

## Internal and external factors promoting the Diels—Alder reaction\*

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The basic chemical and physical factors determining the rate and equilibrium of the Diels—Alder reaction under standard and high hydrostatic pressures were considered. The search for favorable conditions for this process makes it possible to extend the range of potential reactants and to perform reactions that earlier considered to be forbidden.

**Key words:** Diels—Alder reaction, catalysis, high pressure, volume of activation, reaction volume.

It is 85 years since the Diels—Alder reaction (DAR),<sup>1–11</sup> the most popular case of [4+2] cycloaddition, was discovered. B. Arbuzov, A. Wassermann, R. Woodward, M. Dewar, A. Petrov, J. Roberts, V. Tartakovskii, K. Fukui, H. Fujimoto, R. Hoffmann, R. Huisgen, and many other scientists considerably contributed to the development of the theory and practice of the DARs. Deep and detailed works of recent decades by J. Sauer,<sup>12–15</sup> F.-G. Klärner,<sup>16,17</sup> K. Houk,<sup>18,19</sup> R. Sustmann,<sup>20,21</sup> and G. Jenner<sup>22</sup> extended our knowledge about this process.

The first studies were aimed at determining the structural types of substrates to synthesize the possibly large range of new products,<sup>1–4</sup> including polymer adducts formed in the reactions of bis(dienes) and bis(dienophiles).<sup>23–29</sup> Much attention was given to establishment of regularities of the reaction. In this area, the works by K. Alder and coworkers were generally acknowledged. A considerable volume of works is associated with the quantitative studies of the reactivity of diverse systems, whose reaction rates differ by almost 20 (!) orders of magnitude.<sup>12–15,30–35</sup> The problems of the influence of the solvent, formation of intermolecular complexes, and effect of catalytic and salt additives were studied in detail; successful attempts of generalized taking into account the energy of orbital interactions of the reactants, the energy balance of bond cleavage and formation, and structural regularities of diene—dienophile pairs upon transition state formation were performed.<sup>30–35</sup> Much attention has recently been paid to the synthesis of biologically active reaction products and directed construction of target molecules on the basis of the DAR.<sup>7–11</sup> A substantial decrease in the volume upon the formation of cyclic structures provide broad possibilities for a favorable change in the reaction

rate and equilibrium under the conditions of elevated hydrostatic pressure.<sup>22,35–45</sup> Reliable quantitative data on the structure of products, their ratio, and the rate and equilibrium constants of usual and catalytic systems formed a powerful basis for understanding many features of the mechanism of the process. To date there are more than 500 000 works in the field of the DAR and, hence, their full analysis is impossible. A number of books<sup>6–11</sup> and reviews<sup>12,16,22,33–35</sup> reflects various aspects of the DAR.

In this review, the factors determining the diene—dienophile reactivity in the DAR of the most abundant type "diene as donor, dienophile as acceptor" were generalized on the basis of quantitative data mainly obtained at our laboratory on the influence of the catalysts and high hydrostatic pressure.

Merits of O. Diels and K. Alder were acknowledged by the Nobel Prize in 1950, but they are not reduced to the discovery of only coupling of various carbo- and heterodienes and dienophiles to form different cyclohexene derivatives. The main regularities of this reaction were revealed and described in subsequent studies.<sup>46–65</sup>

### Factors determining the Diels—Alder reaction rate

Orbital interactions make a significant but not a single contribution to the formation of the activation barrier in the DAR.<sup>66–72</sup>

To predict the rate of the DARs involving different classes of reactants, it was proposed<sup>31,33–35</sup> to take into account three main parameters: (1) energies of frontier orbitals of diene and dienophile; (2) balance of energies of bond cleavage and formation, and (3) change in the coefficients of orbital overlapping, which is mainly determined by the difference in the distance between the reacting atoms C(1)—C(4) in diene ( $R_{C(1)-C(4)}$ ).

\* Dedicated to the Academician of the Russian Academy of Sciences S. M. Aldoshin on the occasion of his 60th birthday.

When taking into account three factors in combination, the general correlation for the whole massive of the reactions was found<sup>31</sup> ( $r = 0.972$ ,  $n = 92$ )

$$\log k_2 = -28.81 + 316.3/(IP_D - E_A) - 69.9R_{C(1)-C(4)}/(IP_D - E_A) - 0.054\Delta H_{\text{react}}, \quad (1)$$

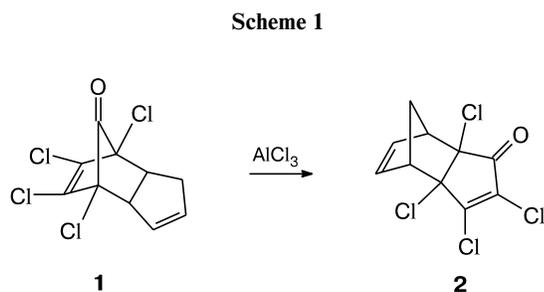
where  $k_2/\text{L mol}^{-1} \text{s}^{-1}$  is the rate constant;  $IP_D/\text{eV}$  and  $E_A/\text{eV}$  are the ionization potential of diene and the energy of electron affinity of dienophile, respectively;  $R_{C(1)-C(4)}/\text{\AA}$  is the distance between the reacting atoms C(1)—C(4) in diene;  $\Delta H_{\text{react}}/\text{kJ mol}^{-1}$  is the reaction enthalpy;  $r$  is the correlation coefficient; and  $n$  is the number of reactions.

It should be noted for a more distinct representation of the influence of these contributions (see Eq. (1)) on the Diels—Alder reaction rate ( $\log k_2$ ) that the effect of the difference in the reaction enthalpies is comparable with the contribution of changing the overlapping coefficients of the reacting orbitals of the reactants and each contribution is half the contribution of differences in the value of  $(IP_D - E_A)^{-1}$ .

The data obtained make it possible to explain reasons for the usual and "abnormal" ratio between the activity and selectivity and diversity in the ratio of the kinetic reactivity and thermodynamic stability allows one to purposefully choose substrates for obtaining necessary products, especially in competitive processes and to predict the rates of yet unstudied examples of the DAR with normal electronic requirements.

### Catalysis in the Diels—Alder reaction

It was experimentally found that the solvent noticeably affected the DAR rate only in the case of specific interactions with reactants.<sup>31,73–75</sup> As reported<sup>76</sup> in 1955, the reactions between anthracene and  $\beta$ -chlorovinyl alkyl ketones in toluene occur only in the presence of tin chloride. It was noticed a little later<sup>77</sup> that aluminum chloride sharply accelerates the rearrangement of tetrachlorodicyclopentadien-8-one **1** to isomeric ketone **2** (Scheme 1).



Since the exchange DARs proceed *via* the decomposition—formation mechanism, it is clear that the reactivity of dienophiles with  $p$ -donor centers in activating groups in

the presence of Lewis acids can sharply increase. This fact served as a powerful stimulus for a wide study of the acceleration effect in the DARs: many kinetic data on this effect and on the enthalpy of formation of the catalyzed reactions, as well as the enthalpy of formation of  $n, \nu$ -complexes, enthalpy of catalyzed reactions, and the influence of the medium on the solvation of reactants,  $n, \nu$ -complexes, and transition state were obtained during recent 40 years.<sup>24,27,31,35,78–99</sup>

The formation of stable  $n, \nu$ -complexes sharply increases the rate of the process (up to  $10^7$  times for complex **3**— $2\text{GaCl}_3$ , Table 1), which makes it possible to involve very inert (under normal conditions) reactants into the reaction. It was shown<sup>31</sup> that an increase in the rate of catalyzed DARs of the type "diene as donor, dienophile as acceptor" in comparatively inert (towards Lewis acids) media (benzene, toluene, dichloromethane, 1,2-dichloroethane) was fairly constant, being  $\sim 1, 3, 4, 5$ , and 6 orders of magnitude in the presence of  $\text{SnCl}_4$ ,  $\text{BBr}_3$ ,  $\text{GaCl}_3$ ,  $\text{AlCl}_3$ , and  $\text{AlBr}_3$ , respectively (see Table 1).

In the reactions with the reverse electronic character of reactants, *i.e.*, "diene as acceptor, dienophile as donor," the coordination of these Lewis acids with the heteroatom of diene also increases the rate (see Table 1), although the acceleration effect is appreciably lower in this case.<sup>31,88,89</sup>

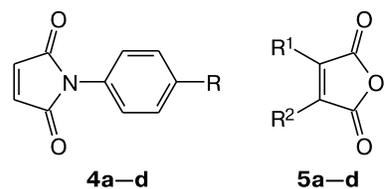
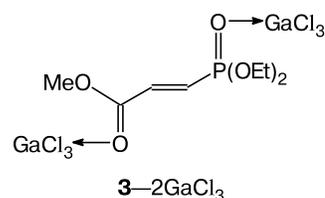
The observed effect of acceleration of the DAR involving activated dienophiles is usually explained by the enhancement of the  $\pi$ -acceptor properties of the double bond for  $n, \nu$ -complex formation.<sup>100,101</sup> It was experimentally found<sup>86,90</sup> that the energy of the charge-transfer band maximum in the  $\pi, \pi$ -complex between hexamethylbenzene ( $\pi$ -donor) that does not enter the DAR and dienophiles **4**

and **5** activated by the formation of the  $n, \nu$ -complex is considerably lower than that in the  $\pi, \pi$ -complex with usual dienophiles (Fig. 1, Table 2).

