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ORIGINAL PAPER

# Secondary α-deuterium kinetic isotope effects in [2+4] cycloaddition of (*E*)-2-phenylnitroethene to cyclopentadiene

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**Abstract** Secondary α-deuterium kinetic isotope effects confirm that [2+4] cycloaddition between (*E*)-2-phenylnitroethene and cyclopentadiene occurs in concerted manner, on both the pathway leading to 6-*endo*-phenyl-5-*exo*-nitronorbornene and the pathway leading to the corresponding 6-*exo*-phenyl-5-*endo*-nitro isomer. According to Hammond terminology the transition states on competitive pathways should be considered in terms of symmetrical early states.

**Keywords** Diels–Alder reaction · Nitroalkene · Secondary kinetic isotope effects · Mechanism

## Introduction

The [2+4] cycloadditions of simple nitroalkenes with conjugated dienes proceed according to a concerted mechanism, as confirmed by kinetic studies and by stereospecificity observed in the reactions [1–4]. However, the results are insufficient to assess symmetry and the degree of formation of new σ bonds in the postulated transition complexes. Therefore, pursuing our studies on reactivity of nitroalkenes in [2+4] π-electron cycloadditions [5–9], we decided to explore the α-secondary kinetic isotope effect (SKIE). For our investigations we selected (*E*)-2-phenylnitroethenes (**1a**–**1d**) with varied degree of deuteration at the nitrovinyl moiety as the 2π-electron components, and cyclopentadiene (**2**) as the 4π-electron component. Recently [10], we have confirmed by means of high-performance liquid chromatography (HPLC) and $^1$H nuclear magnetic resonance (NMR) spectroscopy that in nitromethane the [2+4] cycloaddition of these reactants is stereoselective and leads to 6-*endo*-phenyl-5-*exo*-nitro- (**3a**–**3d**) and 6-*exo*-phenyl-5-*endo*-nitronorbornenes (**4a**–**4d**) in quantitative yields (Scheme 1).

Based on the combination of femtosecond time-resolved observation of the intermediates [11] and quantum-chemical simulation of the reaction pathways [12], analysis of SKIEs [13, 14] gives excellent insight into the symmetry of the transition states, knowledge which is vital for better understanding of the underlying reaction mechanism. It has been known [1, 2, 4, 15] for some time now that, in the case of extremely π-deficient dienophiles, a two-stage mechanism with a zwitterionic intermediate or a one-step two-stage mechanism, involving formation of a heterodiene, may compete with the concerted mechanism. This was confirmed by experimental studies [16–20] and quantum-chemical calculations [21–25].

## Results and discussion

The α-secondary deuterium kinetic isotope effects result from changes in oscillation behavior of C–H bonds not participating directly in the chemical reaction, upon substitution of one of the hydrogen atoms with its heavier isotope [13, 14]. In the cycloaddition in question, these are the C–H bonds in the nitrovinyl moiety of phenylnitroethene **1a**. During the course of the reaction, the hybridization of $C_\alpha$ and $C_\beta$ atoms of the moiety changes from trigonal to tetrahedral. This leads to increase of the frequency of out-of-plane bending of $C_\alpha$–H and $C_\beta$–H bonds, which is closely related to the system zero-point energy (ZPE). The difference between the ZPE of

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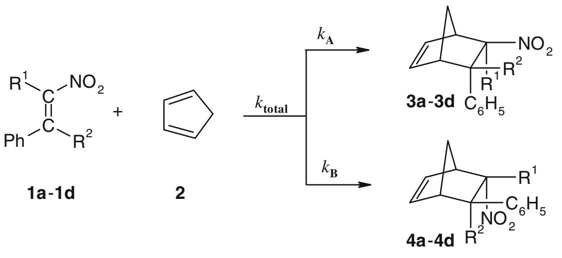

