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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES. 54*. THE REGIOSELECTIVITY OF [2+3] CYCLOADDITION OF C,C,N-TRIPHENYL- AND Z-C,N-DIPHENYLNITRONES WITH β- AND α-SUBSTITUTED NITROETHYLENES IN LIGHT OF FRONTIER MOLECULAR ORBITAL THEORY

R. Jasinski, A. Ciezkowska, A. Lyubimtsev, and A. Baranski

Using quantum-chemical calculations we have carried out an analysis of frontier molecular orbital interactions in the [2+3] cycloaddition reactions of C,C,N-triphenyl- and Z-C,N-diphenylnitrones with β- and α-substituted nitroethylenes. In all of the examples studied the orbital effects lead to the formation of the corresponding 4-nitroisoxazolidines.

Keywords: nitroalkenes, nitrones, regioselectivity, [2+3] cycloaddition, frontier molecular orbitals.

The greatest contribution towards the stabilization of transition states in [2+3] cycloaddition reactions is the contribution of the effects related to overlap of the frontier molecular orbitals of the reagents (FMO) [2, 3]. Hence, by analysis of the molecular properties of the stationary states of the 1,3-dipole and the dipolarophile it might be possible to predict which of the theoretically possible regioisomers in the reaction route might be kinetically preferred.

As follows from the work [4-7], in the case of nitrones and conjugated alkenes the predictions made on the basis of FMO theory correlate well with the observed experimental data regarding selectivity hence we have used the indicated route to describe the [2+3] cycloaddition involving C,C,N-triphenylnitrone (**1**) and *Z*-C,N-diphenylnitrone (**2**) with the β- and α-substituted nitroethylenes **3a-e** and **4a-d** which are the targets of our systematic investigations [4-6, 8-10]. In theory, these reactions can lead to a mixture of the corresponding regioisomeric adducts. Our work is an attempt to establish the most likely route for the reaction studied.

Since literature data regarding the electronic structure of the nitrones **1**, **2** and the nitroolefins **3a-e**, **4a-d** is absent we have used the AM1 method [11, 12] from the MOPAC-93 program package to describe these properties. The choice of method was dictated by the better correlation of the obtained results with experimental data as compared with alternative methods [4-6, 8, 10].

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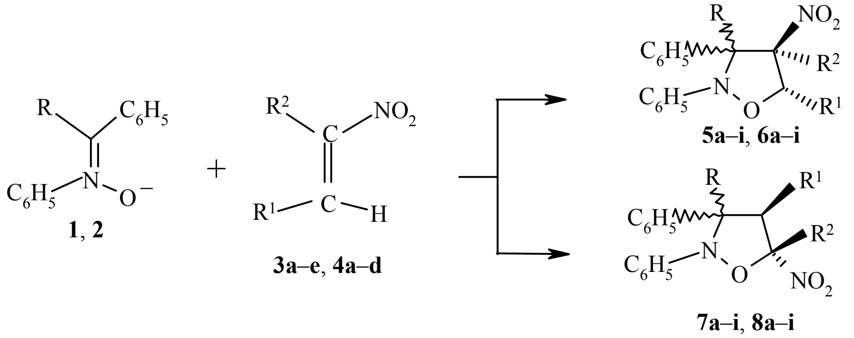
* For Communication 53 see [1].

Institute of Organic Chemistry and Technology, Cracow University of Technology 31-155 Cracow, Poland; e-mail: pcbarans@usk.pk.edu.pl. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 243-248, February, 2004. Original article submitted June 16, 2003.



