



Pergamon

Tetrahedron 55 (1999) 12201–12210

TETRAHEDRON

Volume, Enthalpy and Entropy of Activation of the Diels-Alder Reaction of Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with 1-Hexene

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Received 21 May 1999; revised 19 July 1999; accepted 5 August 1999

Abstract: Pressure and temperature effects on the reaction rate of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with 1-hexene were investigated. The activation volume ($-26.7 \text{ cm}^3 \text{ mol}^{-1}$, 298.1 K) is in agreement with the conservation of all four nitrogen atoms in transition state. Densitometry, ^1H NMR and calorimetric studies of the reaction indicate nitrogen molecule loss by the intermediate just after its formation. Partial molar volumes in acetone of diene (127.2), 1-hexene (127.6) and the resulting adduct ($206.9 \text{ cm}^3 \text{ mol}^{-1}$) were determined. © 1999 Elsevier Science Ltd. All rights reserved.

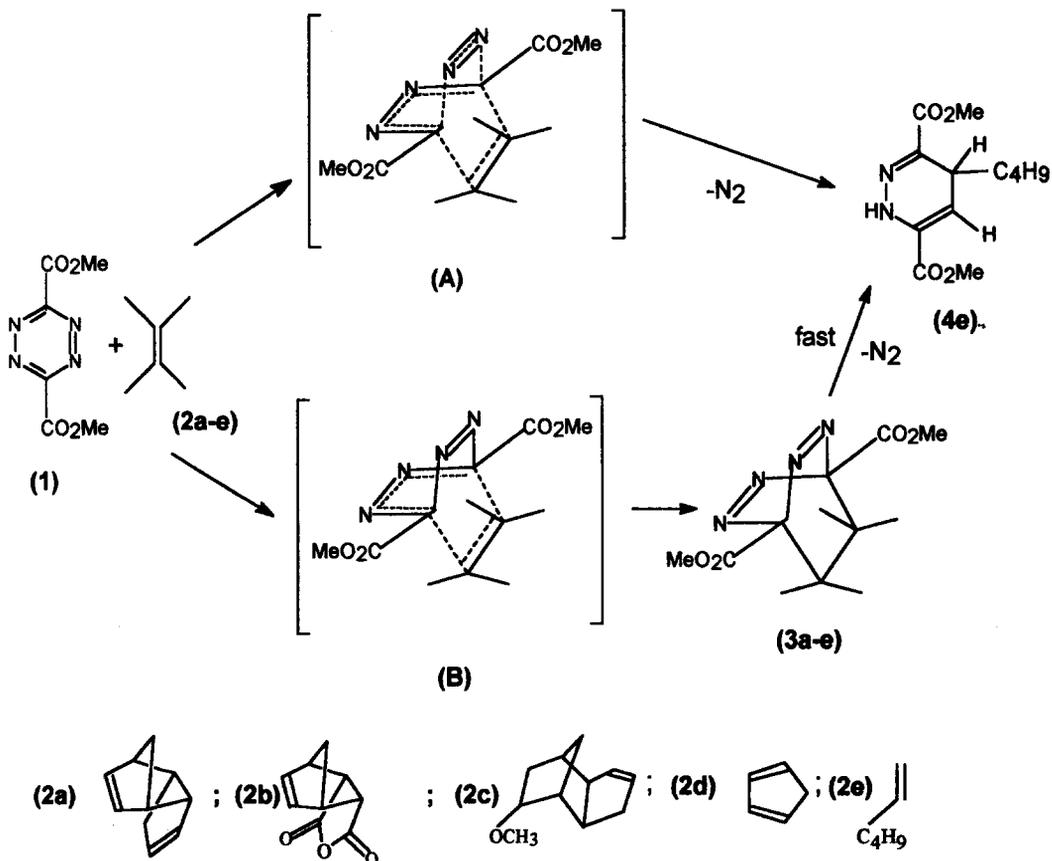
INTRODUCTION

For the common Diels-Alder reaction there are many known examples confirming the "Alder rule".¹ Dewar² predicted the possibility of realization of the inverse electronic demands that was confirmed from the rate measurements of the Diels-Alder reaction with dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate.^{3,4} This diene exhibits enhanced activity in reactions with nonactivated alkenes and especially with cycloalkenes. As was shown⁵, the reaction rate can be predicted more precisely taking into account orbital interactions, the energy balance of breaking and making bonds and the distance between the C₁ and C₄ reacting atoms of 1,3-diene. The more exothermic are reactions, the greater is the stabilization of the activation barrier and in the reaction rate enhancement.⁵⁻⁷ This fact can be clearly seen from the comparison of cyclopentadiene and 9,10-dimethylantracene activity in the Diels-Alder reaction with cyanoethylenes.⁸ For the reaction in dioxane of tetracyanoethylene (electron affinity, EA=2.88 eV, $\Delta H_{r-n} = -88 \text{ kJ mol}^{-1}$) 9,10-dimethylantracene (IP=7.04 eV) is 30 times more active than cyclopentadiene (IP=8.57 eV, $\Delta H = -113 \text{ kJ mol}^{-1}$), but for the reaction with a weak acceptor like acrylonitrile (EA =0.02 eV) it is cyclopentadiene that is 12 times more active.