**(a)** $R^1 = R^2 = H$; **(b)** $R^1 = H$, $R^2 = D$; **(c)** $R^1 = D$, $R^2 = H$; **(d)** $R^1 = R^2 = D$

**Scheme 1**

substrates and the ZPE of transition complexes is lower for D-substituted dienophiles than for H-substituted dienophile [14]. Therefore, in the case of a concerted mechanism, the rate constant ($k_D$) of the [2+4] cycloaddition of phenylnitroethenes **1b–1d** with cyclopentadiene should be higher than the corresponding rate constant ($k_H$) of the reaction of **1a**. However, in the case of a two-stage process, one of the $k_D$ values should be equal to $k_H$. When the $k_H/k_D$ ratio (SKIE) is known, the degree of rehybridization of $C_\alpha$ and $C_\beta$ atoms in the transition state may be estimated, and consequently information can be obtained about the degree of formation of new $\sigma$ bonds and the transition state symmetry.

The data in Table 2 show that the SKIE, which results from substitution of the hydrogen atom at $C_\alpha$ position of dienophile **1a** with deuterium, is low. In particular, the SKIE is 0.95 for the reaction **1b** + **2** → **3b** (pathway A) and 0.94 for the reaction **1b** + **2** → **4b** (pathway B). If it is assumed that the configuration of the $C_\alpha$ atom is fully tetrahedral within the transition state, the frequency of out-of-plane bending of the $C_\alpha$–H bond should increase from 970 $cm^{-1}$ [26] to about 1,430 $cm^{-1}$ [10], which corresponds to SKIE of about 0.7 [14, 27]. Therefore, the SKIE data indicate that, in both transition states, the configuration at the $C_\alpha$ atom is much closer to the trigonal configuration found in nitroalkene **1a** than to the tetrahedral configuration found in the cycloadducts **3a** and **4a**. The $C_\alpha$ atom of the dienophile substructure tends to adopt the tetrahedral configuration of the C-6 atom in the cycloadduct. However, the conjugation of $\pi$ bonds of the phenyl ring and the nitrovinyl moiety tends to retain the configuration of the dienophile. Both tendencies compete within the two structures.

When the hydrogen atom at $C_\beta$ position of dienophile **1a** is substituted with deuterium, SKIE is 0.95 for both reactions **1c** + **2** → **3c** and **1c** + **2** → **4c**. This confirms that the rehybridization of the reaction site is not far advanced. The competition of two opposite tendencies is also visible in this case. The $C_\beta$ atom of the dienophile substructure tends to adopt the tetrahedral configuration of the C-5 atom in the cycloadduct. However, the conjugation of the nitro group with the vinylidene fragment of the nitroalkene restrains that process.

As could be expected on the basis of the rule of geometric mean [28], the SKIE values for the reactions **1d** + **2** → **3d** and **1d** + **2** → **4d** are very close to the products of the corresponding SKIE values obtained for the reactions **1b** + **2** and **1c** + **2**, confirming the reliability of our results.

The presented data indicate that rehybridization of the $C_\alpha$ and $C_\beta$ atoms of the nitroethenyl moiety of the dienophile is not very advanced in both stereoisomeric transition states. Hence, the transition states of the reaction studied can be interpreted as synchronous early transition states.

The results obtained are consistent with quantum-chemical calculations. In particular, our B3LYP/6-31G* simulation of the reaction paths has confirmed that: (1) the reaction proceeds by a concerted mechanism, (2) the distances between the reaction sites in both transition states differ only insignificantly (Fig. 1), and (3) the calculated SKIE values correlate well with the experimental data (Table 2). Moreover, it should be noted that B3LYP/6-311G** calculations also confirm the one-step mechanism of the reaction under study. Detailed analysis of the