In the complexes

with the same  $\pi$ -donor, the difference in the charge-transfer energy corresponds to the difference in the energy of electron affinity of the  $\pi$ -acceptors.<sup>66,67</sup>

The data presented in Table 2 show that the differences in the charge-transfer energy in the  $\pi, \pi$ -complexes of hexamethylbenzene with usual and activated dienophiles are fairly high (0.75—1.0 eV).<sup>86</sup> In the case of activation with aluminum chloride, the differences in the transfer energy are still higher.<sup>86,90</sup>



**4:** R = H (**a**), Me (**b**), Br (**c**),  $\text{NO}_2$  (**d**);  
**5:**  $\text{R}^1 = \text{R}^2 = \text{H}$  (**a**);  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$  (**b**);  
 $\text{R}^1 = \text{Cl}$ ,  $\text{R}^2 = \text{H}$  (**c**);  $\text{R}^1 = \text{R}^2 = \text{Cl}$  (**d**)

**Table 1.** Enthalpies of formation of the molecular  $n,v$ -complexes ( $\Delta H_{MC}$ ), rate constants ( $k_2$ ), enthalpies ( $\Delta H^\ddagger$ ) and entropies ( $\Delta S^\ddagger$ ) of activation, and the observed acceleration rate ( $k_{2,cat}/k_{2,noncat}$ ) in the catalyzed Diels–Alder reactions in benzene at 25 °C<sup>31,35,79–90</sup>

Reaction	Lewis acid	$-\Delta H_{MC}$ /kJ mol <sup>-1</sup>	$k_2$ /L mol <sup>-1</sup> s <sup>-1</sup>	$\Delta H^\ddagger$ /kJ mol <sup>-1</sup>	$-\Delta S^\ddagger$ /J mol <sup>-1</sup> K <sup>-1</sup>	$k_{2,cat}/k_{2,noncat}$
9,10-Dimethylanthracene + + methyl acrylate	—	—	$7.8 \cdot 10^{-7}$	63	150	—
	AlCl <sub>3</sub>	—	0.15	31	155	$1.9 \cdot 10^5$
9,10-Dimethylanthracene + + methyl methacrylate	GaCl <sub>3</sub>	52	$3.5 \cdot 10^{-2}$	—	—	$4.5 \cdot 10^4$
	—	—	$1.3 \cdot 10^{-7}$	63	163	—
9,10-Dimethylanthracene + + dimethyl fumarate	AlCl <sub>3</sub>	—	$3.8 \cdot 10^{-2}$	35	155	$2.8 \cdot 10^5$
	—	—	$6.7 \cdot 10^{-6}$	52	167	—
Anthracene + <i>N</i> -( <i>p</i> -nitro- phenyl)maleinimide	AlCl <sub>3</sub>	—	0.43	23	171	$6.4 \cdot 10^4$
	—	—	$8.5 \cdot 10^{-5}$	57	129	—
Anthracene + <i>N</i> -( <i>p</i> -bromo- phenyl)maleinimide	AlCl <sub>3</sub>	—	8.2	33	113	$9.6 \cdot 10^4$
	GaCl <sub>3</sub>	48	1.0	—	—	$1.2 \cdot 10^4$
Anthracene + <i>N</i> -( <i>p</i> -methoxy- phenyl)maleinimide	—	—	$2.5 \cdot 10^{-5}$	60	129	—
	AlCl <sub>3</sub>	—	2.9	34	121	$1.2 \cdot 10^5$
Anthracene + <i>N</i> -( <i>p</i> -tolyl)- maleinimide	GaCl <sub>3</sub>	53	0.65	34	135	$2.6 \cdot 10^4$
	—	—	$8.1 \cdot 10^{-6}$	68	112	—
Anthracene + <i>N</i> -phenyl- maleinimide	AlCl <sub>3</sub>	—	1.2	38	113	$1.5 \cdot 10^5$
	—	—	$7.3 \cdot 10^{-6}$	68	112	—
Anthracene + <i>N</i> -( <i>p</i> -tolyl)- maleinimide	AlBr <sub>3</sub>	78	5.7	—	—	$7.9 \cdot 10^5$
	GaCl <sub>3</sub>	55	0.35	—	—	$4.9 \cdot 10^4$
9,10-Dimethylanthracene + + <i>N</i> -phenylmaleinimide	—	—	$6.8 \cdot 10^{-6}$	68	113	—
	AlCl <sub>3</sub>	—	1.2	41	105	$1.8 \cdot 10^5$
Anthracene + + maleic anhydride	GaCl <sub>3</sub>	57	0.35	—	—	$5.2 \cdot 10^4$
	—	—	$3.0 \cdot 10^{-2}$	—	—	—
Anthracene + + 1,4-naphthoquinone	SnCl <sub>4</sub>	8	$3.6 \cdot 10^{-2}$	—	—	1.2
	Et <sub>2</sub> O · BF <sub>3</sub>	5	$3.0 \cdot 10^{-2}$	—	—	1.0
Anthracene + + 1,3-diphenylisobenzofuran + + diethyl β-methoxycarbonyl- vinylphosphonate	—	—	$6.0 \cdot 10^{-6}$	65	126	—
	BCl <sub>3</sub>	—	$4.1 \cdot 10^{-2}$	—	—	$6.9 \cdot 10^3$
Anthracene + + 1,4-benzoquinone	GaCl <sub>3</sub>	41	0.40	—	—	$6.7 \cdot 10^4$
	AlCl <sub>3</sub>	—	1.6	—	—	$2.6 \cdot 10^5$
1,3-Diphenylisobenzofuran + + diphenyl β-methoxycarbonyl- vinylphosphonate	AlBr <sub>3</sub>	—	7.2	—	—	$1.2 \cdot 10^6$
	—	—	$1.8 \cdot 10^{-7}$	66	140	—
1,3-Diphenylisobenzofuran + + diethyl β-methoxycarbonyl- vinylphosphonate	GaCl <sub>3</sub>	54	2.3	34	120	$1.3 \cdot 10^7$
	2 GaCl <sub>3</sub>	—	600	—	—	$3.4 \cdot 10^8$
1,3-Diphenylisobenzofuran + + diphenyl β-methoxycarbonyl- vinylphosphonate	—	—	$2.4 \cdot 10^{-6}$	64	123	—
	GaCl <sub>3</sub>	53	1.9	—	—	$7.8 \cdot 10^5$
9,10-Dimethylanthracene + + diethyl β-methoxycarbonyl- vinylphosphonate (3)	—	—	$7.0 \cdot 10^{-4}$	—	—	—
	GaCl <sub>3</sub>	90	0.37	—	—	$5.3 \cdot 10^2$
Tetraphenylcyclopentadienone + + <i>trans</i> -stilbene	—	—	$3.7 \cdot 10^{-5}$	58	121	—
	GaCl <sub>3</sub>	76	$3.4 \cdot 10^{-2}$	42	121	$9.2 \cdot 10^2$
Tetraphenylcyclopentadienone + + norbornadiene	—	—	$8.9 \cdot 10^{-10}$	90	155	—
	2 GaCl <sub>3</sub>	148 (2 : 1, P=O, C=O)	$1.7 \cdot 10^{-2}$	40	140	$1.9 \cdot 10^7$
Tetraphenylcyclopentadienone + + <i>N</i> -phenylmaleinimide	—	—	$2.8 \cdot 10^{-8}$	70	144	—
	AlCl <sub>3</sub>	39 (C=O)	$5.6 \cdot 10^{-5}$	39	185	$2.0 \cdot 10^3$
Tetraphenylcyclopentadienone + + <i>N</i> -phenylmaleinimide	—	—	$6.0 \cdot 10^{-7}$	64	137	—
	AlCl <sub>3</sub>	39 (C=O)	$5.0 \cdot 10^{-4}$	34	181	$8.4 \cdot 10^2$
Tetraphenylcyclopentadienone + + <i>N</i> -phenylmaleinimide	—	—	$3.9 \cdot 10^{-5}$	59	120	—
	GaCl <sub>3</sub>	55 (imide)	$1.4 \cdot 10^{-4}$	—	—	3.6
Tetraphenylcyclopentadienone + + <i>N</i> -phenylmaleinimide	AlCl <sub>3</sub>	—	$1.1 \cdot 10^{-3}$	45	137	28
	2 AlCl <sub>3</sub>	—	$4.2 \cdot 10^{-5}$	—	—	1.2

(to be continued)