Although there are extensive investigations of the high pressure effect on the Diels-Alder reaction rate available⁹ there are no data about the activation volume of reaction with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. The additional interest in the study of this reaction is caused by the fact that the adducts with the alkenes are stable to decomposition, so this type of bis-diene can be a prospective cross-linking agent. In all cases the adducts of alkenes with tetrazine are dihydropyridazine derivatives.

RESULTS AND DISCUSSION

The question about the step in the course of the reaction in which two nitrogen atoms are lost was still open: either the formation of the two new C-C bonds of the diene with alkene and the cleavage of the two C-N bonds in the transition state take place at the same time (A), or this cleavage takes place as the second step (B, scheme 1).



Scheme 1

The rate constants of the Diels-Alder reaction of diene (1) with different alkenes are collected in Table 1. The reaction rate constant of diene (1) with the more strained $\Delta^{8,9}$ double bond of dicyclopentadiene (2a) is about 220 times greater than with a $\Delta^{3,4}$ double bond such as in (2c). Comparing the reactivity of diene (1) in the reaction with cycloalkenes, with their ionization potentials, it is easy to come to the wrong conclusion about electronic demands in these reactions, because here the change of the reaction rate is controlled by the change in the energy balance of the bonds. The large value of the heat of reactions with the diene (1) exceeds by about twice that with the usual dienes,⁵ most probably due to nitrogen ejection from intermediate (3). It is of particular interest to note that in reaction with 3-methylcyclopropene the diene access is impeded only from one side and its activity is higher than that of the cyclopropene.

Table 1. Ionization potentials (IP) of the dienophiles, rate constants (k_2), enthalpies of hydrogenation (ΔH_{hydr}) and reaction (ΔH_{m}) with diene (1) in dioxane at 298 K.

Dienophile	IP, eV	k_2 , l mol ⁻¹ s ⁻¹	$-\Delta H_{\text{hydr}}$, kJ mol ⁻¹	$-\Delta H_{\text{m}}$, kJ mol ⁻¹
(2a)	8.76 ^a	3.87	139 ($\Delta^{8,9}$) ^b 108 ($\Delta^{3,4}$) ^b	293 -
(2b)	9.85 ^c	0.0064	-	-
(2c)	8.86 ^a	0.0174	-	264
(2d)	8.57 ^c	1.38	99 ^d	252
(2e)	9.46 ^c	0.044	125 ^d	284
Cyclohexene	8.94 ^c	0.087 ^e	117 ^d	-
Cyclopentene	9.01 ^c	0.235 ^e	112 ^d	-
Cyclobutene	9.43 ^c	3.29 ^e	128 ^f	-
Cyclopropene	9.86 ^g	448 ^e	224 ^f	-
3-Methyl cyclopropene	9.6 ^h	549 ^e	-	-
3,3-Dimethylcyclopropene	9.42 ⁱ	0.087 ^e	-	-
Ethylene	10.5 ^c	0.360 ^e	136 ^d	-

^a From Ref. 10. ^b From Ref. 11. ^c From Ref. 12. ^d From Ref. 13. ^e 293 K, Ref. 4. ^f From Ref. 14.

^g Ref. 15. ^h Estimated value, Ref. 16. ⁱ From Ref. 17.

