MECHANISM OF THE HETERODIENE SYNTHESIS

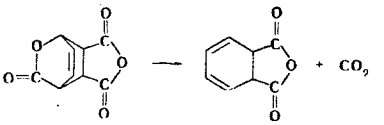
N. Sh. Padyukova and V. L. Florent'ev

UDC 547.787:543.422.25:541.127

The kinetics of the reaction of diethyl azodicarbonate with various oxazoles were studied, and a model of the activated complex with partial separation of the charges of opposite sign is proposed. The results of the calculations, which were made via the Hückel MO method, are in good agreement with the two-step mechanism of the heterodiene synthesis.

Two mechanisms have been proposed for the Diels–Alder reaction: a one-step mechanism and a two-step mechanism with the intermediate formation of diradical or zwitterion structures. The currently generally accepted one-step mechanism satisfactorily explains a number of peculiarities of the occurrence of the diene synthesis such as the predominant formation of endo adducts and retention of the stereochemical state of the dienophile.

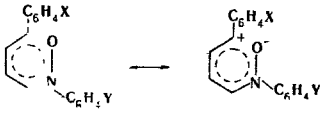
However, the two-step mechanism cannot be completely rejected as a special case of the Diels–Alder reaction for the following reasons. First of all, on the basis of a study of ^{13}C and ^{18}O isotope effects, it has been persuasively demonstrated [1] that the disintegration of adduct I proceeds in two steps.



I

Second, catalyzed Diels–Alder reactions proceed in two steps with the formation (probably) of a dipolar intermediate. Proof in favor of a two-step mechanism for the catalyzed diene synthesis is the preparative isolation of a dicyclopentyl derivative in the dimerization of cyclopentadiene [2] and the isolation of two isomeric products of the reaction of phenylcyclohexenone with butadiene [3].

In our opinion, the concept of a two-step mechanism for the diene synthesis is particularly productive in the examination of reactions in which one of the reacting molecules is strongly polarized due to inclusion of a heteroatom, i.e., heterodiene synthesis reactions. In this respect, papers [4, 5] in which the kinetics of the reaction of substituted 1-phenylbutadienes and methyl 4-phenylbutadiene-1-carboxylate with substituted p-nitrosobenzenes are studied are of interest. Using the Hammett correlation, Kresze and coworkers [4, 5] concluded that the mechanism of the reaction depends substantially on the nature of the substituents. Thus, in the case of 1-phenylbutadienes the reaction probably proceeds via a two-step mechanism through a polar transition state with a high contribution of dipolar structure II:



II

Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 600-607, May, 1973. Original article submitted May 22, 1972.

TABLE 1. Kinetics of the Reaction of 5-Ethoxyoxazoles with Diethyl Azodicarbonate

Kinetic parameters	5-Ethoxy-oxazole	4-Methyl-5-ethoxy-oxazole	2-Methyl-5-ethoxy-oxazole	2,4-Dimethyl-5-ethoxy-oxazole	2-Methyl-4-carbethoxy-5-ethoxy-oxazole
k, $mole^{-1} \cdot sec^{-1}$ in methanol at 20°	0,0046±0,0002	0,063±0,002	0,0015±0,0001	0,022±0,0015	$<10^{-8}$
k_{rel}	1	13,7	0,33	4,7	
E_a^* (Arrhenius), kcal/mole	6,42±0,8	4,94±0,7	6,51±0,9	4,57±0,5	
log A†	0,1±0,6	0,74±0,5	-0,25±0,6	0,13±0,5	
k, $mole^{-1} \cdot sec^{-1}$, in methnol at 20°	0,015±0,001	1,52±0,5	0,013±0,001	0,25±0,015	
k, $mole^{-1} \cdot sec^{-1}$, in ethanol at 20°		0,16±0,01			
k, $mole^{-1} \cdot sec^{-1}$, in heptane at 20°		0,56±0,06			

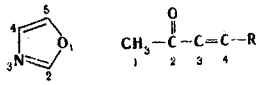
* For reaction in dibutyl ether. These values were determined at 20 to 60°.