**Table 1** (*continued*)

Reaction	Lewis acid	$-\Delta H_{MC}$ /kJ mol <sup>-1</sup>	$k_2$ /L mol <sup>-1</sup> s <sup>-1</sup>	$\Delta H^\ddagger$ /kJ mol <sup>-1</sup>	$-\Delta S^\ddagger$ /J mol <sup>-1</sup> K <sup>-1</sup>	$k_{2,cat}/k_{2,noncat}$
Tetraphenylcyclopentadienone + + <i>N</i> -( <i>p</i> -tolyl)maleinimide	—	—	$6.3 \cdot 10^{-5}$	57	121	—
	GaCl <sub>3</sub>	57 (imide)	$1.5 \cdot 10^{-4}$	—	—	2.4
	AlCl <sub>3</sub>	—	$7.1 \cdot 10^{-4}$	—	—	11
	2 AlCl <sub>3</sub>	—	$6.5 \cdot 10^{-5}$	—	—	1.0
<i>C</i> -Phenyl- <i>N</i> -methylnitron + + <i>N</i> -phenylmaleinimide	—	—	$2.0 \cdot 10^{-4}$	—	—	—
	GaCl <sub>3</sub>	55 (imide)	50	—	—	$2.5 \cdot 10^5$
9,10-Dimethylantracene + + acrylonitrile	—	—	$2.2 \cdot 10^{-6}$	63	146	—
	GaCl <sub>3</sub>	51	0.13	36	130	$5.9 \cdot 10^4$
9-Methylantracene + + acrylonitrile	—	—	$1.1 \cdot 10^{-7}$	74	122	—
	GaCl <sub>3</sub>	51	$1.7 \cdot 10^{-2}$	42	126	$1.5 \cdot 10^5$
Anthracene + acrylonitrile	—	—	$8.6 \cdot 10^{-9}$	76	138	—
	GaCl <sub>3</sub>	51	$5.3 \cdot 10^{-4}$	47	141	$6.2 \cdot 10^4$
9-Chloroanthracene + + acrylonitrile	—	—	$1.9 \cdot 10^{-9}$	79	140	—
	GaCl <sub>3</sub>	51	$1.6 \cdot 10^{-4}$	49	145	$8.4 \cdot 10^4$
9-Methylantracene + + methyl acrylate	—	—	$5.8 \cdot 10^{-8}$	—	—	—
	GaCl <sub>3</sub>	52	$1.3 \cdot 10^{-2}$	—	—	$2.2 \cdot 10^5$
9,10-Dimethylantracene + + cyanoacetylene	—	—	$4.0 \cdot 10^{-6}$	—	—	—
	GaCl <sub>3</sub>	—	1.1	—	—	$2.8 \cdot 10^5$
9,10-Dimethylantracene + + methyl propionate	—	—	$2.0 \cdot 10^{-8}$	—	—	—
	GaCl <sub>3</sub>	—	$6.0 \cdot 10^{-3}$	—	—	$3.0 \cdot 10^5$
9,10-Dimethylantracene + + maleic anhydride	—	—	$1.2 \cdot 10^{-2}$	43	138	—
	GaCl <sub>3</sub>	41	$2.8 \cdot 10^2$	—	—	$2.3 \cdot 10^4$
	AlCl <sub>3</sub>	—	$2.0 \cdot 10^3$	—	—	$1.7 \cdot 10^5$
9-Methylantracene + + maleic anhydride	—	—	$3.4 \cdot 10^{-4}$	53	134	—
	GaCl <sub>3</sub>	41	12.8	27	140	$3.8 \cdot 10^4$
	AlCl <sub>3</sub>	—	95.2	—	—	$2.8 \cdot 10^5$
9-Chloroanthracene + + maleic anhydride	—	—	$1.4 \cdot 10^{-6}$	67	130	—
	GaCl <sub>3</sub>	41	$5.2 \cdot 10^{-2}$	36	153	$3.7 \cdot 10^4$
	AlCl <sub>3</sub>	—	0.38	—	—	$2.8 \cdot 10^5$
Anthracene + + citraconic anhydride	—	—	$1.5 \cdot 10^{-8}$	73	135	—
	GaCl <sub>3</sub>	49	$1.3 \cdot 10^{-4}$	—	—	$9.0 \cdot 10^3$
	AlCl <sub>3</sub>	—	$8.3 \cdot 10^{-3}$	32	164	$5.7 \cdot 10^5$
9-Chloroanthracene + + citraconic anhydride	—	—	$1.5 \cdot 10^{-8}$	73	135	—
	GaCl <sub>3</sub>	49	$1.3 \cdot 10^{-4}$	—	—	$9.0 \cdot 10^3$
	AlCl <sub>3</sub>	—	$8.3 \cdot 10^{-3}$	32	164	$5.7 \cdot 10^5$
9-Methylantracene + + citraconic anhydride	—	—	$8.5 \cdot 10^{-7}$	64	135	—
	GaCl <sub>3</sub>	49	$2.0 \cdot 10^{-2}$	41	129	$2.3 \cdot 10^4$
	AlCl <sub>3</sub>	—	0.14	28	154	$1.7 \cdot 10^5$
9,10-Dimethylantracene + + citraconic anhydride	—	—	$2.4 \cdot 10^{-5}$	45	169	—
	GaCl <sub>3</sub>	49	0.44	31	137	$1.9 \cdot 10^4$
	AlCl <sub>3</sub>	—	2.2	29	128	$9.1 \cdot 10^4$
Anthracene + + chloromaleic anhydride	—	—	$3.1 \cdot 10^{-6}$	62	128	—
	GaCl <sub>3</sub>	40	0.11	—	—	$3.6 \cdot 10^4$
	AlCl <sub>3</sub>	—	2.3	—	—	$7.5 \cdot 10^5$
9-Chloroanthracene + + chloromaleic anhydride	—	—	$6.8 \cdot 10^{-7}$	—	—	—
	GaCl <sub>3</sub>	40	$2.3 \cdot 10^{-2}$	—	—	$3.4 \cdot 10^4$
	AlCl <sub>3</sub>	—	0.14	—	—	$2.1 \cdot 10^5$
9-Methylantracene + + chloromaleic anhydride	—	—	$2.3 \cdot 10^{-4}$	49	139	—
	GaCl <sub>3</sub>	40	11.9	28	118	$5.3 \cdot 10^4$
	AlCl <sub>3</sub>	—	39.7	—	—	$1.8 \cdot 10^5$
9,10-Dimethylantracene + + chloromaleic anhydride	—	—	$6.4 \cdot 10^{-3}$	46	118	—
	GaCl <sub>3</sub>	40	$2.4 \cdot 10^2$	—	—	$3.8 \cdot 10^4$
	AlCl <sub>3</sub>	—	$1.4 \cdot 10^3$	—	—	$2.2 \cdot 10^5$
Tetracyclone + <i>N</i> -( <i>p</i> -nitro- phenyl)maleinimide	—	—	$4.0 \cdot 10^{-5}$	64	100	—
	GaCl <sub>3</sub>	48 (imide)	$2.8 \cdot 10^{-4}$	—	—	7.1
	AlCl <sub>3</sub>	—	$1.2 \cdot 10^{-3}$	57	96	30

*(to be continued)*

Table 1 (continued)

Reaction	Lewis acid	$-\Delta H_{MC}$ /kJ mol <sup>-1</sup>	$k_2$ /L mol <sup>-1</sup> s <sup>-1</sup>	$\Delta H^\ddagger$ /kJ mol <sup>-1</sup>	$-\Delta S^\ddagger$ /J mol <sup>-1</sup> K <sup>-1</sup>	$k_{2,cat}/k_{2,noncat}$
Tetracyclone + <i>N</i> -( <i>p</i> -bromophenyl)maleinimide	—	—	$3.6 \cdot 10^{-5}$	64	100	—
	GaCl <sub>3</sub>	53 (imide)	$2.2 \cdot 10^{-4}$	—	—	6.2
	AlCl <sub>3</sub>	—	$1.1 \cdot 10^{-3}$	53	111	29.1
Phencyclone + <i>N</i> -( <i>p</i> -nitrophenyl)maleinimide	—	—	2.12	31	133	—
	GaCl <sub>3</sub>	48 (imide)	36.3	20	135	17.1
	AlCl <sub>3</sub>	—	83.3	—	—	30.3
Phencyclone + <i>N</i> -( <i>p</i> -bromophenyl)maleinimide	—	—	1.42	33	137	—
	GaCl <sub>3</sub>	53 (imide)	21.0	20	140	14.8
	AlCl <sub>3</sub>	—	51.6	—	—	36.3
Phencyclone + <i>N</i> -phenylmaleinimide	—	—	0.76	30	146	—
	GaCl <sub>3</sub>	55 (imide)	9.4	28	121	12.4
	AlCl <sub>3</sub>	—	46.5	14	155	61.2
Phencyclone + <i>N</i> -( <i>p</i> -tolyl)maleinimide	—	—	0.75	34	133	—
	GaCl <sub>3</sub>	57 (imide)	10.4	24	134	13.9
	AlCl <sub>3</sub>	—	40.1	22	127	53.4
Phencyclone + methyl acrylate	—	—	$1.2 \cdot 10^{-3}$	46	133	—
	AlCl <sub>3</sub>	—	0.63	32	129	$5.5 \cdot 10^2$
Phencyclone + methyl methacrylate	—	—	$7.5 \cdot 10^{-4}$	46	139	—
	AlCl <sub>3</sub>	—	0.22	30	144	$2.9 \cdot 10^2$
Phencyclone + dimethyl fumarate	—	—	$4.7 \cdot 10^{-5}$	54	136	—
	AlCl <sub>3</sub>	—	$2.3 \cdot 10^{-2}$	41	126	$4.9 \cdot 10^2$
<i>trans,trans</i> -1,4-Diphenylbutadiene + <i>N</i> -( <i>p</i> -tolyl)maleinimide	—	—	$9.3 \cdot 10^{-7}$	54	168	—
	AlCl <sub>3</sub>	—	$5.9 \cdot 10^{-3}$	38	148	$6.3 \cdot 10^2$
<i>trans,trans</i> -1,4-Diphenylbutadiene + <i>N</i> -phenylmaleinimide	—	—	$1.4 \cdot 10^{-6}$	50	177	—
	AlCl <sub>3</sub>	—	$5.6 \cdot 10^{-3}$	39	143	$3.9 \cdot 10^2$
<i>trans,trans</i> -1,4-Diphenylbutadiene + <i>N</i> -( <i>p</i> -bromophenyl)maleinimide	—	—	$2.1 \cdot 10^{-6}$	48	180	—
	AlCl <sub>3</sub>	—	$7.1 \cdot 10^{-3}$	—	—	$3.4 \cdot 10^2$

A comparison of the DAR rate and energy of electron affinity of normal and activated dienophiles gives the general dependence.<sup>31,86</sup>

The results obtained suggest that the mechanisms of the usual and catalytic reactions are the same. It should be emphasized that rather moderate intrinsic reactivity of maleic anhydride and its derivatives after the formation of

*n,v*-complexes with gallium and especially aluminum halides becomes comparable with that of tetracyanoethylene and even exceeds it in the case of formation of 2 : 1 complexes. Taking into account the change in the energy of electron affinity  $E_A$  in the catalytic processes, Eq. (1) rather exactly predicts the rate for the catalyzed process as well, which makes it possible to choose reaction conditions.

### Solvent effect

Choice of the solvent is very important for the catalyzed reaction, because the Lewis acid is redistributed in the presence of *p*-donor additives due to its binding with both dienophile and competitive *p*-donor. The catalytic effect of reaction acceleration in the presence of Lewis acids can be smoothly changed thus from the maximum value for the reactions in inert (towards Lewis acids) media to the complete inhibition when *p*-donor solvents are used.<sup>75</sup>

The changes in the enthalpy of solvation of the molecular *n,v*-complex (MC) in different solvents were calculated using the thermochemical measurements<sup>24,27,31,75,84–90</sup> from the difference of the cor-

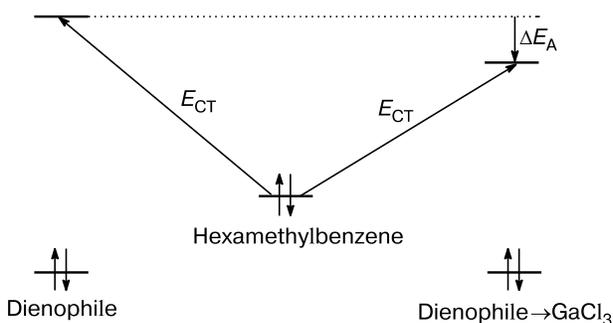


Fig. 1. Energy of the charge-transfer band maximum ( $E_{CT}$ ) of the  $\pi,\pi^*$ -complex of hexamethylbenzene with usual and Lewis acid-activated dienophiles and the change in the energy of electron affinity of dienophile ( $\Delta E_A$ ).

