

Effect of Pressure on the Rate of the Diels–Alder Reaction of Diethyl Azodicarboxylate with 9,10-Dimethylanthracene

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Abstract—The enthalpy, entropy, and volume of activation and volume of the Diels–Alder reaction of diethyl azodicarboxylate with 9,10-dimethylanthracene in 1,2-dichloroethane have been determined. Possible factors responsible for the sharp difference between the volumes of activation and reaction are considered.

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Diethyl azodicarboxylate is widely used in the synthesis of biologically and optically active compounds according to the Mitsunobu reaction [1]. It is also known as dienophile in Diels–Alder reactions, enophile in Alder-ene reactions, and dehydrogenating agent [2, 3]. Kinetic studies have been performed for a limited number of Diels–Alder reactions with diethyl azodicarboxylate because of its low reactivity [4–6]. The rate of a Diels–Alder reaction can be raised by applying a high hydrostatic pressure, which sharply increases the rate and equilibrium constants [5]. Comparison of the volumes of activation (ΔV^\ddagger) and reaction (ΔV_r) shows the difference between the volumes of the activated complex and product [5, 6]. 1,3-Dienes possessing an allylic hydrogen atom are known to react with diethyl azodicarboxylate according to both Diels–Alder and Alder-ene patterns [4, 6]. In the reaction with 9,10-dimethylanthracene, only the Diels–Alder path should be expected.

We were the first to determine the rates of the reaction of diethyl azodicarboxylate with 9,10-dimethylanthracene over a wide range of pressures and temperatures and evaluate the enthalpy, entropy, and volume of activation and volume of reaction.

Useful information follows from the known kinetic parameters of the Diels–Alder reactions of cyclopentadiene and 9,10-dimethylanthracene with C=C and N=N dienophiles (Table 1). Cyclopentadiene is a less conjugated diene and a weaker π -electron donor than 9,10-dimethylanthracene [8]. Increased π -donor ability

of 9,10-dimethylanthracene is reflected in higher rates of its reactions with strong π -acceptors, e.g., with tetracyanoethylene. The rates of the reactions of the above dienes with 4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3,5-dione are also high and comparable. Less conjugated cyclopentadiene is more reactive toward dienophiles that are weak π -acceptors. It was noted [7] that considerable reduction of the reaction rates of these dienes with maleic acid esters as compared to

Table 1. Rate constants k_2 ($1 \text{ mol}^{-1} \text{ s}^{-1}$) for the Diels–Alder reactions of some dienophiles with cyclopentadiene and 9,10-dimethylanthracene

Dienophile	Cyclopentadiene ^a	9,10-Dimethylanthracene ^b
Dimethyl fumarate	7.4×10^{-4}	6.70×10^{-6}
Dimethyl maleate	6.3×10^{-6}	5.64×10^{-9}
Maleic anhydride	5.56×10^{-2}	1.13×10^{-2}
N-Phenylmaleimide	7.05×10^{-2}	3.0×10^{-2} [8]
Diethyl azodicarboxylate ^c	1.67×10^{-3}	1.6×10^{-3}
4-Phenyl-4,5-dihydro-3H-1,2,4-triazole-3,5-dione	$\sim 10^4$ [9]	1.22×10^4 [10]
Tetracyanoethylene ^d	4.8×10^2	1.3×10^4

^a In 1,4-dioxane at 20°C [7].

^b In 1,4-dioxane at 25°C [7].

^c In benzene at 20°C. The rate constant for the reaction with dimethyl azodicarboxylate in 1,4-dioxane at 23.5°C is $0.012 \text{ L} \times \text{mol}^{-1} \text{ s}^{-1}$ [4].

^d In 1,4-dioxane at 20°C [11].