† The dimensions of A are reciprocal moles per second.

TABLE 2. Calculated π-Bonding Energies of the Ground State of Oxazoles and Their Corresponding Localized Cations and Localization Energies

Oxazole	MO energies in increasing order, E^{π}, β units								Ground-state energy, E^{π}, β units	Localization energy, E^{π}, β units
	1	2	3	4	5	6	7	8		
5-Ethoxy-oxazole	3,082	2,181	1,500	0,724	−0,907	−1,379	—	—	7,487	
5-Cation	2,577	1,499	−0,084	−1,192					4,076	3,411
2-Cation	2,822	1,999	1,410	0,034	−1,317				6,231	1,256
2-Cation (ω method)	3,172	2,209	1,564	0,328	−1,053				7,273	0,214
4-Methyl-5-ethoxyoxazole, induction model	3,062	2,182	1,398	0,606	−0,915	−1,632			7,202	
2-Cation, induction model	2,801	1,999	1,238	−0,005	−1,585				6,038	1,164
4-Methyl-5-ethoxyoxazole, heteroatom model	3,094	2,251	2,179	1,340	0,594	−0,914	−1,544		9,458	
2-Cation, heteroatom model	2,844	2,243	1,998	1,159	−0,001	−1,492			8,244	1,214
2-Methyl-5-ethoxyoxazole, heteroatom model	3,109	2,318	1,999	1,468	0,585	−1,060	−1,420		9,479	
2-Cation, heteroatom model	—	—	—	—	—	—	—	—	6,231	3,248
2,4-Dimethyl-5-ethoxy-oxazole, induction model	3,016	2,152	1,366	0,492	−1,160	−1,665			7,026	
2-Cation, induction model	—	—	—	—	—	—	—	—	6,038	0,988
2,4-Dimethyl-5-ethoxy-oxazole, heteroatom model	3,120	2,330	2,236	2,002	1,279	0,483	−1,083	−1,567	11,450	
2-Cation, heteroatom model									8,244	3,206

TABLE 3. Density of the Boundary Electrons on the Reacting Atoms of Oxazole and the Dienophile



R = Alk, R = $COOC_2H_5$; R = COO^-

Compound	q^{π} on the atoms			
	induction model		heteroatom model	
	2	5	2	5
5-Ethoxyoxazole	0,620	0,564	—	—
4-Methyl-5-ethoxyoxazole	0,646	0,104	0,718	0,462
2-Methyl-5-ethoxyoxazole	—	—	0,646	0,430
2,4-Dimethyl-5-ethoxyoxazole	0,836	0,412	0,758	0,368
	3	4	3	4
α,β-Unsaturated ketones	—	—	0,374	0,658
Ethyl β-acetylacrylate (R = $COOC_2H_5$)	—	—	0,586	0,804
Anion of β-acetylacrylic acid (R = COO^-)	—	—	0,568	0,052

We have previously postulated a two-step mechanism for the reaction of 5-alkoxyoxazoles with dienophiles [6]. For additional kinetic investigations of this reaction, we chose the reaction of methyl-substituted 5-ethoxyoxazoles with diethyl azodicarbonate, since, first of all, the reaction proceeds quantitatively and gives an adduct that does not undergo further changes under the investigated conditions (the structure of the adduct was proved by the PMR spectrum – see Fig. 1), second, the presence of a long-wave absorption maximum in the spectrum of the azodicarbonate ester makes it possible to investigate the kinetics of this reaction by spectrophotometry.

The data obtained were introduced into a Nairi computer. The calculation was made from the integral formulas by the method of least squares. The rate constants and activation parameters (Table 1) were obtained directly at the output of the computer.