1 R = C_6H_5; **2** R = H, **3 a** $R^1 = CH_3$, $R^2 = H$, **b** $R^1 = H$, $R^2 = H$, **c** $R^1 = Cl$, $R^2 = H$, **d** $R^1 = COOCH_3$, $R^2 = H$, **e** $R^1 = CCl_3$, $R^2 = H$;
4 a $R^1 = H$, $R^2 = CH_3$, **b** $R^1 = H$, $R^2 = Cl$, **c** $R^1 = H$, $R^2 = COOCH_3$, **d** $R^1 = H$, $R^2 = CCl_3$;
5 a R = C_6H_5, $R^1 = CH_3$, $R^2 = H$, **b** R = C_6H_5, $R^1 = H$, $R^2 = H$, **c** R = C_6H_5, $R^1 = Cl$, $R^2 = H$, **d** R = C_6H_5, $R^1 = COOCH_3$, $R^2 = H$,
e R = C_6H_5, $R^1 = CCl_3$, $R^2 = H$, **f** R = C_6H_5, $R^1 = H$, $R^2 = CH_3$, **g** R = C_6H_5, $R^1 = H$, $R^2 = Cl$, **h** R = C_6H_5, $R^1 = H$, $R^2 = COOCH_3$,
i R = C_6H_5, $R^1 = H$, $R^2 = CCl_3$; **6 a** R = H, $R^1 = CH_3$, $R^2 = H$, **b** R = H, $R^1 = H$, $R^2 = H$, **c** R = H, $R^1 = Cl$, $R^2 = H$,
d R = H, $R^1 = COOCH_3$, $R^2 = H$, **e** R = H, $R^1 = CCl_3$, $R^2 = H$, **f** R = H, $R^1 = H$, $R^2 = CH_3$, **g** R = H, $R^1 = H$, $R^2 = Cl$,
h R = H, $R^1 = H$, $R^2 = COOCH_3$, **i** R = H, $R^1 = H$, $R^2 = CCl_3$

The study of the reactivity of the reagents was started with a determination of the basic parameters of their electronic structures. The data in Table 1 indicates that the electronic structures of the nitrones **1** and **2** are similar. Their HOMO energies are -8.44 and -8.39 eV respectively. In both cases the HOMO's are located on the $2p_z$ orbitals of the carbon, nitrogen, and oxygen perpendicular to the plane defined by the >C=N(O) fragment. The amplitude on the oxygen atom is slightly larger than the value for the carbon atom. In contrast, the difference between the LUMO energy is more marked. For the nitrone **2** E_{LUMO} it is -0.86 eV. Including a third phenyl substituent in the molecule leads to an increase in this energy to -0.43 eV.

The HOMO energy of nitroethylene is -11.95 eV. This orbital is localized on the carbon atom perpendicular to the vinyl fragment of the olefin molecule. The HOMO has a slightly smaller amplitude on the β-carbon atom (0.628) when compared with the α-atom (0.684). The LUMO levels were localized similarly but, in this instance, the energy is -0.90 eV and the amplitude on the α-carbon atom (0.435) markedly less than on the β-atom (0.625).

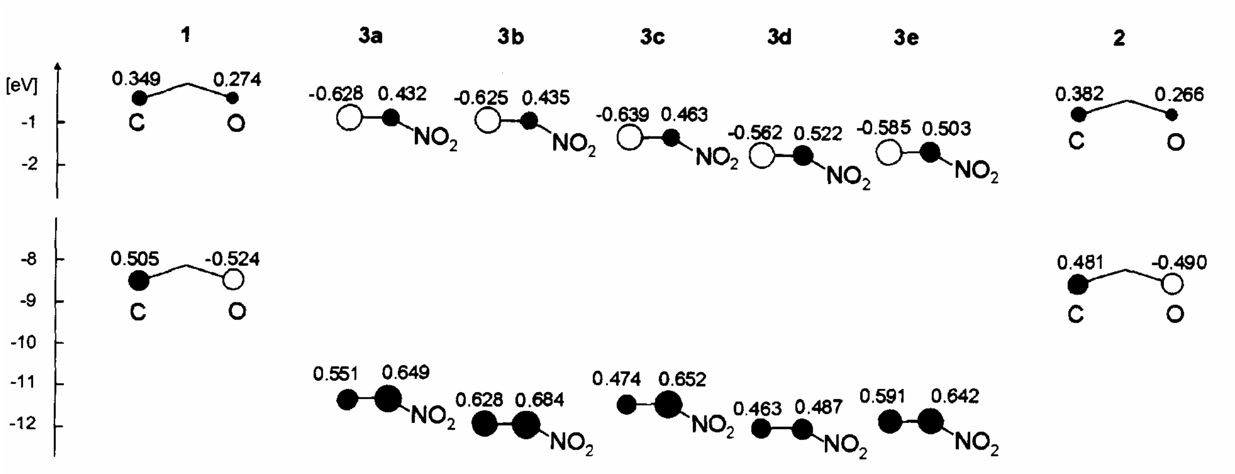
The introduction of a methyl group into the β-position of the nitroethylene caused the HOMO energy to increase by 0.68 eV. The LUMO energy also undergoes a minimal change. The presence of electron acceptor substituents slightly changes the HOMO level with a simultaneous significant decrease in the LUMO energy. Specifically, the LUMO energy is -1.27 eV for β-chloronitroethylene (**3c**), -1.74 eV for carbomethoxynitroethylene (**3d**), and -1.69 eV for trichloromethylnitroethylene (**3e**). A similar kind of FMO energy change is seen when introducing a substituent into the α- position of the molecule of nitroethylene. Thus the HOMO level for α-methylnitroethylene (**4a**) exceeds the HOMO for nitroethylene (**3b**) by 0.74 eV and is -11.21 eV. For the alkene **4a** the LUMO increases by 0.11 eV when compared with the nitroethylene **3b** and is -0.79 eV. When exchanging an electron donor substituent in the α-position of the nitroolefine for a powerful electron acceptor the HOMO energy does not undergo a marked change. At the same time, the LUMO energy decreases to -1.37 eV when $R^2 = COOCH_3$ and to -1.44 eV for $R^2 = CCl_3$.