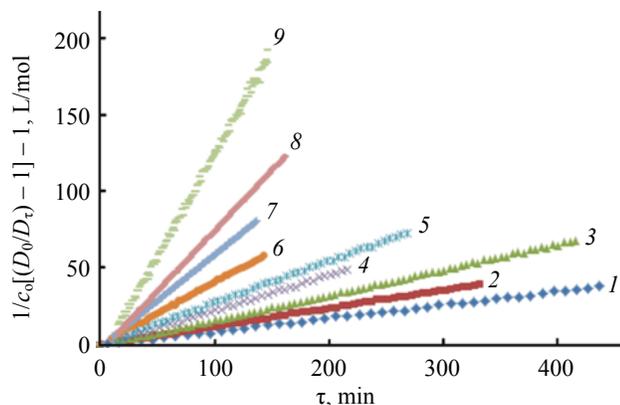


Fig. 1. Effect of pressure (P) on the rate of the reaction **I** + **II** \rightarrow **III** in 1,2-dichloroethane at 25.0°C. $P = (1)$ 1, (2) 242, (3) 429, (4) 601, (5) 749, (6) 991, (7) 1285, (8) 1567, (9) 1930 bar.

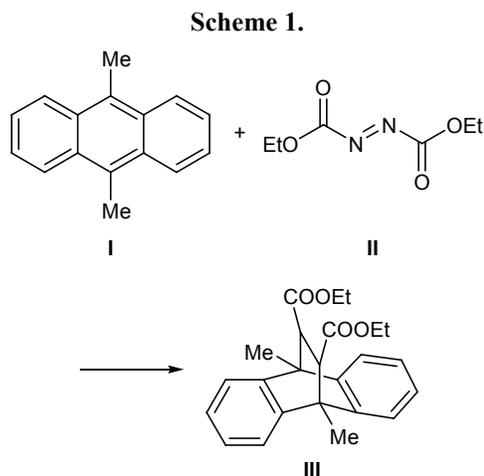
fumaric acid esters is related to deviation from coplanarity of the *cis*-dienophile for steric reasons.

A large difference is observed between the rates of Diels–Alder reactions with 4-phenyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione and its structural analog, *N*-phenylmaleimide: $k(6)/k(4) > 10^5$. It was shown previously that both dienophiles are fairly similar in π -acceptor properties [10]. The higher reactivity of 4-phenyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione was assumed to be determined by the lower energy of cleavage of π -N=N bond as compared to π -C=C [10]. The reactivity difference between dimethyl azodicarboxylate and its C=C analog, dimethyl fumarate, is not so strong (Table 1). Extensive studies on the kinetics of Diels–Alder reactions of 1,3-dienes are restrained by low reaction rates at ambient temperature and concu-

Table 2. Rate constants (k_2) of the reaction **I** + **II** \rightarrow **III** in 1,2-dichloroethane at 25.0°C under elevated hydrostatic pressure (P)

P , bar	k_2 , l mol ⁻¹ s ⁻¹	$\ln(k_P/k_{P=1})$
1	0.00143	0
242	0.00199	0.3304
429	0.00275	0.6539
601	0.00380	0.9786
749	0.00452	1.1515
991	0.00668	1.5414
1285	0.01000	1.9449
1567	0.01314	2.2179
1930	0.02220	2.7424

rent Alder-ene, dehydrogenation, and other processes occurring at elevated temperature [2, 3, 12, 13]. We have found that 9,10-dimethylantracene (**I**) reacts with diethyl azodicarboxylate (**II**) to give Diels–Alder adduct **III** in quantitative yield (Scheme 1).



The rate constants of the reaction **I** + **II** \rightarrow **III** in 1,2-dichloroethane at 15.0, 25.0, 35.0, and 45.0°C were estimated at 1.05×10^{-3} , 1.57×10^{-3} , 2.22×10^{-3} , and 3.17×10^{-3} l mol⁻¹ s⁻¹, respectively. The enthalpy and entropy of activation were calculated from the dependence of $\ln k_2$ on T^{-1} ($R = 0.9998$): $\Delta H^\ddagger = 25.4 \pm 0.3$ kJ/mol, $\Delta S^\ddagger = -213 \pm 3$ J mol⁻¹ K⁻¹. The entropy of activation considerably exceeds values typical of Diels–Alder reactions [7, 8].