For 3,3-dimethylcyclopropene, both sides are hindered for diene access and the reaction rate sharply decreases⁴ in spite of its enhanced donor property (Table 1). A similar steric hindrance was found for the reactions of penta- and hexamethylcyclopentadiene.¹⁸ 1-Hexene was selected as dienophile due to the convenience of the kinetic measurements at high pressure and because of the absence of the steric hindrance. Reaction of diene (1) with 1-hexene (2e, Scheme 1) leads to the adduct (4e), the structure of which was proposed from ¹H NMR data.¹⁹ X-ray analysis is known¹⁰ for the adduct (4a) and confirmed the dihydropyridazine structure and the presence of N-H bond as the result of fast prototropic rearrangement. As the solvent effect on the reaction rate shows (Table 2), the diene activity increases remarkably in the solvents (dichloromethane, chloroform) that are able to form an H-bond with the diene (1). This kind of solvent effect is further confirmation that diene (1) in this reaction behaves as a diene-acceptor. It was also established that diene (1) does not react with maleic anhydride and maleimides for several days. The values of enthalpy and entropy of activation (Table 2) are usual for the Diels-Alder reaction⁵ and from this standpoint they do not contradict pathway (B).

Table 2. Rate constants and activation parameters of the Diels-Alder reaction of diene (1) with 1-hexene in some solvents at 298 K.

Solvent	$k_2, \text{l mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger, \text{kJ mol}^{-1}$	$-\Delta S^\ddagger, \text{J mol}^{-1} \text{K}^{-1}$
Dioxane	0.0440	36	151
Diethyl ether	0.0530	-	-
Acetone	0.0690	31	165
Acetonitrile	0.115	34	149
Benzene	0.142	26	174
Dichloromethane	0.353	19	189
Chloroform	0.719	17	189

The more certain conclusion can be obtained from an analysis of the volume profile of the reaction (Fig.1). Since the salt effect of the lithium perchlorate in diethyl ether on the Diels-Alder reaction rate with the diene (1) and with substituted anthracene is very small, both of these

reactions should be considered as nonpolar.²⁰ For such processes the solvent electrostriction in transition state is expected to be negligible.

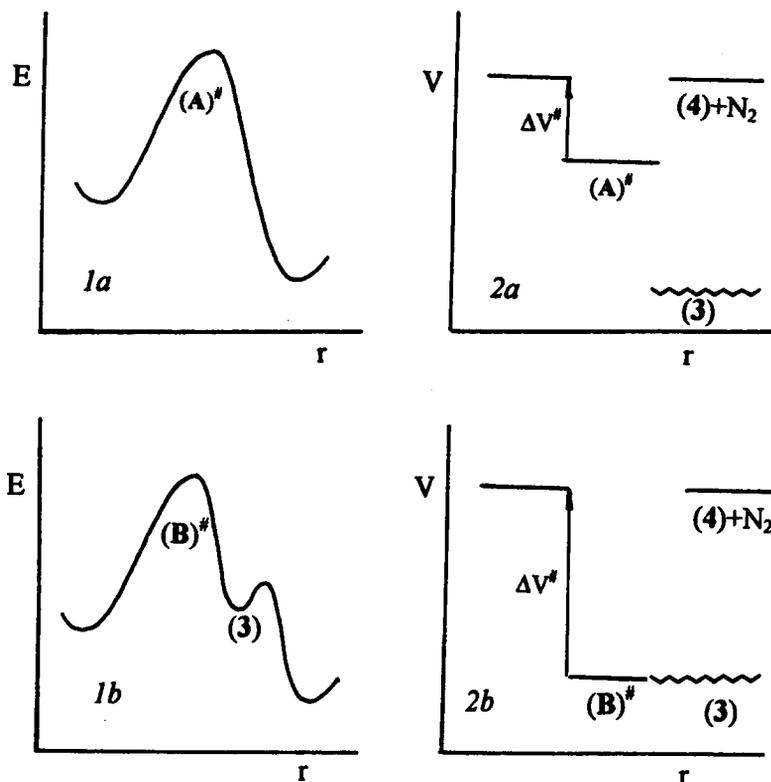


Fig. 1. Energy and volume profile for the reaction with activated complex (A), (1a, 2a) and (B), (1b, 2b).