First of all, one should note the low activation energies and low preexponential factors, which, as it were, occupy the middle position between the activation parameters of the diene synthesis, for which a one-step mechanism is assumed (typical E_a values of 12-17 kcal/mole, log A 5.5-6.5 [7]), and the activation parameters of the catalyzed Diels–Alder reaction (E_a 0-5 kcal/mole, log A from −2 to 2 [8]), which proceeds via a two-step mechanism. The relatively low activation energy and the unusually low preexponential factor (i.e., the high negative activation entropies) make it possible to assert that the formation of an activated complex in the investigated reaction consists in separation of charges of opposite sign. In this case, the reaction should be accelerated as the dielectric constant of the solvent increases. In fact, as seen from Table 1, the rate constant for heterodiene synthesis increases by a factor of 10-20 on passing from dibutyl ether to methanol. However, no distinct correlation between the rate constant and the dielectric constant is observed. This is probably associated with the following peculiarity of the two-step mechanism.

The observed rate constant of the reaction $a + b \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} x \xrightarrow{k_2} c$ is

$$k_{obs} = \frac{k_1 k_2}{k_1 + k_{-1}}.$$

It is natural that on passing to a more polar solvent, k_1 will increase, while k_{-1} and k_2 will decrease. Therefore k_{obs} may depend in a rather complex manner on the polarity of the solvent.

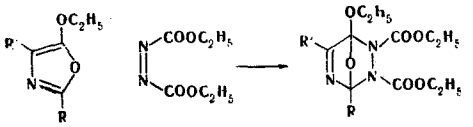
An additional proof in favor of a transition state with partial separation of charges of opposite sign is the qualitatively observed (by us) acceleration of the reaction of 2-methyl-5-ethoxyoxazole with 3-cyclopentenone at 10,000 atm, since it is precisely these activated complexes that are characterized by a negative activation volume [9].

It is apparent from the data presented in Table 1 that the introduction of an electron-donor substituent into the 4 position of oxazole accelerates the reaction, while the introduction of an electron-acceptor sub-

TABLE 4. Molecular Extinction of Diethyl Azodicarbonate in Various Solvents

Solvent	λ_{max}, nm	ε
Dibutyl ether	403	38,9
Methanol	403	22,1
Ethanol	403	38,9

TABLE 5. Conditions Used for the Study of the Condensation of Diethyl Azodicarbonate with Oxazoles



R	R′	Solvent	Temp., °C	Molar concn. of the oxazole, $c \cdot 10^2$	Molar concn. of diethyl azodicarboxylate
1	2	3	4	5	6
H	H	Dibutyl ether	20	11,46	2,26
				114,6	4,52
			30	11,46	2,26
				114,6	4,52
			45	11,46	2,26
				114,6	4,52
			60	11,46	2,26
				114,6	4,52
		Methanol	20	11,46	2,26
				114,6	4,52
CH_3	H	Dibutyl ether	20	11,47	2,8
				24,9	2,26
				101,2	4,78
			30	11,47	2,26
				22,7	2,26
				101,2	4,57
			45	11,47	2,28
				22,8	2,26
				101,2	4,51
			60	11,47	2,18
				21,8	2,26
				101,2	4,38
		Methanol	20	11,47	2,12
				113,6	4,78
H	CH_3	Diisopropyl ether	20	11,46	2,26
				5,75	1,13
				1,15	1,13
				11,46	4,52
				23	2,26
				2,3	2,26
				1,15	2,26
		Dibutyl ether	30	1,15	2,26
			45	1,15	2,26
			60	1,15	2,26
		Methanol	20	11,46	2,26
				1,15	2,26
				11,46	4,52
		Ethanol	20	11,46	2,19
			30	11,46	2,12
			45	11,46	2,03
		Heptane	20	11,46	2,26
			30	11,46	2,26
			45	11,46	2,26
			60	11,46	2,26
CH_3	CH_3	Dibutyl ether	20	10,31	2,44
			30	10,31	2,26
			45	10,31	2,18
			60	10,31	2,62
		Methanol	20	10,31	2,38

