical structures on potential energy hypersurface for the [2+3]cycloaddition of (Z)-C,N-diphenylnitrone with (E)-β nitrostyrene [8] and nitropropylene [13].

Acknowledgments

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