In pathway (A) the concerted partial formation of two C-C bonds between diene (1) and 1-hexene is accompanied by the simultaneous extension of the two C-N bonds in tetrazine fragment. In pathway (B) the partial formation of the two C-C bonds between diene (1) and 1-hexene comes ahead of the subsequent elimination of nitrogen molecule, which takes place in the second step, not determining the reaction rate. It is difficult to predict definitely the energy difference for the path (A, 1a) and (B, 1b, Fig. 1). On the other hand, the activation volume for the path (A, 2a) should be sufficiently different from the activation volume for the path (B, 2b). In the case (A) activation volume reflects the compensation from contributions of the formation of two C-C bonds and the rupture of two C-N bonds. In the case (B) the value of the

activation volume should be almost the same as in nonpolar Diels-Alder reactions. From Neuman's work^{21,22} it is known that the thermal deazotization of some *cis*-azoalkanes has an activation volume from +13 to +22 cm³ mol⁻¹ depending on the reagent structure and the solvent. Thermal decomposition of cyclic azo compound, *cis*-3,6-diphenyl-3,4,5,6-tetrahydropyridazine with the loss of nitrogen was complicated by facile rearrangement to the cyclic hydrazone. The activation volume of the nitrogen loss was estimated²³ for this reaction as +5.5 cm³ mol⁻¹. This value is even less than that in the case of *cis-trans* isomerization of diazenes (from +6 to +10 cm³ mol⁻¹) by a nonradical inversion mechanism²¹.

The activation volume for the nonpolar Diels-Alder reaction of 9-chloranthracene with tetracyanoethylene in 1,2-dichloroethane is²⁴ -28.5 cm³ mol⁻¹ and for the reaction of 9-methanolanthracene with *N*-phenylmaleimide in *n*-heptane is²⁵ -28.6 cm³ mol⁻¹. From this point of view, activation volume on pathway (A) should be in the range from -6 to -20 cm³ mol⁻¹. For pathway (B) the usual value of the activation volume (-25 -30 cm³ mol⁻¹) is expected. The results of the 3 sets of measurements of pressure effect on the rate constant of this reaction are presented in Table 3.

Table 3. Pressure effect on the Diels-Alder reaction rate constants of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with 1-hexene in acetone solution at 298 K.

Set 1		Set 2		Set 3	
<i>P</i> , kg/cm ²	ln <i>k_p</i> /0.0687 ^a	<i>P</i> , kg/cm ²	ln <i>k_p</i> /0.0681 ^a	<i>P</i> , kg/cm ²	ln <i>k_p</i> /0.0693 ^a
0	0	0	0	0	0
490	0.515	330	0.379	240	0.266
730	0.814	555	0.566	650	0.689
770	0.821	750	0.816	835	0.897
820	0.860	1000	1.057	870	0.886

^a In the columns ln*k_p*/*k₀* showed the experimental values of *k₀*, l mol⁻¹ s⁻¹

All sets of data follow the correlation: ln*k_p*/*k₀* = (5.491±9.875)10⁻³ + (1.0564±0.0046)10⁻³ *P* (R = 0.9985, N = 15). The value of the activation volume equals -26.7±0.5 cm³ mol⁻¹. This magnitude

is in accordance with the usual data of activation volumes of nonpolar Diels-Alder reactions, and is in a better agreement with the realization of mechanism (B) for the studied reaction.

Partial molar volumes were determined using the data of densimeter «DMA-602». The apparent molar volume in acetone solution of diene (1) (127.2 ± 0.3), 1-hexene (127.6 ± 0.2) and adduct (4e) ($206.9 \pm 0.9 \text{ cm}^3 \text{ mol}^{-1}$) turned out to be independent of concentration below 0.05 mol l^{-1} . Evidence of the rapid nitrogen loss from intermediate product (3e) at room temperature was obtained from the smooth change of ^1H NMR signals of methyl protons of only diene (1) and adduct (4e) during the reaction with the large excess of 1-hexene in the NMR tube, and also from the smooth and unusually high exothermicity of the reaction in calorimetric measurements (Table 1). The rate constant calculated from the evolved heat in the course of calorimetric measurements is nearly the same as that from spectrophotometric investigations. A near quantitative yield of nitrogen bubble was accumulated over solution when an equimolar mixture of reagents (1) and (2e) in acetone ($10^{-2} \text{ mol l}^{-1}$, 298 K) was placed in the sealed side of U-tube. These data enable us to propose that intermediate (3e) is very unstable at 298 K and one mole of nitrogen evolves from this intermediate (3e) and from the acetone solution. It is known²³ that *cis*-3,6-diphenyl-3,4,5,6-tetrahydropyridazine at 338 K releases nitrogen from solution, but dihydropyridazine (4e) is stable at this temperature.