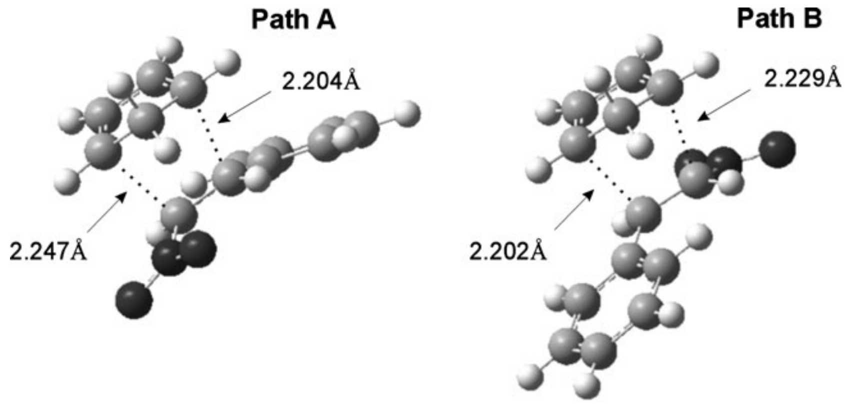

**Fig. 1** Transition structures approximated with B3LYP/6-31G$^*$ method for [2+4] cycloaddition of (*E*)-2-phenylnitroethene to cyclopentadiene in nitromethane (for simulation of the solvent effect the PCM approach was applied)

quantum-chemical results is the subject of a separate paper [29].

## Conclusions

The [2+4] cycloaddition of (*E*)-2-phenylnitroethene and cyclopentadiene occurs in concerted manner, on both the path leading to 6-*endo*-phenyl-5-*exo*-nitronorbornene and the path leading to the corresponding 6-*exo*-phenyl-5-*endo*-nitro stereoisomer. The π deficiency of the dienophile [30] is not sufficient to induce a two-step mechanism. On the basis of degree of rehybridization of the reaction sites, the transition states involved in both competing reaction paths should be considered as symmetrical early states.

## Experimental

### Reagents

(*E*)-2-phenylnitroethenes (**1a–1d**) and cyclopentadiene (**2**) were synthesized according to known procedures [31–33]. Their purity was confirmed by means of HPLC and $^1$H NMR spectroscopy. Pure-grade nitromethane (POCh, Gliwicę, Poland) was used as a solvent; it was dried over 4-Å molecular sieves and distilled before use.

### Kinetic procedure

The rates of the cycloaddition reactions were followed by HPLC using the integrated area (*A*) of the peak corresponding

**Table 1** Results of kinetic measurements of [2+4] cycloaddition of cyclopentadiene **2** with (*E*)-2-phenylnitroethenes **1a–1d**

| Reaction | **1a** + **2** | | **1b** + **2** | | **1c** + **2** | | **1d** + **2** | |
|---|---|---|---|---|---|---|---|---|
| Initial diene concentration (mol/dm$^3$) | 0.005 | | 0.005 | | 0.005 | | 0.005 | |
| Initial alkene concentration (mol/dm$^3$) | 0.10 | | 0.11 | | 0.10 | | 0.11 | |
| Experimental points | *t* (s) | $A_\infty - A_t$ | *t* (s) | $A_\infty - A_t$ | *t* (s) | $A_\infty - A_t$ | *t* (s) | $A_\infty - A_t$ |
| 1 | 3,540 | 1.72 | 3,600 | 1.81 | 3,480 | 1.82 | 3,600 | 1.82 |
| 2 | 7,200 | 1.59 | 7,260 | 1.62 | 7,080 | 1.62 | 7,200 | 1.65 |
| 3 | 10,800 | 1.39 | 10,800 | 1.45 | 10,620 | 1.48 | 10,800 | 1.50 |
| 4 | 16,200 | 1.21 | 14,460 | 1.28 | 16,200 | 1.23 | 16,200 | 1.25 |
| 5 | 25,140 | 0.97 | 19,800 | 1.11 | 21,540 | 1.13 | 21,720 | 1.14 |
| 6 | 30,820 | 0.83 | 25,200 | 0.95 | 27,000 | 0.93 | 27,720 | 0.95 |
| 7 | 37,840 | 0.68 | 32,760 | 0.80 | 34,560 | 0.75 | 32,400 | 0.78 |
| 8 | 86,700 | 0.18 | | | 52,680 | 0.45 | 39,600 | 0.61 |
| 9 | | | | | | | 52,140 | 0.43 |
| Number of points | 8 | | 7 | | 8 | | 9 | |
| Correlation coeff. *R* | 0.999 | | 0.998 | | 0.999 | | 0.998 | |
| Student *t* | 143.44 | | 39.96 | | 60.94 | | 40.48 | |
| Exner's Ψ | 0.020 | | 0.073 | | 0.046 | | 0.074 | |
| Standard dev. (10$^2$ s) | 0.02 | | 0.02 | | 0.02 | | 0.03 | |