Large negative values of the entropy of activation for Diels–Alder reactions are often accompanied by increased negative values of the volume of activation (ΔV^\ddagger) [5, 14], which can be calculated from the dependence of the reaction rate constant on external pressure (Fig. 1). The calculated rate constants are given in Table 2.

Taking into account solvent compressibility, the volume of activation ($\Delta V_{\text{corr}}^\ddagger$) is calculated by Eq. (1) [14]:

$$\Delta V_{\text{corr}}^\ddagger = -RT \partial \ln(k_P) / \partial P + (n-1)RT \beta_T. \quad (1)$$

Here, β_T is the solvent compressibility factor (80.1×10^{-6} bar⁻¹ [15]), and n is the order of reaction.

The experimental $\ln(k_P/k_{P=1})$ — P curve (Fig. 2) is described by second-order Eq. (2):

$$\ln(k_P/k_{P=1}) = -0.000000141 P^2 + 0.0016944 P - 0.026969; R = 0.9992. \quad (2)$$

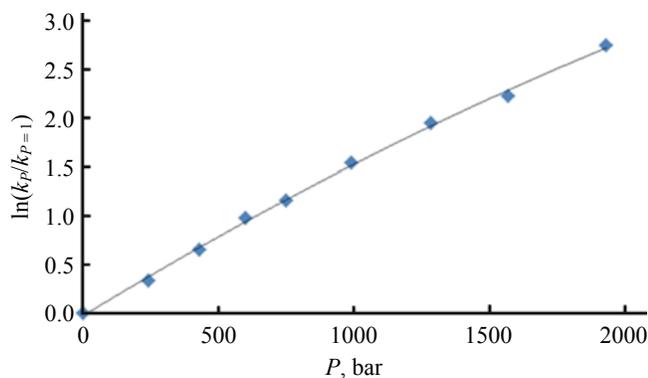


Fig. 2. Pressure dependence of the rate constant of the reaction **I** + **II** → **III**.

Then $\Delta V_{\text{exp}}^{\ddagger} = -42.0 \pm 2.1 \text{ cm}^3/\text{mol}$, and the corrected value is $\Delta V_{\text{corr}}^{\ddagger} -40.1 \pm 2.1 \text{ cm}^3/\text{mol}$. The experimental curve shown in Fig. 2 was also approximated by the Tait equation (3):

$$\ln(k_P/k_{P=1}) = 8.798 \ln[(5306 + P)/5306]; \quad (3)$$

$$R = 0.9987.$$

From Eq. (3) we obtained $\Delta V_{\text{exp}}^{\ddagger} = -41.0 \pm 2.5 \text{ cm}^3/\text{mol}$ and $\Delta V_{\text{corr}}^{\ddagger} = -39.1 \pm 2.5 \text{ cm}^3/\text{mol}$. The volumes of activation calculated using the above equations were similar. Equation (2) implies a false maximum at $P = 6 \text{ kbar}$, whereas Eq. (3) ensures not only reliable evaluation of $\Delta V_{\text{exp}}^{\ddagger}$ at any pressure but also calculation of acceleration effect at higher pressure. For instance,

