JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15**: 78–82
DOI:10.1002/poc.451

Substituent effect on the [2 + 3] cycloaddition of (*E*)-β-Nitrostyrene with (*Z*)-*C,N*-Diarylnitrones[†]

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Received 3 May 2001; revised 1 August 2001; accepted 23 August 2001

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ABSTRACT: The kinetics of the title reaction were studied in toluene at 80 °C by means of HPLC. The overall rate constant (k_{total}) of the reaction of (*E*)-β-nitrostyrene (**1**) with (*Z*)-*C*-phenyl-*N*-arylnitrones (**2a–g**) was found to increase with increasing Hammett σ-constant, whereas in the case of (*Z*)-*C*-aryl-*N*-phenylnitrones (**2g–p**) and the same nitrostyrene the rate decreased. The substituent effect in these reactions is inconsistent with FMO treatments of cycloaddition rates. For both reaction series good linear relationships were obtained between log k_{total} and the net charge on the carbon atom in the >C=N(O)— moiety of the nitrones calculated by the AM1 method. Copyright © 2001 John Wiley & Sons, Ltd.

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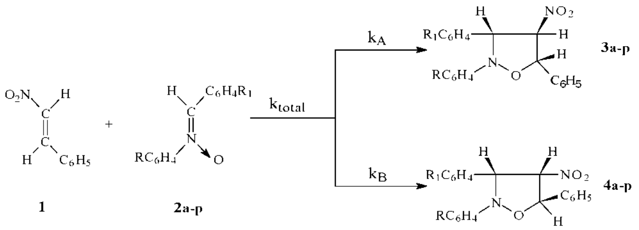
KEYWORDS: [2 + 3] cycloaddition; nitrones; nitroalkenes; kinetics; substituent effect; AM1 calculations

INTRODUCTION

During the past two decades, pericyclic reactions of nitroalkenes have aroused considerable interest and much effort has been made to establish their capability for thermally allowed cycloadditions.[1–6] Despite this, the reactions of conjugated nitroalkenes with nitrones have not been investigated thoroughly. As far as we know, only cycloadditions with nitroethylene,[1,7] nitropropylenes,[1,8,9] nitrobutylene,[10] β-nitrostyrenes[1,7,11,12] and some sugar nitroalkenes[13,14] have been studied from the regio- and stereochemical point of view, and data concerning the kinetic aspects of these reactions are scarce.[15] Hence, in this work, we investigated the cycloaddition kinetics using (*E*)-β-nitrostyrene (**1**) and two coherent series of (*Z*)-*C,N*-diarylnitrones (**2a**–**g** and **2g**–**p**) with similar steric requirements but different electron distributions on the reaction centres (Scheme 1, Table 1). Recently,[11,12] we have shown that the [2 + 3] cycloaddition of these reactants is regioselective and affords good yields of 2,3-diaryl-4-nitro-5-phenylisoxazolidines (**3a**–**p** and **4a**–**p**) in the ratio of ca 4–5:1, independently on the type of substituents in the phenyl rings of parent (*Z*)-*C,N*-diphenylnitrone.



Scheme 1.

The aims of this study were (i) to investigate the substituent effect on the reaction rate and (ii) to compare the rate data with FMO treatments of the cycloaddition kinetics.

EXPERIMENTAL

Reagents and equipment. (*E*)-β-Nitrostyrene (**1**) and diarylnitrones **2a**–**p** were prepared according to known procedures[16,17] and were purified by crystallization. Pure-grade toluene (POCh, Gliwice, Poland) was used as a solvent and was dried over molecular sieves 4A and distilled before use. For kinetic measurements, a Knauer HPLC system equipped with a UV–VIS detector and a LiChrospher 100RP column (240 × 4mm i.d.) was applied. Methanol–water (4:1, v/v) or THF–water (52:48, v/v) mixtures were used as eluents. Kinetic experiments were carried out in a glass reactor supplied with a thermostatically controlled heating jacket, magnetic stirrer, thermometer, reflux condenser and sampling

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[†] Part XLV in the series Synthesis and Properties of Azoles and Their Derivatives. Part XLIV: *J. Phys. Org. Chem.* 2000; **13**: 489.

Contract/grant sponsor: Polish Committee of Scientific Research; *Contract/grant number:* C-2/239/DS/97.