**Table 2.** Wavelengths ( $\lambda$ ) and energies of the charge-transfer band maxima ( $E_{CT}$ ) in the complexes between hexamethylbenzene and nonactivated or activated dienophiles **4** and **5** and the increase in the energy of electron affinity of these dienophiles ( $\Delta E_A$ )<sup>86,90</sup>

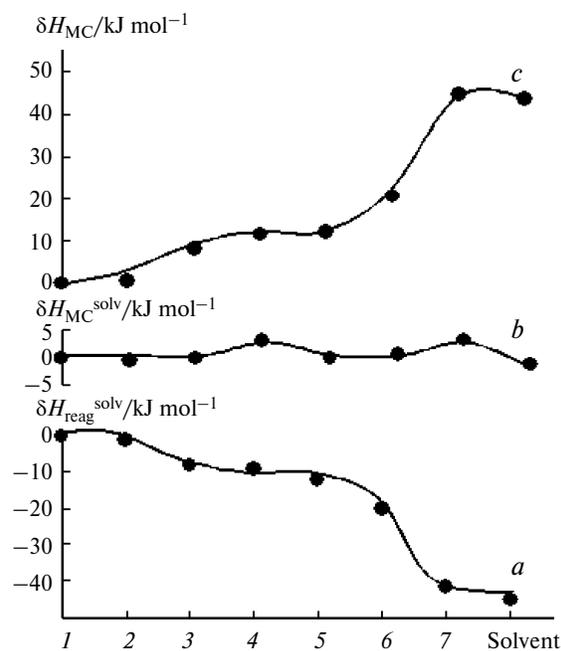
Dienophile	Lewis acid	$\lambda$ /nm	$E_{CT}$ $\Delta E_A$	
			eV	
<i>N</i> -Phenylmaleinimide ( <b>4a</b> )	—	337	3.68	—
	GaCl <sub>3</sub>	470	2.64	1.05
	AlCl <sub>3</sub>	481	2.58	1.10
<i>N</i> -( <i>p</i> -Tolyl)maleinimide ( <b>4b</b> )	—	330	3.76	—
	GaCl <sub>3</sub>	475	2.61	1.15
	AlCl <sub>3</sub>	488	2.54	1.22
<i>N</i> -( <i>p</i> -Bromophenyl)-maleinimide ( <b>4c</b> )	—	345	3.58	—
	GaCl <sub>3</sub>	470	2.64	0.95
	AlCl <sub>3</sub>	480	2.59	1.00
<i>N</i> -( <i>p</i> -Nitrophenyl)maleinimide ( <b>4d</b> )	—	365	3.40	—
	GaCl <sub>3</sub>	464	2.67	0.73
	Maleic anhydride ( <b>5a</b> )	—	353	3.51
GaCl <sub>3</sub>		440	2.82	0.69
AlCl <sub>3</sub>		470	2.64	0.87
Citraconic anhydride ( <b>5b</b> )	—	340	3.65	—
	GaCl <sub>3</sub>	440	2.82	0.83
	AlCl <sub>3</sub>	455	2.73	0.92
Chloromaleic anhydride ( <b>5c</b> )	—	365	3.40	—
	GaCl <sub>3</sub>	480	2.58	0.82
	AlCl <sub>3</sub>	505	2.46	0.94
Dichloromaleic anhydride ( <b>5d</b> )	—	388	3.20	—
	GaCl <sub>3</sub>	500	2.48	0.72

responding enthalpies of dissolution of maleinimides ( $\delta H_{MI}^{sol}$ ) and gallium chloride ( $\delta H_{GaCl_3}^{sol}$ ) and the enthalpy of formation of the *n,v*-complex ( $\Delta H_{MC}$ ) between them in solution

$$\delta H_{MC}^{sol} = \Delta H_{MC}(S_i) - \Delta H_{MC}(S_0) + \delta H_{MI}^{sol} + \delta H_{GaCl_3}^{sol}, \quad (2)$$

where  $S_i$  is the solvent, and  $S_0$  is the reference solvent. In spite of considerable differences in enthalpies of dissolution and formation of the *n,v*-complex, a very weak difference in enthalpies of solvation of the *n,v*-complex itself is observed in a series of solvents (Fig. 2).

This corresponds to the fact that the *v*-acceptor properties of gallium chloride are nearly completely used in the formation of the 1 : 1 *n,v*-complex. Interestingly, loss of the acceptor properties is also observed for tetracyanoethylene in its complex with  $\pi$ -donors<sup>31</sup> and, to a greater extent, in the activated complex of the DAR involving tetracyanoethylene.<sup>73,75</sup> For this reason, the rate of the DAR involving tetracyanoethylene decreases by hundreds of times in a solution of strong  $\pi$ -donors, for example, alkylbenzenes, where considerable stabilization of tetracyanoethylene in the  $\pi,\pi$ -complex occurs and results in its deactivation as a dienophile in the DAR. The absence of



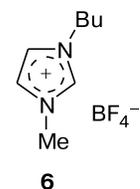
**Fig. 2.** Changes in the enthalpies of solvation of the reactants (gallium chloride and imide **4a**) ( $\delta H_{reag}^{sol}$ ) (*a*) and the *n,v*-complex between them ( $\delta H_{MC}^{sol}$ ) (*b*) and the enthalpies of formation of this complex ( $\delta H_{MC}$ ) (*c*) in chlorobenzene (*1*), benzene (*2*), toluene (*3*), dichloromethane (*4*), *o*-xylene (*5*), mesitylene (*6*), nitromethane (*7*), and nitrobenzene (*8*).

such interactions of the solvent with the tetracyanoethane fragment in the adduct and activated complex is the main reason for the very weak effect of the medium on the rate of adduct decomposition.<sup>102–105</sup> A similar pattern is observed for the nonspecific solvation of the reactants in a series of solvents, when the difference in the energy of extrusion of solvent molecules upon the achievement of the nonpolar and more compact transition state of the DAR can exert a noticeable effect on its rate.<sup>106,107</sup>

### Salt effects

The whole series of reactants (furan and cyclopentadiene derivatives, vinyl ethers) cannot be activated by Lewis acids because of their easy polymerization and/or resinification. It can be assumed by analogy that upon the solvation of electrolyte cations a dienophile can also be more reactive in the DAR. For instance, it was found that in a 5 M solution of lithium perchlorate in diethyl ether many DARs occurs much more rapidly,<sup>91,108–114</sup> and the reactants and products are stable under these conditions (Table 3).

The enthalpies of dissolution and partial molar volumes of lithium and magnesium perchlorates and ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate (**6**), were determined in a series of



**Table 3.** Rate constants for some Diels–Alder reactions in the absence of salt ( $k_2$ ) and in solutions of lithium perchlorate ( $k_{LP}$ ) of different concentrations ( $c_{LP}$ ) at 25 °C<sup>113</sup>

Reaction	Solvent	$k_2$	$k_{LP}$	$c_{LP}$ /mol L <sup>-1</sup>	$k_{LP}/k_2$
		L mol <sup>-1</sup> s <sup>-1</sup>			
Anthracene + tetracyanoethylene	Et <sub>2</sub> O	0.24	4.4	4.2	18
3,6-Dimethoxycarbonyltetrazine + hex-1-ene	Et <sub>2</sub> O	$5.3 \cdot 10^{-2}$	$5.4 \cdot 10^{-1}$	3.6	10
9,10-Dimethylanthracene + acrylonitrile	Et <sub>2</sub> O	$1.9 \cdot 10^{-6}$	$2.0 \cdot 10^{-5}$	3.8	11
9,10-Dimethylanthracene + maleic anhydride	Et <sub>2</sub> O	$9.4 \cdot 10^{-3}$	$9.4 \cdot 10^{-2}$	3.6	10
	Me <sub>2</sub> CO	$8.8 \cdot 10^{-3}$	$1.5 \cdot 10^{-1}$	4.5	17
Furan + <i>N</i> -phenylmaleinimide	Et <sub>2</sub> O	$6.6 \cdot 10^{-6}$	$5.3 \cdot 10^{-3}$	4.0	803
	Me <sub>2</sub> CO	$1.3 \cdot 10^{-5}$	$6.6 \cdot 10^{-4}$	4.1	49
Cyclopentadiene + acrylonitrile	Et <sub>2</sub> O	$8.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-4}$	4.6	44
	EtOH	$2.9 \cdot 10^{-5}$	$2.5 \cdot 10^{-4}$	4.4	9
Cyclopentadiene + dimethyl maleate	Et <sub>2</sub> O	$1.4 \cdot 10^{-5}$	$1.0 \cdot 10^{-2}$	3.1	729
Cyclopentadiene + dimethyl fumarate	Et <sub>2</sub> O	$7.2 \cdot 10^{-4}$	$4.3 \cdot 10^{-2}$	4.0	60
Cyclopentadiene + maleic anhydride	Et <sub>2</sub> O	$2.3 \cdot 10^{-2}$	38	4.6	1638
Cyclopentadiene + methyl vinyl ketone	Et <sub>2</sub> O	$3.3 \cdot 10^{-5}$	$1.4 \cdot 10^{-2}$	4.6	424
	EtOH	$5.4 \cdot 10^{-4}$	$4.9 \cdot 10^{-2}$	7.4	91
Cyclopentadiene + <i>N</i> -phenylmaleinimide	Et <sub>2</sub> O	$2.4 \cdot 10^{-2}$	79	4.6	3347
	AcOEt	$6.3 \cdot 10^{-2}$	3.7	3.1	59
	EtOH	0.59	4.6	3.9	8
2,3-Dimethylbutadiene + 1,4-naphthoquinone <sup>a</sup>	Me <sub>2</sub> CO	$1.0 \cdot 10^{-5}$	$8.1 \cdot 10^{-3}$	4.0	814
<i>trans,trans</i> -1,4-Diphenylbutadiene + + <i>N</i> -phenyltriazolinedione <sup>b</sup>	Me <sub>2</sub> CO	0.85	4.3	3.0	5
2,3-Dimethylbutadiene + <i>p</i> -bromonitrosobenzene <sup>b</sup>	Me <sub>2</sub> CO	$3.7 \cdot 10^{-3}$	$1.6 \cdot 10^{-2}$	3.0	4

<sup>a</sup> 30 °C, data of Ref. 114.<sup>b</sup> 20 °C, data of Ref. 114.