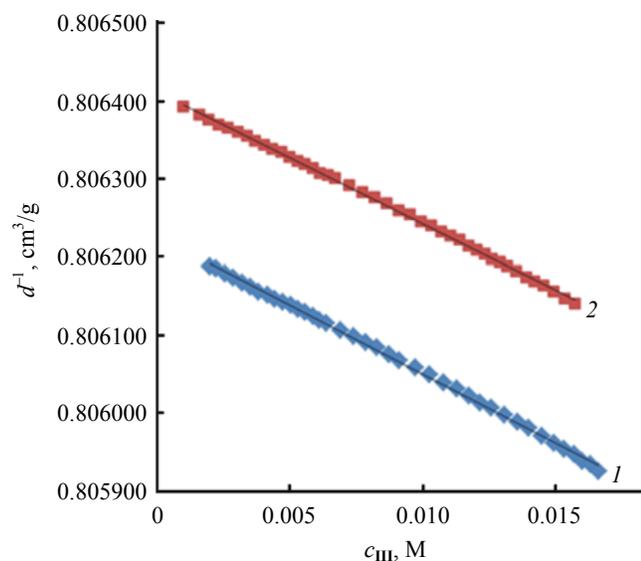


Fig. 3. Change of the specific volume during the reaction **I** + **II** → **III**: (1) $d^{-1} = -0.016951 c_{\text{III}} + 0.806411$, $R = 0.9995$; $\Delta V_r = -21.0 \text{ cm}^3 \text{ mol}^{-1}$; $c_{\text{I}}^0 = 1.920 \times 10^{-2}$, $c_{\text{II}}^0 = 0.2287 \text{ M}$; (2) $d^{-1} = -0.01763 c_{\text{III}} + 0.806226$, $R = 0.9994$; $\Delta V_r = -21.8 \text{ cm}^3 \text{ mol}^{-1}$; $c_{\text{I}}^0 = 1.905 \times 10^{-2}$, $c_{\text{II}}^0 = 0.2173 \text{ M}$.

according to Eq. (3), the expected $k_P/k_{P=1}$ value at 10 kbar is 11200.

It is worthwhile to compare the volume of activation and the volume of reaction. The latter was calculated from the dependence of the density of the reaction mixture on the adduct concentration. The overall volume of the reaction mixture at a given moment of time (V_τ) can be calculated using Eqs. (4) and (5):

$$V_\tau = V_S + (c_{\text{I}}^0 - c_{\text{III},\tau})V_1 + (c_{\text{II}}^0 - c_{\text{III},\tau})V_2 + c_{\text{III},\tau}V_{\text{III}}; \quad (4)$$

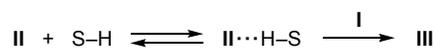
$$V_\tau = [V_S + (c_{\text{I}}^0 V_1 + c_{\text{II}}^0 V_2)] + c_{\text{III},\tau}(V_{\text{III}} - V_1 - V_2) \\ = V_{(\tau=0)} + c_{\text{III},\tau} \Delta V_r; \quad (5)$$

$$1/d_\tau = 1/d_{(\tau=0)} + c_{\text{III},\tau} \Delta V_r / 1000 d_{(\tau=0)}. \quad (6)$$

Here, V_S is the volume of the solvent; V_1 , V_2 , and V_{III} are the partial molar volumes of diene **I**, dienophile **II**, and adduct **III** in the reaction solution; c_{I}^0 and c_{II}^0 are the initial reactant concentrations, and $c_{\text{III},\tau}$ is the current adduct concentration. Division of both parts of Eq. (5) by the weight of one liter of the solution ($1000 d_{\tau=0}$) gives Eq. (6), which is convenient to calculate the volume of reaction ΔV_r from the $1/d_\tau - c_{\text{III},\tau}$ dependence (Fig. 3).

The resulting value $\Delta V_r = -21.4 \pm 0.4 \text{ cm}^3/\text{mol}$ is considerably lower than the volume of activation $\Delta V_{\text{corr}}^{\ddagger} = -39.1 \pm 2.5 \text{ cm}^3/\text{mol}$. The anomalously large negative volume of activation is consistent with the high negative entropy of activation $\Delta S^{\ddagger} = -213 \pm 3 \text{ J} \times \text{mol}^{-1} \text{ K}^{-1}$. This may be rationalized by the following. First, strong charge separation in the transition state due to electrostriction of the solvent and its rigid orientation in the solvation of the transition state may be presumed. However, in this case, appreciable acceleration of the reaction in polar medium should be expected, which is not observed experimentally. The rate of addition to the N=N bond increases in going from acetonitrile to benzene, 1,2-dichloroethane, and chloroform [4, 16, 17]. Second, increased rate of the Diels–Alder reaction between cyclopentadiene and diethyl azodicarboxylate (**II**) in proton-donor solvents (S–H) may be related to formation of H-complexes involving nitrogen atoms of the dienophile [4] (Scheme 2).

Scheme 2.