Table 1. Essential molecular properties of (*E*)-*β*-nitrostyrene (**1**) and (*Z*)-*C*,*N*-diarylnitrones (**2a–p**) in the gas phase as calculated by the AM1 method, and the overall rate constants for their [2 + 3] cycloadditions in toluene at 80 °C[a]

				Charge distribution on the atoms (e)							Regression analysis of kinetic data by Eqn. (1)			
No.	R	R_1	σ_{R/R_1}	C/C_β	N	O/C_α	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_1 (eV)	ΔE_2 (eV)	$K_{total} \times 10^4$	*r*	SD	*n*
1	—	—	—	−0.219	—	−0.009	−9.89	−1.34	—	—	—	—	—	—
2a	*p*-CH_3O	H	−0.27	−0.208	0.349	−0.458	8.32	−0.80	9.09	6.98	2.88	0.999	0.02	9
2b	*p*-CH_3	H	−0.17	−0.202	0.342	−0.458	−8.35	−0.84	9.05	7.01	3.44	0.998	0.03	9
2c	*p*-Cl	H	0.23	−0.194	0.339	−0.457	−8.49	−1.08	8.81	7.15	4.31	0.999	0.03	10
2d	*p*-Br	H	0.23	−0.191	0.336	−0.457	−8.52	−1.14	8.75	7.18	4.28	0.996	0.04	9
2e	*p*-$COOCH_3$	H	0.46	−0.185	0.330	−0.457	−8.58	−1.36	8.53	7.24	6.28	0.999	0.01	8
2f	*p*-NO_2	H	0.78	−0.172	0.325	−0.455	−8.83	−1.86	8.03	7.49	9.26	0.998	0.03	9
2g	H	H	0.00	−0.201	0.341	−0.457	−8.39	−0.86	9.03	7.05	4.08	0.998	0.03	9
2h	H	*p*-$(CH_3)_2N$	−0.83	−0.173	0.324	−0.474	−7.72	−0.65	9.24	6.28	5.32	0.994	0.06	8
2i	H	*p*-CH_3O	−0.27	−0.191	0.335	−0.463	−8.16	−0.82	9.07	6.82	3.71	0.999	0.02	7
2j	H	*p*-F	0.06	−0.202	0.342	−0.456	−8.45	−1.00	8.89	7.11	3.34	0.998	0.03	7
2k	H	*p*-Cl	0.23	−0.207	0.345	−0.453	−8.48	−1.00	8.89	7.14	2.47	0.991	0.06	10
2l	H	*p*-Br	0.23	−0.211	0.347	−0.449	−8.54	−1.04	8.85	7.20	2.48	0.999	0.03	8
2m	H	*m*-Cl	0.37	−0.209	0.346	−0.449	−8.56	−0.98	8.91	7.22	2.65	0.999	0.02	10
2n	H	*m*-Br	0.39	−0.210	0.346	−0.449	−8.57	−0.99	8.90	7.23	2.56	0.993	0.06	10
2o	H	*m*-NO_2	0.71	−0.225	0.354	−0.436	−8.93	−1.31	8.58	7.59	1.83	0.999	0.02	9
2p	H	*p*-NO_2	0.78	−0.231	0.359	−0.434	−9.05	−1.55	8.34	7.71	1.73	0.999	0.02	10

[a] $\Delta E_1 = |E_{HOMO}(\mathbf{1}) - E_{LUMO}(\mathbf{2})|$, $\Delta E_2 = |E_{HOMO}(\mathbf{2}) - E_{LUMO}(\mathbf{1})|$
r = correlation coefficient
SD = standard deviation
n = number of data.

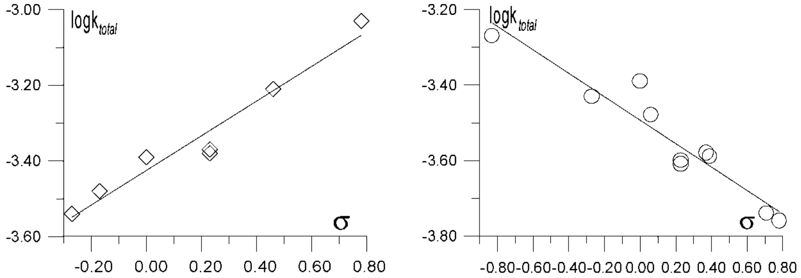

Figure 1. Hammett plots for cycloaddition of (*E*)-*β*-nitrostyrene (**1**) to (*Z*)-*C*-phenyl-*N*-arylnitrones **2a–g** (◇) and (*Z*)-*C*-phenyl-*N*-arylnitrones **2g–p** (○)

device. The molecular properties of the reactants were calculated on a Pentium III (733 MHz) computer using the HYPERCHEM-5 program package.