*p*-donor solvents (Table 4). The thermochemical determination of the enthalpies of dissolution of lithium perchlorate<sup>115–117</sup> and magnesium perchlorate<sup>118,119</sup> showed that in all media the dissolution process is exothermic. The heat of dissolution of the salt in the region is low concentration was observed for two solvents: diethyl ether and nitromethane.<sup>117,119</sup> Just these solvents exhibit a sharper increase in the reaction rates in the region of low concentrations of lithium perchlorate.<sup>113,116</sup>

It is interesting that the dissolution of lithium and magnesium perchlorates is accompanied by a considerable heat release in all *p*-donor solvents studied. The enthalpies of dissolution of 1-butyl-3-methylimidazolium tetrafluoroborate (**6**) are much lower (see Table 4). The values of partial molar volumes of these salts in the most solutions are noticeably smaller than the molar volumes in the crystalline state and even lower than the van der Waals volumes (for magnesium perchlorate, 85.4 and 67.3 cm<sup>3</sup> mol<sup>-1</sup>, respectively; for lithium perchlorate, 43.8 and 34.3 cm<sup>3</sup> mol<sup>-1</sup>, respectively). In the first approximation, the volume of a dilute solution can be presented as follows:

$$V = V_A N_A + V_S N_S + (V_S^* - V_S) n N_A, \quad (3)$$

where  $V_A$ ,  $V_S$ , and  $V_S^*$  are the molar volumes of the solute, free solvent, and solvent in the solvate sphere of substance A, respectively;  $n$  is the number of solvent mole-

cules in the solvate sphere;  $N_A$  and  $N_S$  are the numbers of moles of the solute and solvent, respectively. Whence it follows that the partial molar volume of substance A in a solution ( $V_A$ ) is determined by the equation

$$\partial V / \partial N_A = V_A + n(V_S^* - V_S). \quad (4)$$

In the absence of specific interactions in a solution ( $V_S^* - V_S = 0$ ), the partial molar volume of the solute can be calculated from the data on the density of the solution and even using the additive scheme of increments of bonds or atoms.<sup>120,121</sup> If the interaction of the solute with the medium is high, the additivity rule is not fulfilled because of the great contribution of the change in the solvent volume on its transfer to the solvate shell. In these cases, there are frequent examples of negative values of the calculated partial molar volumes<sup>117–119,122</sup> (see Table 4). Evidently, this problem remains for infinitely diluted solutions. Since it is impossible to experimentally determine  $n(V_S^* - V_S)$  and  $V_A$  separately, all changes in these values are attributed to the molar volume of the solute ( $V_A$ ). In this method of determination of partial molar volumes of products and reactants, their difference gives true values of the reaction volume in solution.

Note that the angular coefficient of the dependence of changing partial molar volumes of solvated ions for lithium perchlorate on the electrostriction parameter

**Table 4.** Partial molar volumes of magnesium and lithium perchlorates and ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate) ( $V_{MP}$ ,  $V_{LP}$ , and  $V_{IL}$ , respectively) and their enthalpies of dissolution ( $\Delta H_{MP}^{sol}$ ,  $\Delta H_{LP}^{sol}$ ,  $\Delta H_{IL}^{sol}$ ) in different solvents at 25 °C<sup>117–119</sup>

Solvent	$V_{MP}$	$V_{LP}$	$V_{IL}$	$\Delta H_{MP}^{sol}$	$\Delta H_{LP}^{sol}$	$\Delta H_{IL}^{sol}$
	cm <sup>3</sup> mol <sup>-1</sup>			kJ mol <sup>-1</sup>		
Formamide	82.3	47	190.3	-190	-45.2	7.0
Water	67.3	44.2	188.0	-153	-26.3	15.8
Dimethyl sulfoxide	62.3	38.7	184.2	-242	-75.3	-5.6
Dimethylformamide	42.6	26.0	173.5	-247	—	-12.2
Acetone	-2.4	-2.0	147.2	-191	-66.1	-10.2
Propylene carbonate	56.7	37.1	183.7	-189	—	-2.3
<i>N</i> -Methylformamide	71	40	187.4	—	—	—
Ethyl acetate	46.6	25.1	165.9	-142	-37.2	-1.1
Diethyl ether	24	14.5	—	—	-25.9	—
Acetonitrile	20.3	20.1	167.5	-198	-38.5	-5.0
Nitromethane	63.9	36.4	177.4	-270	-61.9	-5.1
Methanol	-4.7	—	168.8	-205	—	18.5
Ethanol	2.5	—	167.4	-171	—	24.5
Propan-1-ol	36.3	—	180.6	-178	—	27.0
Propan-2-ol	41.3	—	176.8	-163	—	26.4
Ethylene glycol	73.4	—	185.8	—	—	16.3
Standard state	85.4 (cr)	43.8 (cr)	188.2 (liq)	—	—	—

( $\partial(1/\epsilon)/\partial p$ ) is nearly 20 times higher than that for a contact ion pair.<sup>123</sup> That is, the electrostriction of the solvent during solvation of the contact ion pair is only ~5% of the electrostriction of solvated ions. For the DARs, the electrostriction effect is close to zero.

The enthalpies of dissolution of the ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate (**6**)) are low, but the change in partial molar volumes for this liquid and lithium perchlorate are comparable (see Table 4). In the majority of cases, the solvent effect is not proportional to the changes in the enthalpy of dissolution and partial molar volume.

There is a simple relationship between the acceleration of the DAR ( $\ln(k_{cat}/k_{noncat})$ ) in the presence of Lewis acids ( $AlHal_3$ ,  $GaHal_3$ ,  $BHal_3$ ) and the enthalpy of complex formation with dienophiles ( $\Delta H_{MC}/kJ\ mol^{-1}$ )<sup>31</sup>

$$\ln(k_{cat}/k_{noncat}) = 0.19\Delta H_{MC} \quad (5)$$

The effect of the medium on the enthalpies of dissolution and partial molar volumes of the  $\nu$ -acceptor (gallium chloride) and  $\pi$ -acceptor (tetracyanoethylene (**7**)) is shown in Table 5.

In spite of a considerably lower exothermicity of gallium chloride dissolution (see Table 5) compared to the dissolution of lithium and especially magnesium perchlorate (see Table 4), the acceleration effect of the reaction of 9,10-dimethylanthracene with acrylonitrile in a medium of acrylonitrile in the presence of  $LiClO_4$ ,  $Mg(ClO_4)_2$ , and  $GaCl_3$  is 18, 160, and 59 000, respectively.<sup>35,119</sup>

The solubility of reactants often decreases in salt media, which can be a reason for the observed acceleration (salting-out effect). Another explanation of the acceleration of the reactions in solutions of lithium perchlorate is related to the assumption on the activation of the reactant (usually dienophile) due to the formation of a complex between the  $p$ -donor center of the substituent in dienophile and lithium cation.<sup>124</sup> However, it remains unclear why the activation of the same dienophile with lithium cation results in a greater acceleration of one DARs (for example, the reactions of maleinimides with cyclopentadiene or furan) and does not almost accelerate the reactions with other dienes (see Table 3). This sharply distin-

**Table 5.** Partial molar volumes ( $V$ ) and enthalpies of dissolution ( $\Delta H^{sol}$ ) of gallium chloride and tetracyanoethylene (**7**) in some solvents<sup>103</sup>

Solvent	$V_{GaCl_3}$	$V_7$	$\Delta H_{GaCl_3}^{sol}$	$\Delta H_7^{sol}$
	cm <sup>3</sup> mol <sup>-1</sup>		kJ mol <sup>-1</sup>	
Benzene	74.8±0.1	108.4±0.3	9.6±0.6	14.9±0.4
Toluene	68.7±0.1	104.4±0.4	2.5±0.6	9.7±0.5
<i>o</i> -Xylene	67.1±0.1	102.2±0.3	-0.8±0.4	1.4±0.1
Mesitylene	64.8±0.4	98.1±0.2	-7.1±0.6	-2.7±0.4
1,2-Dichloroethane	73.4±0.4	107.8±0.2	5.1±0.6	21.3±0.3
Ethyl acetate	60.7±0.3	112.8±0.1	-65.7±2.1	9.2±0.5
Acetonitrile	61.9±0.3	109.8±0.1	-71.1±2.0	15.2±0.2
1,4-Dioxane	61.5±0.5	106.1±0.2	-74.0±2.0	4.3±0.2

guishes the activation of the DARs in the presence of magnesium and lithium perchlorates from the DAR activation by usual Lewis acids.<sup>113,119</sup> In the presence of aluminum or gallium halides, the acceleration effects are rather stable for all cases of DARs with normal electronic requirements (see Table 1). If the reaction is carried out in the presence of gallium chloride in a medium of acrylonitrile or ethyl acrylate, when the maximum coordination of gallium chloride with these dienophiles should be expected, the acceleration effect ( $1.9 \cdot 10^4$  and  $3.1 \cdot 10^4$ , respectively) almost coincides with the acceleration effect of the reaction in an inert solvent.<sup>113</sup> After the addition of diethyl ether or acetonitrile, gallium chloride is redistributed between *p*-donors due to the competitive formation of *n,v*-complexes, and the acceleration effect decreases sharply. Reliability of the scheme of gallium chloride distribution was confirmed by the constant calculated ratio of equilibrium constants of the *n,v*-complexes.<sup>113</sup> Another dependence is observed for the reactions in the presence of lithium or magnesium perchlorates. In this case, the addition of a competitive *p*-donor (diethyl ether) does not decrease and even increases the reaction rate as exemplified for the reaction of cyclopentadiene with acrylonitrile.<sup>113</sup> If the activation mechanism involving lithium and magnesium perchlorates would be the same as in the case of usual Lewis acids, then the effect of the addition of the competitive *p*-donor solvent should coincide at least qualitatively, which is not experimentally observed.