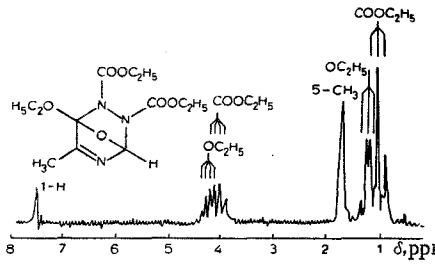
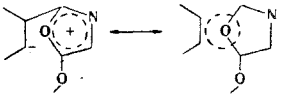


Fig. 1. PMR spectrum of the adduct of 4-methyl-5-ethoxyoxazole and diethyl azodicarbonate.

stituent into the 4 position inhibits the reaction. Thus 2-methyl-4-carbethoxy-5-ethoxyoxazole reacts with the azodicarbonate ester more slowly (by a factor of at least 100,000) than in the case of 2-methyl-5-ethoxyoxazole. On this basis, it can be concluded that the positive charge is localized on the oxazole portion of the molecule in the transition state.

Thus the data obtained are in good agreement with the model of an activated complex with partial separation of charges of opposite sign; from the point of view of the heterodiene, this model can be called "electrophilic."

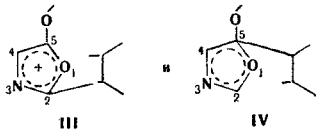


An examination of this model in MO terms makes it possible to deepen the understanding of the mechanism of the heterodiene synthesis. Relying on the "electrophilic" reaction mechanism, we selected the localization energy[10] andthe boundary electron density [11] as the reactivity indexes. The calculations were made by the Hückel MO (HMO) method with a BÉSM-4 computer and the following parameters: $h_{\dot{N}} = 0.5$, $h_{\ddot{O}} = 2$, $h_{\ddot{O}} = 1$, CH_3 (induction model) $h_C = -0.5$, CH_3 (heteroatom model) $h_X = 2$, VIP = $0.1h_X$, $k_{C=C} = 1$, $k_{C=N} = 1$, $k_{C-O} = 0.8$, $k_{C=O} = 1$, $k_{C-CH_3} = 0.7$.

The results of the calculations are presented in Table 2. As one should have expected, the introduction of a CH_3 group into both the 2 and 4 positions of oxazole lowers the energy of the ground state.

Since localization of the positive charge in the "oxazole" portion of the molecule increases in the transition state, the stabilizing effect of methyl groups should be exerted still more sharply. In fact, the introduction of a CH_3 group into the 4 position of the oxazole molecule accelerates the reaction by a factor of ~ 14, but 2-methyloxazoles react slower by a factor of three than the corresponding 2-unsubstituted compounds.

However, this apparent contradiction is readily explained within the framework of the two-step mechanism of the heterodiene synthesis. Since only one bond is initially formed, the intermediate zwitterion compound (and it serves precisely as a model of the transition state in calculations of the localization energy) may have two isomeric structures (III and IV):



III IV

The alkoxy group in III is conjugated with the localized cation and participates in resonance stabilization, while that in IV is excluded from conjugation, and this leads to an increase of 2.155 β in the energy of this structure. Within the framework of the two-step mechanism, this means that initially, in the step that limits the rate, a bond is formed with the 2 position of the diene molecule. If this is so, the 2-CH_3 group, which stabilizes the ground state, is partially cut off from the conjugated system of the cation in the transition state, and this leads to an increase in the activation energy and slowing down of the reaction.

Thus the localization energies are in qualitative agreement with the experimental data and do not contradict the two-step mechanism of the heterodiene synthesis. However, the absence of a linear correlation between the localization energies and the relative rate constants and the very low β values indicate substantial deficiencies of this reactivity index as applied to the investigated reaction. This is partially due to the intrinsic inadequacies of the HMO method in calculations of charged systems and partially due to the crude model of the transition state, which assumes complete localization of the two electrons. A test calculation of the localization energy by the more correct ω method ($\omega = 1.4$) is presented in Table 2.

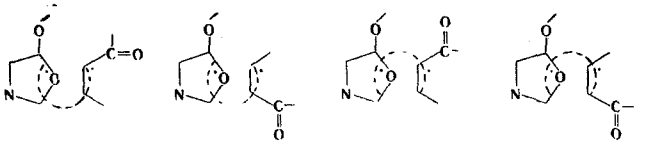
In addition, the method of localization energies does not take into account the dienophile and thus does not make it possible to examine the problem of orientation in the heterodiene synthesis.