Kinetic measurements. The rates of the cycloaddition reactions were followed by measuring the area of the HPLC peak corresponding to the nitrones **2a**–**p**. The reactions were started by mixing a weighed quantity of nitrone with 50 ml of (*E*)-*β*-nitrostyrene solution in toluene at constant temperature while stirring. The initial concentration of the former reactant was 0.20–0.26 mol^{-1} l, whereas the latter was always in an 11–15-fold molar excess. The kinetic runs were carried out up to 70–80% completion at 80 ± 0.2 °C. During the runs, 0.2 ml samples were taken periodically from the reaction mixture with a pipette, quenched with cold methanol and diluted to 5 or 10 ml in a volumetric flask. The solution was immediately analysed by HPLC at the wavelength characteristic of the K-band of particular nitrones.[18] It was found that for that band, the Bouguer–Beer plots were linear within the concentration range studied.

RESULTS AND DISCUSSION

Regression analysis of the experimental data with the MATCAD-6 program showed that the semilogarithmic plot of HPLC peak area (S) versus time (t) was linear for all kinetic runs, according to the first-order kinetic equation.

$$\ln S = k_{\text{obs}}t + \text{constant} \qquad (1)$$

where k_{obs} is the apparent first-order rate constant, calculated from the slope of the line by means of a least-squares fit.

The second-order rate constants k_{total}, being the sum of k_{A} and k_{B} (cf. Scheme 1), were obtained according to a typical method,[19] by division of k_{obs} by the concentration of nitrostyrene **1**. The results are given in Table 1, along with parameters of the regression analysis.

We found by independent experiments that under the reaction conditions used in this study, adducts **4** are partially converted into adducts **3**, suggesting that **3** is more stable thermodynamically than **4**. Therefore, the molar ratio of the stereoisomers, $\alpha = [\mathbf{3}]/[\mathbf{4}]$, changes with the reaction progress, shifting towards the value characteristic of thermodynamic equilibrium. For example, in the reaction of **1** with **2f**, α was equal to 4.6 after 150 min, 5.1 after 450 min and 5.2 after 720 min, whereas in the reaction of **1** with **2p**, α was equal to 4.5 after 60 min and 5.0 after 460 min. Tanaka *et al.*[8] described a similar phenomenon for the cycloaddition of *C*-phenyl-*N*-methylnitrone with (*E*)-3,3,3-trifluoro-1-nitropropene. Consequently, k_{total} was applied instead of k_{A} and k_{B} for the study of the substituent effect.

As shown in Table 1, substituents in the phenyl rings of the parent nitrone affect the overall reaction rates in both reaction series, but in different manners. In the first series, on passing from (*Z*)-*C*-phenyl-*N*-(*p*-methoxyphenyl)nitrone (**2a**) to (*Z*)-*C*-phenyl-*N*-(*p*-nitrophenyl)nitrone (**2f**), the rate constant (k_{total}) of their reaction with (*E*)-*β*-nitrostyrene increases by a factor of 3.2, whereas in the second series, on going from (*Z*)-*C*-(*p*-methoxyphenyl)-*N*-phenylnitrone (**2i**) to (*Z*)-*C*-(*p*-nitrophenyl)-*N*-phenylnitrone (**2p**), k_{total} decreases by a factor of 2.1. The substituent effect on the reaction rate was tested using $\sigma, \sigma^{+}, \sigma^{-}$ and σ^{R} sets of Hammett constants.[19] For both series, the best correlation was obtained when the values of k_{total} were plotted on a logarithmic scale against normal σ-constants [Fig. 1, Eqns (2) and (3)]:

$$\log k_{\text{total}} = 0.46\sigma - 3.42 \qquad (r = 0.973, \psi = 0.15) \quad (2)$$

$$\log k_{\text{total}} = -0.31\sigma - 3.49 \qquad (r = 0.957, \psi = 0.12) \quad (3)$$

The ρ value is positive for nitrones **2a**–**g** and negative for nitrones **2g**–**p**. Both values are in good agreement with the Huisgen[20] hypothesis of ρ values which are characteristic of concerted [2 + 3] cycloaddition reactions.

In order to understand better the experimentally obtained reactivity orders, we performed FMO analysis, using AM1-calculated frontier orbitals. The FMO energies were obtained for fully optimized structures of reactants (r.m.s. gradient of 0.09). As follows from Table

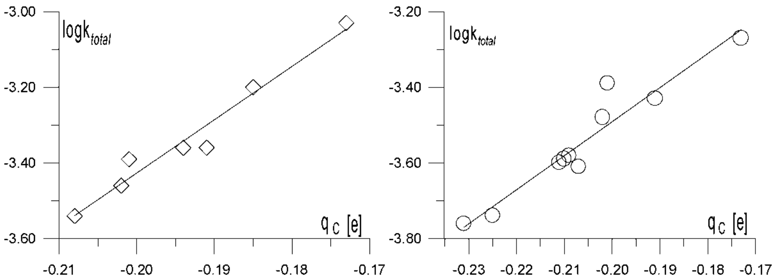

Figure 2. Plots of log k_{total} versus local charge (q_c) on the carbon end of 1,3-dipoles **2a–g** (◇) and **2g–p** (○) for [2 + 3] cycloaddition with β-nitrostyrene