Unlike the salting-out effect of lithium perchlorate in diethyl ether, which is usual for lowly polar reagents towards the polar reagent (*C,N*-diphenylnitron (8)), the solubility in this medium increases (salting-in effect). Interestingly, the salting-out effect manifests itself and the rate and equilibrium constants increase in a solution of lithium perchlorate for equilibrium reactions involving furan, while these characteristics decrease for the reactions with *C,N*-diphenylnitron (8).<sup>113</sup>

A series of new cycloaddition products was obtained for the first time in a medium of lithium perchlorate in diethyl ether due to a favorable change in the rate and equilibrium under these conditions.<sup>113,125–127</sup>

An analysis of the accumulated data on the acceleration effects of the DARs in the presence of aluminum, gallium, and boron halides is consistent with the assumption about the enhancement of the orbital interaction and, therefore, these salts are favorable for orbital-controlled processes. It can be expected that in solutions of lithium and magnesium perchlorates in organic solvents the resulting influence on the rate of polar reactions is determined by the stabilization of charged states. For nonpolar processes this influence is determined by the difference in salting-in effects and salting-out effects for reactants, prod-

ucts, and even activated complexes.<sup>113,125</sup> The examples of the influence of salt solutions on the reaction rates are reviewed.<sup>108</sup> It is mentioned<sup>113,125</sup> that the salting-out effect of reactants in salt solutions of *p*-donor solvents is similar, to a considerable extent, to the effect of hydrophobic acceleration of the reactions.<sup>128,129</sup> In some cases, the effect of hydrophobic acceleration can somewhat be overestimated. For instance, the apparent powerful increase in the dimerization rate of cyclopentadiene in water<sup>130</sup> entirely corresponds to the dimerization rate in a droplet of pure cyclopentadiene with the concentration corresponding to the pure reagent.

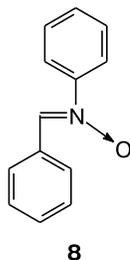
### Reactions under elevated pressure

The action of physical energy ( $P\Delta V$ ) upon compression of reactant solutions often exerts a favorable effect on the rate and equilibrium of chemical reactions. In all cycloaddition reactions, the volume of the reacting system decreases on going from the reactants to the activated complex and further to cyclic adducts. The dependence of the rate ( $k$ ) and equilibrium ( $K$ ) constants of the process on the external pressure ( $p$ ) is described by the equations

$$(\partial \ln k / \partial p)_T = -1/RT(\partial G^\ddagger / \partial p)_T = -\Delta V^\ddagger / RT, \quad (6)$$

$$(\partial \ln K / \partial p)_T = -1/RT(\partial G_{\text{react}} / \partial p)_T = -\Delta V_{\text{react}} / RT, \quad (7)$$

where  $\Delta V^\ddagger$  and  $\Delta V_{\text{react}}$  are the activation and reaction volumes, respectively. Whence it follows that for processes that occur with the volume decreases the rate and equilibrium constants increase with an increase in the hydrostatic pressure.<sup>36–43</sup> Of course, Eqs (6) and (7) are fulfilled only in the ideal case where the value of the rate or equilibrium constant changes with pressure only due to the contribution of  $P\Delta V^\ddagger$  or  $P\Delta V_{\text{react}}$ . Elevated hydrostatic pressure induces the change in all properties of the system: density ( $d$ ), refractive index ( $n$ ), dielectric constant ( $\epsilon$ ), viscosity ( $\eta$ ), and others. Therefore, Eqs (6) and (7) are valid only under the conditions  $(\partial \ln k / \partial p)_{T,d,n,\epsilon,\eta}$  and  $(\partial \ln K / \partial p)_{T,d,n,\epsilon,\eta}$ . The properties of the medium cannot be retained constant with the pressure increase and, hence, it is necessary to take into account the additional influence of changing these parameters  $(\partial \ln k / \partial d, \partial \ln k / \partial n, \partial \ln k / \partial \epsilon, \partial \ln k / \partial \eta)$  on the reaction rate and equilibrium. The reliable kinetic data for the isopolar DAR under normal and elevated pressure assert the absence or a very weak influence on the process rate of the change in the properties of the solvent induced by high pressure. The influence of the concentration increase with pressure  $(\partial c / \partial p)$  should be taken into account by the data on solvent compressibility  $(\partial V / \partial p)$ . For polar and ionic processes the contribution  $\partial \ln k / \partial \epsilon$  induced by pressure  $(\partial \epsilon / \partial p)$  can be significant, and it is usually attributed to the electrostriction effect.<sup>40,131</sup> Viscosity can increase strongly with pressure



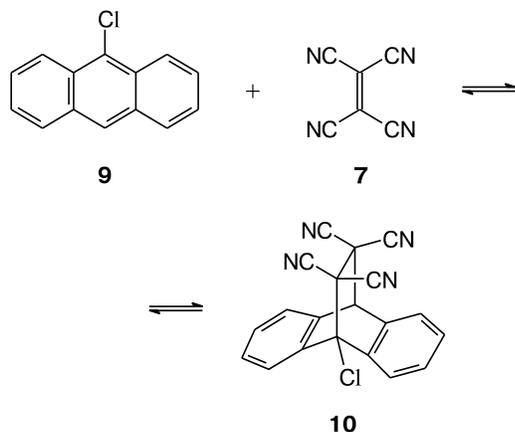
( $\partial\eta/\partial p$ ) and achieve such values at which the DAR rate can be diffusionally controlled ( $\partial\ln k/\partial\eta$ ).<sup>132</sup>

The activation volume can be calculated only from the dependence of the reaction rate on the external pressure if the change in the reaction rate under elevated pressure (see Eq. (6)) is determined by the contribution  $P\Delta V^\ddagger$  only. The reaction volume can be determined from the dependence of the equilibrium constant on the external pressure (see Eq. (7)) and, independently, from the difference in partial molar volumes of products and reactants. This makes it possible to check the presence or absence of possible difficulties for the determination of volume parameters from the dependence of the reaction rate or equilibrium on the external pressure.<sup>131</sup>

There are data that the  $\pi,\pi$ -complexes between diene and dienophiles lie in the reaction route and, hence, the experimental activation enthalpy is determined by the sum of the enthalpy of complex formation and the enthalpy of its activation.<sup>73</sup> The experimental value of the activation volume of the DAR is also determined by the sum of the volumes of complex formation and activation.<sup>106</sup> It is known<sup>67,73,133</sup> that the  $\pi$ -acceptor dienophile, tetracyanoethylene, forms complexes with many solvents. It was shown that in a medium of  $\pi$ -donor solvents the specific interactions proportionally affect the changes in the enthalpy of solvation of tetracyanoethylene, its partial molar volume, enthalpies and free energies of formation of its  $\pi,\pi$ -complexes with the solvent and on the DAR rate.<sup>103,134–137</sup>

The study of the DAR rate in a high-pressure cell<sup>138,139</sup> with direct spectrophotometric monitoring made it possible to carry out the full cycle of independent measurements.<sup>131</sup> The equilibrium reaction of 9-chloroanthracene (**9**) with tetracyanoethylene (**7**) in 1,2-dichloroethane (Scheme 2) turned out to be convenient for these purposes.

Scheme 2



The volume of this reaction in 1,2-dichloroethane was determined<sup>131,140–143</sup> by three independent methods:

(1) from the data on the pressure effect on the equilibrium constant ( $-20.6 \pm 1.5 \text{ cm}^3 \text{ mol}^{-1}$ ); (2) from the difference in partial molar volumes of adduct **10** ( $255.5 \text{ cm}^3 \text{ mol}^{-1}$ ), 9-chloroanthracene (**9**) ( $170.7 \text{ cm}^3 \text{ mol}^{-1}$ ), and tetracyanoethylene (**7**) ( $107.8 \text{ cm}^3 \text{ mol}^{-1}$ ) ( $-23.0 \pm 2.0 \text{ cm}^3 \text{ mol}^{-1}$ ); and (3) from the difference in activation volumes for the forward ( $-28.5 \text{ cm}^3 \text{ mol}^{-1}$ ) and backward ( $-6.5 \text{ cm}^3 \text{ mol}^{-1}$ ) processes, which also results in rather close value of the reaction volume ( $-22.0 \pm 1.5 \text{ cm}^3 \text{ mol}^{-1}$ ). It is interesting that both negative and positive values of activation volumes are observed during activation for the decomposition of adduct **10**:  $-7.9$ ,  $-6.5$ ,  $-2.2$ ,  $-7.2$ ,  $+1.5$ , and  $+3.0 \text{ cm}^3 \text{ mol}^{-1}$  in acetonitrile, 1,2-dichloroethane, chlorobenzene, toluene, ethyl acetate, and butyl acetate, respectively.<sup>105,106</sup>