Using the obtained parameters for the stationary states of the reagents we have carried out an analysis of the FMO interaction. As is apparent in the FMO diagram (Fig. 1) in the case of the nitrones and also nitroethylene and its β- substituted analogs the $\text{HOMO}_{\text{nitrone}}$ - $\text{LUMO}_{\text{alkene}}$ difference (ΔE_1) is significantly less that the alternative $\text{HOMO}_{\text{alkene}}$ - $\text{LUMO}_{\text{nitrone}}$ difference (ΔE_2). Hence we are concerned with so called normal electron control processes [13]. Similar types of orbital effects are observed for the same nitrones and α-substituted analogs of nitroethylene (Fig. 2). As might be expected, in both cases the preference for the $\text{HOMO}_{\text{nitrone}}$ - $\text{LUMO}_{\text{alkene}}$ interaction ($\Delta\Delta E = \Delta E_2 - \Delta E_1$) increases with an increase in the electron acceptor properties of the substituent in the alkene molecule.

TABLE 1. Basic Molecular Properties of the Stationary States of the Nitrones **1,2** and Nitroalkenes **3a-e**, **4a-d** from the Semiempirical AM1 Method

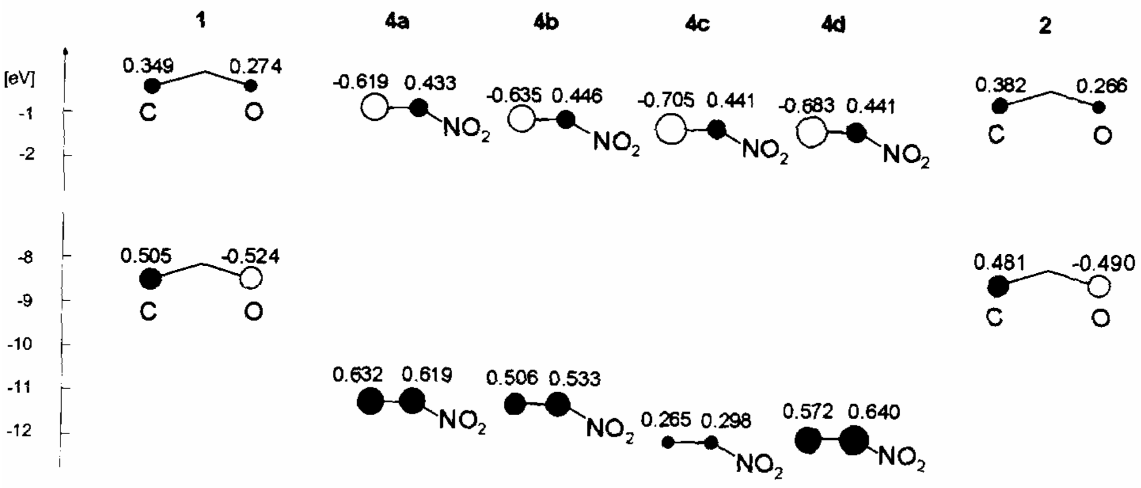
Compound	AO Coefficients for the HOMO		E_{HOMO}, eV	AO Coefficients for the LUMO		E_{LUMO}, eV
	C/C$_\alpha$	O/C$_\beta$		C/C$_\alpha$	O/C$_\beta$	
1	0.505	-0.524	-8.44	0.349	0.274	-0.43
2	0.481	0.490	-8.39	0.382	0.266	-0.86
3a	0.649	0.551	-11.27	0.432	-0.628	-0,87
3b	0.684	0.628	-11.95	0.435	-0.625	-0.90
3c	0.652	0.474	-11.38	0.463	-0.639	-1.27
3d	0.487	0.463	-12.20	0.522	-0.562	-1.74
3e	0.642	0.591	-12.09	0.503	-0.585	-1.69
4a	0.619	0.632	-11.21	0.433	-0.619	-0.79
4b	0.533	0.506	-11.26	0.446	-0.635	-1.12
4c	0.298	0.265	-12.08	0.441	-0.705	-1.37
4d	0.640	0.572	-11.90	0.441	-0.683	-1.44