1, in all cases the energy gap between the HOMO of nitrones and the LUMO of (*E*)-β-nitrostyrene (ΔE_2) is smaller than that between the HOMO of (*E*)-β-nitrostyrene and the LUMO of nitrones (ΔE_1). Moreover, in both reaction series ΔE_2 increases with increase in the substituent σ-constants. These facts suggest that the reactions under study are type II or I according to Sustmann's classification.[21] Therefore, we should expect an L-shape or linear Hammett relationships with negative ρ values.[20] Most likely, factors other than FMO energies need to be taken into account to rationalise observed reactivity orders.

It is noteworthy that Samuilov and co-workers[22,23] have already reported similar incompatibility for [2 + 3] cycloaddition of *N*-phenylmaleimide to *C*-aryl-*N*-phenyl- and *C*-phenyl-*N*-arylnitrones. The authors explained the experimental results in terms of π-localization theory,[24] assuming that the transition state in these reactions is the late one. We found it difficult to extrapolate this approach to our results, because according to our recently published data,[25,26] the reactions under study occur rather via an early transition state. It should be noted that FMO theory also failed in several cases[8,12,14,27] to describe the regioselectivity of nitrone [2 + 3] cycloadditions. Such disagreement can be found when the HSAB theory is applied to these reactions.[27]

An alternative approach for predicting the reactivity in cycloadditions of polarized substrates considers coulombic interactions between charges on the reaction centres.[28] In particular, for the reactants under study, these interactions can be estimated from a simplified form of the second term of the Salem–Klopman equation:[28–30]

$$\log k \sim \Delta E_q = -[(q_C q_{C\beta}/\varepsilon R_{C,C\beta}) + (q_O q_{C\alpha}/\varepsilon R_{O,C\alpha})] \quad (4)$$

where: q_i is the effective charges on the reaction centres in the isolated molecules, R_i are the distances between the reaction centres in transition states and ε is the dielectric constant of the solvent. The activation energy is lower for the reactants for which a larger ΔE_q is obtained.

As can be seen from Table 1, the α-carbon atom of dipolarophile **1** has a much smaller negative charge than the β-carbon atom. This is due to the polarization effect resulting from the electron-withdrawing properties of the nitro group. In the nitrones **2a**–**g**, the oxygen atom of the >C=N(O)— moiety has about twice the charge of the carbon atom. Moreover, the charge on the oxygen atom is practically constant, whereas the charge on carbon atom decreases considerably with increase in the σ-constant of substituent R. On the other hand, in the nitrones **2g**–**p**, the charge on the carbon atom increases with increase in the σ-constant of substituent R_1, whereas that on oxygen decreases slightly. As the charge on the α-carbon of dipolarophile **1** is negligibly small, the term $q_O q_{C\alpha}/\varepsilon R_{O,C\alpha}$ in Eqn. (4) can be neglected. Hence it should be possible to predict the reactivity orders from the electrostatic repulsion between charges on the β-carbon of nitrostyrene **1** and the carbon end of 1,3-dipoles **2a**–**p**. As the expression $q_{C\beta}/\varepsilon R_{C,C\beta}$ remains constant within the reaction series, the reactivity is controlled by the magnitude of the charge q_C. The preferred reaction corresponds to the nitrone with less negative charge on the carbon end of the 1,3-dipole. Indeed, by plotting the k_{total} values on a logarithmic scale versus q_C, satisfactory linear relationships ($r \geq 0.95$) were obtained for both reaction series (Fig. 2). Since the q_C of nitrones **2** correlates with the σ-constants of substituents R and R_1 in a linear manner, the plots of log k_{total} versus Hammett σ-constants are also linear (Fig. 1).

Finally, it should be noted that the approach presented in this paper was also applied by us with success to account for the reactivity of the nitrones in [2 + 3] cycloaddition with *N*-phenylmaleimide as described previously by Samuilov and co-workers.[22,23]

CONCLUSIONS

From the results presented in this paper, it follows that the reactivity of *C,N*-diarylnitrones in [2 + 3] cycloaddition with (*E*)-β-nitrostyrene cannot be described by using FMO theory. Owing to the highly polarized structures of both reactants, coulombic interactions between charges on the reaction centres override FO preferences and probably influence the reactivity orders. Nevertheless, more detailed investigations on similar lines are called for.

Acknowledgements

The authors thank the Polish Committee of Scientific Research for financial support (grant No. C-2/239/DS/97) and Mrs E. Grodowska and Mr W. Taborski for technical assistance.

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