There are data²⁶ concerning the volumes of the very fast photochemical decomposition of 2,3-diazabicyclo[2,2,1]hept-2-ene to bicyclo[2,1,0]pentane and nitrogen molecule both in acetonitrile solution at room temperature, determined by two methods (51 ± 8 and $48.5 \pm 5 \text{ cm}^3 \text{ mol}^{-1}$). The molar volume of crystalline 2,3-diazabicyclo[2,2,1]hept-2-ene was unknown and for the liquid state is estimated as $93 \text{ cm}^3 \text{ mol}^{-1}$, using the molar volume of bicyclo[2,2,1]hept-2-ene (109.6) and the difference in the molar volumes of benzene and pyridazine ($16.8 \text{ cm}^3 \text{ mol}^{-1}$). The molar volume of liquid bicyclo[2,1,0]pentane at 298.1 K is $86.2 \text{ cm}^3 \text{ mol}^{-1}$. From these data the molar volume of nitrogen in acetonitrile can be estimated as $57 \pm 8 \text{ cm}^3 \text{ mol}^{-1}$. Assuming the value of molar volume of nitrogen in acetone is the same as in acetonitrile, the reaction volume (Scheme 1) in dilute acetone solution ($\leq 10^{-3} \text{ mol l}^{-1}$), where all reagents and products are in solution, can be estimated as $+9 \pm 8 \text{ cm}^3 \text{ mol}^{-1}$.

EXPERIMENTAL

Materials and methods. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) was prepared by the known method²⁷, m. p. 446–448 K, (lit.,²⁷ 446–448). 1-Hexene was twice distilled with sodium. *endo*-Tricyclo[5,2,1,0^{2,6}]deca-3,8-diene (**2a**) was distilled in vacuum, dried and redistilled. 8-Methoxy-*exo*-tricyclo [5,2,1,0^{2,6}]deca-3-ene (**2c**) was prepared according to known methods.²⁸ Cyclopentadiene, after cracking of dicyclopentadiene (**2a**) at 420–430K, was dried with calcium chloride and redistilled before use. Adduct (**4e**) was prepared from an equimolar mixture of reagents (10^{-2} mol l⁻¹) in boiling (2 h.) acetone and the solvent was then removed in vacuo. The resultant yellow oil was crystallized from ether solution by slow evaporation; m.p. = 328–329.5 K (lit.,¹⁹ 328.1–329). All the solvents were purified by known procedures.²⁹

¹H NMR spectra of diene (**1**) and adduct (**4e**) in CDCl₃ were registered using a "Varian - 100" spectrometer and were the same as reported.^{19,27} No additional signals which could be assigned to intermediate adduct (**3e**) were found during the reaction.

The enthalpies of the reactions in solution were measured at 298 K in a differential calorimeter (the volume of each vessel is 180 cm³), as previously reported.³⁰ Calibration of the calorimeter by the heat of solution of KCl in water at 298.1 K gave 17.4 ± 0.2 kJ mol⁻¹ (precise data,³¹ 17.57 ± 0.05 kJ mol⁻¹).

Reaction rates were measured, following the changes in diene (**1**) optical density (19230 cm⁻¹, $\epsilon=540$) with a "Specord UV-VIS" spectrophotometer. The diene concentration in the studied reactions was less than that of the dienophile by 10–100 times. All dienophiles and their adducts are optically transparent at this wavelength. The procedure for rate measurement under high pressure has been recently described.²⁴ The values of rate constants were calculated assuming the concentrations of 1-hexene to be pressure independent.

The calculations of partial molar volumes were performed from solvent and solution density data using the densimeter "DMA 602". The temperature was maintained within (1–2) 10⁻³ K, using a three-level thermostat.²⁴

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (grant no. 98-03-33053). We are deeply grateful to Professors N. S. Isaacs (University of Reading) and W. J. le Noble (State University of N. Y.) for the interest expressed in the work.

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