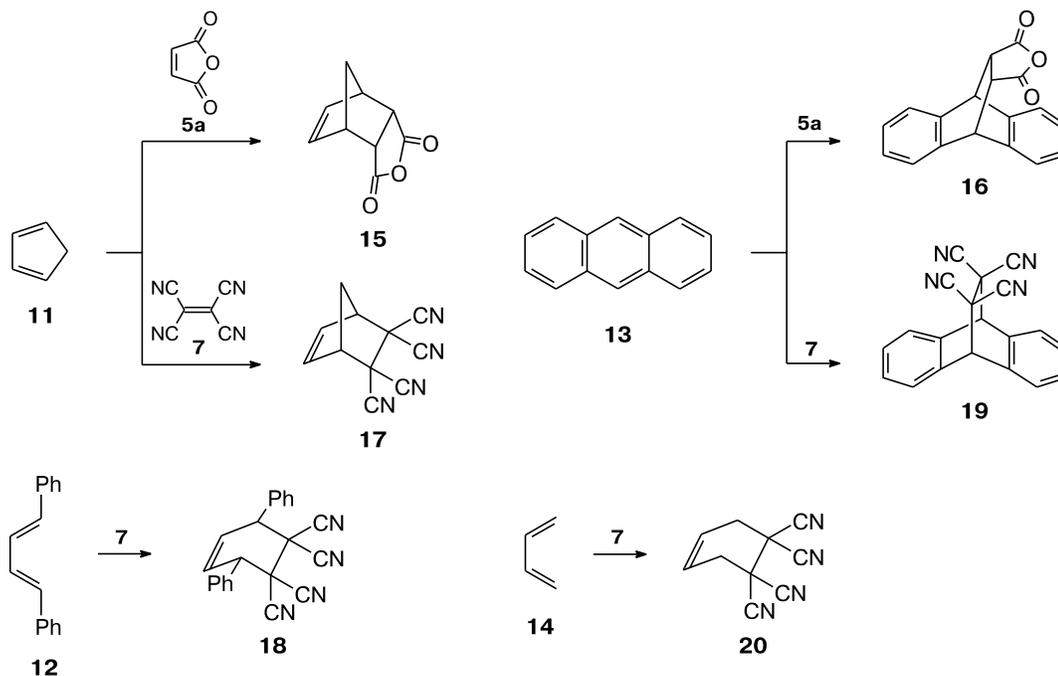
As can be seen from an analysis of numerous data on values of the activation volume and DAR volume,<sup>37–43</sup> in approximately 50% of cases, the activation volume of the forward DAR is lower by modulus than the reaction volume ( $\Delta V^\ddagger/\Delta V_{\text{react}} < 1$ ), which corresponds to the commonly accepted position of the transition state (TS) on the reaction coordinate between the reactants and products. However, the data on the pressure effect on the rates of other studied DARs show that the TS are more compact than the reaction adducts and, hence,  $\Delta V^\ddagger/\Delta V_{\text{react}} > 1$ . A few examples on the pressure effect on the decomposition rate of the adducts confirm<sup>22,38,105,106</sup> that the molar volume of the adduct can be larger than the molar volume of the TS. Electrostriction of the solvent during the solvation of the TS with a high charge separation could explain this anomalous change in the volume profile of the reaction. However, numerous kinetic data on the weak influence of the medium on the rates of the forward and backward DARs allow one to exclude electrostriction from consideration.<sup>106</sup>

The solvent effect on the change in packing of the reactants, activated complex, and products in solution in the course of the reaction is the main reason for the difference and diversity of the values of partial molar volumes and activation and reaction volumes, and, hence, differences in the pressure effect on the rate and equilibrium. It was shown<sup>105,106</sup> that for the isopolar DARs (Scheme 3) the change in packing can depend substantially on accessibility of the surface of molecules of the reactants, adduct, and transition state (Table 6).

This can result in significant differences in reaction volumes in a series of different solvents (Table 7).

The difference in accessibility of the molecular surface upon solvation by the solvent was observed for a series of three-dimensional molecules. For example, the partial molar volume of adamantane in hexane and benzene is  $136.9$  and  $142.7 \text{ cm}^3 \text{ mol}^{-1}$ , and that of congressane is  $160.2$  and  $177.4 \text{ cm}^3 \text{ mol}^{-1}$ , respectively.<sup>144</sup> The transition from the solid phase to solution is usually accompanied by an increase in the partial molar volumes by

Scheme 3



10–15% (see Table 6). Ball molecules, such as fullerene  $C_{60}$ , have more intermolecular cavities ( $V_{cr} = 429 \text{ cm}^3 \text{ mol}^{-1}$ ) in the solid phase compared to those in solution ( $350\text{--}400 \text{ cm}^3 \text{ mol}^{-1}$ ).<sup>144</sup> For this reason, fullerene  $C_{60}$  is dissolved with heat evolution.<sup>145</sup>

This different accessibilities of sterically hindered three-dimensional structures of the adduct and TS for solvation can become a reason for the "abnormal" change in the activation volume of the isopolar forward and backward cycloaddition processes (Fig. 3).

If in the retro reaction the intramolecular cavity in the adduct is inaccessible in size for the insertion of solvent molecules  $S_i$  (see Fig. 3, *a*) but becomes accessible with its increase in the transition state, the activation volume of the retro reaction can be negative. The activation volume of the retro reaction is positive if the cavity in the adduct is accessible for the solvation by solvent  $S_j$  (see Fig. 3, *b*).<sup>107</sup>

As already mentioned, for such isopolar processes as DARs, the pressure-induced change in the properties of the solvent exerts a weak effect on the rate and equilibrium

**Table 6.** Partial molar volumes ( $V$ ) of some reactants and adducts in different solvents and their van der Waals volumes ( $V_W$ ) and molar volumes of crystals ( $V_{cr}$ ) at  $25^\circ\text{C}$ <sup>107</sup>

Reactant or adduct	$V/\text{cm}^3 \text{ mol}^{-1}$								$V_W$ $\text{cm}^3 \text{ mol}^{-1}$	$V_{cr}$
	Benzene	Toluene	Chloro- benzene	Aceto- nitrile	Ethyl acetate	Cyclo- hexanone	1,4-Di- oxane	1,2-Dichloro- ethane		
<b>5a</b>	72.2±0.3	71.1±0.2	73.9±0.1	70.4±0.1	69.2±0.3	74.5±0.2	71.3±0.2	71.1±0.3	43.9	65.4
<b>7</b>	108.4±0.3	104.6±0.4	109.2±0.2	108.7±0.2	112.1±0.3	110.4±0.4	105.7±0.2	107.8±0.2	62.6	97.5
<b>11</b>	83.2±0.1	82.4±0.1	82.4±0.2	82.6±0.1	83.8±0.1	81.4±0.2	81.8±0.2	83.6±0.1	41.4	82.9 (I)
<b>12</b>	199.3±0.3	199.8±0.2	—	200.0±0.3	195.2±0.3	201.7±0.3	200.4±0.3	202.7±0.8	123.8	179.4
<b>13</b>	158.6±0.3	158.0	160.1±0.1	158.2±0.2	153.7±0.5	159.8±0.4	159.5	161.9±0.1	101.3	141.6
<b>15</b>	123.7±0.6	123.6±0.05	125.4±0.6	122.3±0.6	120.0±0.6	124.7±1.2	125.0±0.6	125.2±0.1	81.7	107.8
<b>16</b>	—	208.6±0.4	210.7±0.6	202.1±0.2	198.9±0.7	207.1±0.2	205.2±0.1	207.8±0.5	141.2	200.2
<b>17</b>	159.6±0.3	158.3±0.2	159.6±0.5	150.6±0.3	150.3±0.3	157.5±0.4	151.6±0.2	154.7±0.1	100.9	—
<b>18</b>	280.8±0.1	279.9±0.3	—	275.5±0.3	272.8±0.3	278.1±0.3	279.8±0.1	278.8±0.2	183.2	267.5
<b>19</b>	—	—	—	237.9±0.6	234.3±0.5	244.8±0.6	234.6±1.1	242.3±0.3	160.6	235.5
<b>20</b>	161.9±0.5	159.7±0.3	—	157.6±0.3	155.4±0.2	158.6±0.3	156.1±0.3	154.4±0.3	97.6	—

**Table 7.** Reaction volumes ( $\Delta V_{\text{react}}$ ) in different solvents and in the standard state ( $\Delta V_{\text{st}}$ ) and the van der Waals reaction volumes ( $\Delta V_{\text{react,W}}$ )<sup>107</sup>

Reaction	$\Delta V_{\text{react}}/\text{cm}^3 \text{ mol}^{-1}$								$\Delta V_{\text{st}}$	$\Delta V_{\text{react,W}}$ $\text{cm}^3 \text{ mol}^{-1}$
	Benzene	Toluene	Chloro- benzene	Aceto- nitrile	Ethyl acetate	Cyclo- hexanone	1,4-Di- oxane	1,2-Dichloro- ethane		
<b>11 + 5a → 15</b>	-31.7	-29.9	-30.9	-30.7	-33.4	-31.2	-28.1	-29.4	—	-3.6
<b>13 + 5a → 16</b>	—	-20.5	-23.3	-26.3	-24.2	-27.7	-25.6	-25.2	-6.8 (cr)	-4.0
<b>11 + 7 → 17</b>	-32.0	-28.7	-32.0	-40.7	-45.6	-34.3	-35.9	-36.7	—	-3.1
<b>12 + 7 → 18</b>	-26.9	-24.5	—	-33.2	-34.5	-34.0	-26.3	-31.7	-9.4 (cr)	-3.2
<b>13 + 7 → 19</b>	—*	—*	—*	-29	-31.3	-25.9	-30.6	-27.4	-3.6 (cr)	-3.3
<b>14 + 7 → 20</b>	-33.5	-31.9	—	-38.1	-43.7	-38.8	-36.6	-40.4	—	-3.7

\* Not dissolved.

constants and, hence, does not violate the determined values of  $\Delta V^\ddagger$  and  $\Delta V_{\text{react}}$ . For polar and ionic processes the influence of electrostriction of the solvent can be very high.<sup>122</sup>

Compressibility of the liquid ( $\partial V/\partial P$ ) is the main reason for electrostriction.<sup>39,40</sup> Organic solvents differ sharply in physical and chemical properties, which results in great differences in the solvation energy. This explains the strong medium effect on the rate and equilibrium of polar and ionic processes. Compressibility of the liquid is determined by the balance of intermolecular attraction and repulsion forces.<sup>38–40</sup> The decrease in the liquid volume ( $\Delta V/V_0$ ) with a moderate elevation of pressure (up to  $\sim 3$  kbar) is related to the compression of inter-

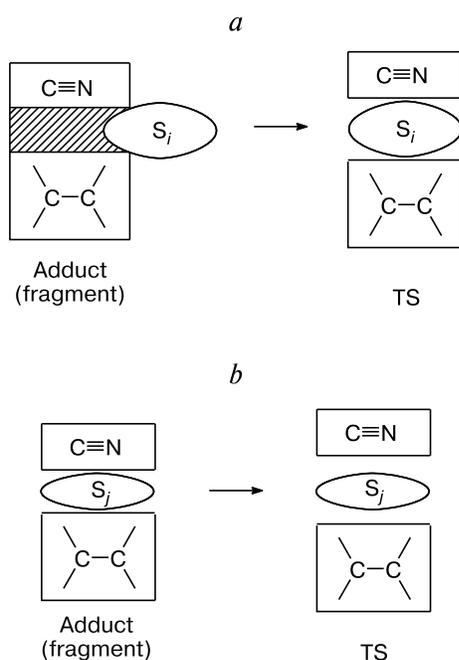
molecular cavities<sup>38–40</sup> and reliably described by Tait's equation

$$\Delta V/V_0 = C \ln[(B + P)/B], \quad (8)$$

where  $C$  and  $B$  are coefficients.