In the fundamental process of cycloaddition, novel σ-bonds are formed between atoms little differentiated in the atomic coefficient values (the Fukui and Fujimoto rule [2]). Hence by comparing the AO coefficient values we can propose that, in the reactions involving diphenyl- and triphenylnitrones with the nitroolefins **3a-b**, the formation of adducts with a nitro group in position 4 of the azolidine ring would be



$\Delta E_1 = [E_{\text{HOMO nitrone 1}} - E_{\text{LUMO alkene}}]$	7.57 7.52	7.54 7.49	7.17 7.12	6.70 6.65	6.75 6.70	$\Delta E_1 = [E_{\text{HOMO nitrone 2}} - E_{\text{LUMO alkene}}]$
$\Delta E_2 = [E_{\text{HOMO alkene}} - E_{\text{LUMO nitrone 1}}]$	10.84 10.41	11.52 11.09	10.95 10.52	11.77 11.34	11.66 11.23	$\Delta E_2 = [E_{\text{HOMO alkene}} - E_{\text{LUMO nitrone 2}}]$
$\Delta\Delta E = E_2 - E_1$	3.27 2.89	3.98 3.60	3.78 3.40	5.07 4.69	4.92 4.53	$\Delta\Delta E = E_2 - E_1$

Fig. 1. Diagram of the FMO interaction for the [2+3] cycloaddition of C,C,N-triphenyl- and *Z*-C,N-diphenylnitrones with the nitroalkenes **3a-e**.



$\Delta E_1 = [E_{\text{HOMO nitrone 1}} - E_{\text{LUMO alkene}}]$	7.65 7.60	7.32 7.27	7.07 7.02	7.00 6.95	$\Delta E_1 = [E_{\text{HOMO nitrone 2}} - E_{\text{LUMO alkene}}]$
$\Delta E_2 = [E_{\text{HOMO alkene}} - E_{\text{LUMO nitrone 1}}]$	10.78 10.35	10.83 10.40	11.65 11.22	11.47 11.04	$\Delta E_2 = [E_{\text{HOMO alkene}} - E_{\text{LUMO nitrone 2}}]$
$\Delta\Delta E = E_2 - E_1$	3.13 2.75	3.51 3.13	4.58 4.20	4.47 4.09	$\Delta\Delta E = E_2 - E_1$

Fig. 2. Diagram of the FMO interaction for the [2+3] cycloaddition of C,C,N-triphenyl- and *Z*-C,N-diphenylnitrones with the nitroalkenes **4a-d**.

preferred. This suggestion found support in the studies [8, 10] in which it was shown that the reaction investigated occurs regioselectively in most cases to give the corresponding 4-nitroisoxazolidines. Hence the theoretical calculations correlate well with the observed experimental results.

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