If the major reaction channel leading to adduct **III** involves intermediate formation of the complex

$\text{II}\cdots\text{H-S}$, coordination of three molecules in the activated complex should be characterized by increased negative values of both entropy and volume of activation. Studies directed toward elucidation of the reaction mechanism are now in progress.

EXPERIMENTAL

The ^1H NMR spectrum was recorded on a Bruker Avance 400 spectrometer. Commercial diethyl azodicarboxylate (**II**) (97%, Alfa Aesar), $n_{\text{D}}^{20} = 1.4201$ [18] and 9,10-dimethylantracene (**I**) (99%, Alfa Aesar), mp 183–184°C [19] were used without additional purification; 1,2-dichloroethane was purified according to standard procedure [20].

Diethyl 1,2-(9,10-dimethyl-9,10-dihydroanthracene-9,10-diyl)hydrazine-1,2-dicarboxylate (III). White crystals (from benzene), mp 153–154°C. ^1H NMR spectrum (400 MHz, CDCl_3 , 25°C), δ , ppm: 0.89 t (6H, CH_2CH_3), 2.56 s (6H, 9- CH_3 , 10- CH_3), 3.80 m (4H, OCH_2).

Normal pressure kinetic measurements. The rate of the reaction $\text{I} + \text{II} \rightarrow \text{III}$ was monitored by spectrophotometry (Hitachi U-2900) following variation in the absorbance of the initial reactants. The temperature effect on the reaction rate was determined in two ways. In the first case, the reaction was carried out under pseudofirst-order conditions at 15, 25, 35, and 45°C. The progress of the reaction was monitored by the absorbance of 9,10-dimethylantracene. The initial reactant concentrations were $c_{\text{I}}^0 = (1.9\text{--}2.0) \times 10^{-4}$ and $c_{\text{II}}^0 = 0.06\text{--}0.07$ M. The enthalpy and entropy of activation in 1,2-dichloroethane were estimated at 25.4 ± 0.3 kJ/mol and -213 ± 3 J mol $^{-1}$ K $^{-1}$, respectively. In the second case, the reaction rates were measured at 15.0 and 38.8°C at equal reactant concentrations, $c_{\text{I}}^0 = c_{\text{II}}^0 = 0.04$ M. Adduct **III** does not absorb in the region λ 400–435 nm corresponding to the analytical wavelength. The activation parameters were fairly similar: $\Delta H^\ddagger = 28.3 \pm 2.0$ kJ/mol, $\Delta S^\ddagger = -205 \pm 6$ J mol $^{-1}$ K $^{-1}$. The reaction was assumed to be complete when no absorption of the initial reactants was observed.

Elevated pressure kinetic measurements. Experiments were conducted at 25°C in 1,2-dichloroethane in a high-pressure setup equipped with an HP-500 high-pressure pump and a PCI-500 high-pressure optical cell with sapphire windows (Syn, Japan) which was compatible with a Scinco spectrophotometer (Korea). Stock solutions of **I** and **II** with equal concentrations (0.0418 M) were prepared, and working solutions were

obtained by mixing equal volumes (1 mL) of these stock solutions. In all cases, the kinetic dependences at elevated pressure were characterized by a correlation coefficient exceeding 0.999 (Fig. 1). The data on the effect of pressure on the rate constants are presented in Table 2. The volume of activation under normal pressure was calculated from the $\partial \ln(k_p)/\partial P$ value using Eqs. (2) and (3).

The density of the reaction mixture was measured with the aid of a DSA 5000 M precision density meter (Anton Paar, Austria) at $25 \pm 0.002^\circ\text{C}$ in 2-min intervals. In the first series of measurements, the reactant concentrations were $c_{\text{I}}^0 = 1.920 \times 10^{-2}$, $c_{\text{II}}^0 = 0.2287$ M, and in the second, $c_{\text{I}}^0 = 1.905 \times 10^{-2}$, $c_{\text{II}}^0 = 0.2173$ M. The concentration of adduct $c_{\text{III},\tau}$ was calculated from the kinetic equation. Calculation of the volume of reaction according to this procedure does not require determination of partial volumes of all reaction components.

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