**Table 2** Rate constants of cycloaddition of cyclopentadiene with (*E*)-2-phenylnitroethenes and the corresponding SKIEs

| Reaction | $k_{\mathrm{total}}$ 10$^4$ (dm$^3$/mol s) | γ | Path A | | | Path B | | |
|---|---|---|---|---|---|---|---|---|
| | | | $k_{\mathrm{A}}$ 10$^4$ (dm$^3$/mol s) | SKIE | | $k_{\mathrm{B}}$ 10$^4$ (dm$^3$/mol s) | SKIE | |
| | | | | Exp. | Calc. | | Exp. | Calc. |
| **1a** + **2** | 2.25 | 0.201 | 0.38 | – | – | 1.87 | – | – |
| **1b** + **2** | 2.38 | 0.199 | 0.40 | 0.95 | 0.95 | 1.98 | 0.94 | 0.94 |
| **1c** + **2** | 2.37 | 0.200 | 0.40 | 0.95 | 0.93 | 1.97 | 0.95 | 0.95 |
| **1d** + **2** | 2.50 | 0.202 | 0.42 | 0.90 | 0.88 | 2.08 | 0.90 | 0.89 |

to the cycloadducts **3** and **4**. A Knauer system (Smartline 1000 HPLC pump and Smartline 4000 thermostat) equipped with Smartline 2500 UV–Vis detector and LiChrospher 100-10 RP column (4 × 240 mm i.d.) was applied for analysis. Methanol–water (50:50 v/v) at flow rate of 1.3 $cm^3$/min was used as the eluent. Analyses were carried out at 25 °C and $\lambda = 254$ nm. At these conditions both cycloadducts had the same retention times ($t = 11.3$ min). The starting reaction mixtures were prepared by adding a weighed quantity of suitable (*E*)-2-phenylnitroethene to the solution of freshly distilled cyclopentadiene in dry nitromethane. The initial concentration of the latter reactant was 0.05 mol/$dm^3$, whereas the former one was always used in 20–22-fold molar excess. The mixtures were placed in ampoules of 1 $cm^3$ capacity and thermostated at 70 ± 0.2 °C. During kinetic runs, the ampoules were taken periodically from the thermostat and immediately cooled in an ice bath. Samples of 250 $mm^3$ were taken from the ampoules with a microsyringe and were diluted with 1,000 $mm^3$ methanol. The solutions were analyzed by HPLC at analytical wavelength 210 nm. It was found that, for this wavelength, the Bouguer–Beer plot was linear within the concentration range studied. Second-order rate constants $k_{total}$ (Table 1) were obtained by a routine method [34]. Control experiments showed that, under the conditions used for the kinetic measurements, the concentrations of **3** and **4** were measured with an error less than 3%. After completion of the reaction, the ratio of the cycloadducts in product mixture, $\gamma = [\mathbf{3}]/[\mathbf{4}]$, was determined by HPLC. The analyses were carried out at 5 °C, using LiChrospher 100-5 RP column (4 × 240 mm i.d.), methanol–water (55:45 v/v) mixture as eluent, and eluent flow rate of 0.5 $cm^3$/min. At these conditions, the peaks corresponding to the cycloadducts were clearly separated [$t(\mathbf{3}) = 203$ min, $t(\mathbf{4}) = 224$ min]. The $k_{total}$ and $\gamma$ values were converted to the rate constants $k_A$ and $k_B$ (Table 2) according to the following formulas:

$$k_A = \gamma k_{total}/(\gamma + 1) \quad k_B = k_{total}/(\gamma + 1).$$

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