In this connection, we turned to the method of boundary electrons, which is based on a transition state model that is close to that of the starting compounds. The π-electron densities of the upper occupied MO

(for dienes) and lower antibonding MO (for the dienophiles), which were calculated by the HMO method, are presented in Table 3. In all cases, q_2^{π} for the oxazoles exceeds q_5^{π}, i.e., a bond is first formed with the 2 position of the oxazole molecule. In conformity with the calculated values, one should expect that the reaction of 5-alkoxyoxazoles with ethyl β-acetylacrylate, just as with α,β-unsaturated ketones, will lead to a product in which the acetyl group will be in the 4 position, while reaction with β-acetylacrylic acid should lead to the 5-acetyl derivative. This prediction is in complete agreement with the experimental data.

It should be noted that the calculated data, which were obtained using the induction model of the methyl group, are in substantially poorer agreement with the experimental values obtained on the basis of the heteroatom model. This again confirms the inapplicability of the induction model to calculations of carbonium ions.

For comparison, we calculated the energies of the diradical transition states. We selected a model with elongation of the conjugated system in which the newly formed bond was assigned a β value of 0.7. Although the order of change of the energies coincides with the values calculated for the "electrophilic" model, the quantitative differences, however, are so small that this coincidence is accidental and cannot serve as a reliable basis for correlations with the experimental data.



$\mathcal{L}$, β units	1.133	1.150	1.161	1.137
$\Delta\mathcal{L}$, β units	0	0.017	0.027	0.004

Thus the results obtained are in good agreement with the two-step mechanism for the heterodiene synthesis. In addition, the theoretical approach that we proposed makes it possible to evaluate both the relative reactivities of oxazoles in the diene synthesis and the orientation of the unsymmetrical dienophiles.

EXPERIMENTAL

The PMR spectra were recorded with a JEOL JNM-H-100 spectrometer. The kinetics of the reaction of diethyl azodicarbonate with the oxazoles were recorded with an EPS-3T double-beam spectrophotometer.

The reaction of diethyl azodicarbonate with the various oxazoles was investigated in a number of solvents at various temperatures. In the kinetic experiments, the change in the diethyl azodicarbonate concentration was recorded spectrophotometrically with allowance for the change in its molecular extinction on passing from one solvent to another (Table 4).

The oxazoles and the conditions under which the reaction was studied are presented in Table 5.

The authors thank A. S. Ol'khovyi and V. G. Tumanyan for their assistance in performing the calculations.

LITERATURE CITED

1. M. J. Goldstein and G. L. Thayer, J. Am. Chem. Soc., 87, 1933 (1965).
2. C. F. Blakeley, R. J. Gillespie, L. Roubinek, A. Wassermann, and R. F. M. White, J. Chem. Soc., 1939 (1961).
3. H. W. Thompson and D. G. Mellillo, J. Am. Chem. Soc., 92, 3218 (1970).
4. G. Kresze and W. Kosbahn, Tetrahedron, 27, 1931 (1971).
5. G. Kresze, H. Saitner, J. Firl, and W. Kosbahn, Tetrahedron, 27, 1941 (1971).
6. I. A. Drobinskaya, L. V. Ionova, M. Ya. Karpeiskii, and V. L. Florent'ev, Khim. Geterotsikl. Soedin., 37 (1970).
7. A. Wasserman, J. Chem. Soc., 1028 (1936).
8. W. Rubin, H. Stiner, and A. Wassermann, J. Chem. Soc., 3046 (1949).
9. J. Buchanan and S. Hamann, Trans. Faraday Soc., 49, 1425 (1953).
10. G. W. Wheland, J. Am. Chem. Soc., 64, 900 (1942).
11. G. W. Wheland and L. Pauling, J. Am. Chem. Soc., 57, 2086 (1935).