Reliability of quantitative data on the rate and equilibrium of the DAR, for which electrostriction should be excluded from consideration, shows that for nonpolar processes the contribution of the change in the intermolecular packing in solution considerably exceeds the change in the van der Waals volume. In other words, these volume parameters are formed not only due to the change in the intrinsic volume of the reactants (change in the van der Waals volume) on going to the activated complex or adduct but also due to the change in the volume of intermolecular cavities (packing) during the reaction in solution. The value of the latter contribution often exceeds the change in the van der Waals volume, which is rather constant for the DAR, being only  $-5$ – $8 \text{ cm}^3 \text{ mol}^{-1}$ .<sup>38</sup> The change in the volume of intermolecular cavities in the course of the reaction is determined by the difference in packing coefficients ( $V_{\text{W}}/V$ ) of the reactants, activated complex, and reaction products. It is shown using the isopolar DAR that the change in the packing coefficients is considerably higher in the reaction involving small reactant molecules.<sup>104,137,146–151</sup> For this reason, the values of activation and reaction volumes are more negatives for the DARs involving small reactants. For instance, in the reactions of dienophiles with cyclopentadiene and alkylbutadienes the activation and reaction volumes are  $-35$ – $40 \text{ cm}^3 \text{ mol}^{-1}$ , whereas in the reaction with the anthracene derivatives these parameters are only  $-20$ – $25 \text{ cm}^3 \text{ mol}^{-1}$ . Reliable kinetic data for DARs assert unambiguously that the difference in volume parameters is caused, in this case, not by the electrostriction of the medium, but a high difference in the change in the packing coefficients of the starting reactants during the reaction in solution.

The valuable semiempirical equations have earlier<sup>152,153</sup> been proposed for the recalculation of the volume

**Fig. 3.** Possible decrease (a) and increase (b) in the activation volume in the retro reaction on going from the adduct to transition state (TS) ( $S_i$ ,  $S_j$  are solvent molecules).

reaction parameters to the equal values of temperature and pressure, which enhances the reliability of the conclusions about the reaction mechanism and the accuracy of prediction of the pressure effect on the rate and equilibrium. These details should be taken into account when interpreting the reaction mechanism by the data on the activation and reaction volumes.

The volumes of intermolecular cavities in solution decrease with pressure and, hence, the absolute values of  $\Delta V^\ddagger$  and  $\Delta V_{\text{react}}$  also decrease approaching the van der Waals values. Therefore, the most optimum increase in the rate and equilibrium should be expected with the pressure increase to 10–15 kbar.

### Catalyzed Diels–Alder reaction under elevated pressure

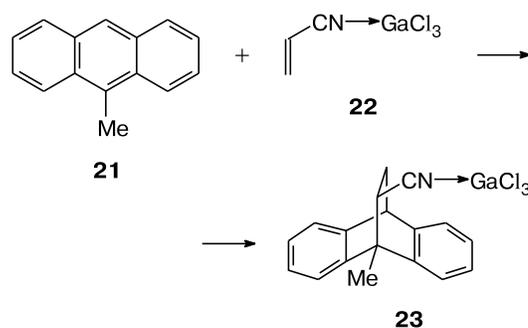
Catalyzed processes under elevated pressure are of special interest. Here the total acceleration effect is determined by the product  $(k_{\text{cat}}/k_{\text{noncat}}) \cdot (k_p/k_{p=1})$ . Since high pressure affects the rate and equilibrium of the process, this complex action is very desirable for slow and equilibrium reactions.

The very high sensitivity of the catalytic reaction to the change in the bond energy in the  $n, \nu$ -complex (see Eq. (5)) makes it the most convenient model for checking the possible change in the bond energy in this complex under elevated pressure. It should be mentioned that the contribution of the reaction involving nonactivated reactants to the total rate is usually much lower than 1% because of the high acceleration effect ( $k_{\text{cat}}/k_{\text{noncat}}$ ) and a high strength of the dienophile complexes with the Lewis acid. If the bond of dienophile with the Lewis acid becomes stronger under elevated pressure, the increase in the reaction rate is caused not only by the contribution  $P\Delta V^\ddagger$  (as in the reaction without a Lewis acid) but additionally by an increase in the reactivity of the dienophile in the  $n, \nu$ -complex with pressure. It follows from Eqs (5) and (6) that if the bond energy in the  $n, \nu$ -complex increases by 1.0 kJ mol<sup>-1</sup> only at an external pressure of 1000 bar, then the additional contribution to the change in the catalyzed reaction rate under pressure ( $\ln(k_{\text{cat},p=1000}/k_{\text{cat},p=1})$ ) is equivalent to the additional decrease in the activation volume by 5 cm<sup>3</sup> mol<sup>-1</sup>. Modern barostats with direct monitoring the reaction rate under pressure allow one to determine the activation volume with the inaccuracy not higher than  $\pm 1$  cm<sup>3</sup> mol<sup>-1</sup>.<sup>22,38,138</sup> Results of such measurements can serve as an experimental basis for discussion of the problem about the change in or retention of the character of bonds in the activated complex of the reaction under elevated external pressure. The study of the catalyzed reaction rates in a medium of  $p$ -donor solvents (for example, acetonitrile, diethyl ether) is related to serious problems in interpretation of the obtained results because of the catalyst redistribution between these  $p$ -donor solvents and dienophiles. It has recently been shown<sup>154,155</sup> that the addi-

tion of only 0.5% (vol/vol) of dibutyl ether to 1,2-dichloroethane almost completely suppresses the effect of acceleration by aluminum chloride of the reaction between 9,10-dimethylantracene and maleic anhydride, because almost all the catalyst is bound in a complex with ether.

The pressure effect on the DAR rate in toluene was also studied<sup>148,156,157</sup> for the reaction of 9-methylantracene (**21**) with acrylonitrile in the  $n, \nu$ -complex with gallium chloride (**22**) (Scheme 4).

Scheme 4



The calculated activation volume of the catalyzed reaction was  $-16.9 \pm 1.0$  cm<sup>3</sup> mol<sup>-1</sup>.<sup>148</sup> The activation volume of the noncatalyzed reaction of acrylonitrile and 9,10-dimethylantracene is  $-18.0 \pm 1.0$  cm<sup>3</sup> mol<sup>-1</sup>.<sup>158</sup> Close values of the activation volumes of the usual and catalyzed processes suggest that an increase in the pressure to 1 kbar does not enhance the strength of the bond in the  $n, \nu$ -complex of dienophile with gallium chloride. These data can be considered as an experimental confirmation that the character of bonds in the transition state of the reaction under elevated pressure remains unchanged or changes insignificantly at least when the pressure increase to 1000 bar. The equal activation volumes correspond to the absence of electrostriction of the solvent, which excludes the polar type of the transition state in the catalytic process.

A large array of data on the pressure effect on the rate of polar reactions is available.<sup>37–40,159,160</sup> A considerable influence of the medium on the change in the activation volume for reactions with the polar transition state is explained by high differences in baric permittivity and compressibility coefficients.<sup>39,40</sup> Since the properties of the solvent always change with pressure, it is desirable to have independent information about the influence of electrostriction on the values of partial molar volumes under normal pressure for a polar or ionic model compound.

### "Forbidden" reactions under elevated pressure

It is interesting to study the influence of high hydrostatic pressure on the rate, equilibrium, and properties of

molecules from the viewpoint of more detailed understanding of the reason for the effects observed and also for the practical application in synthesis of poorly available compounds. In the applied aspect, the extent of increasing the reaction rate and equilibrium under elevated pressure is important rather than the reason for the formation of the negative values of activation and reaction volumes. A large massive of data on the successful use of elevated pressure in synthesis of various poorly available products has been accumulated.<sup>22,36,161</sup> A classical example (Scheme 5) is the synthesis of cantharidin (**31**), which is actively used for the treatment of non-malignant tumors.<sup>162</sup> The seemingly simple scheme of its synthesis *via* the DAR between furan (**24**) and dimethylmaleic anhydride (**25**) with the formation of *exo*-adduct **26** followed by hydrogenation cannot be performed in practice without applying high pressure.

The reason is that the rate of formation of adducts **26** and **27** is very low ( $<10^{-10}$  L mol<sup>-1</sup> s<sup>-1</sup> at 25 °C).<sup>90</sup> Classical approaches for enhancing reactivity are inappropriate because of equilibrium shifting towards the starting compounds at elevated temperature and because of easy furan polymerization in the presence of Lewis acids. Cantharidin (**31**) was obtained in low yield only under a pressure of ~40 kbar, when both the rate and equilibrium constants of this reaction increase noticeably.<sup>161</sup> A more convenient method for the synthesis of cantharidin *via* the DAR between furan and strained bicyclic dienophile **28** was then found. Increased strain of the endocyclic double bond in bicyclic dienophiles always results in a sharp increase in

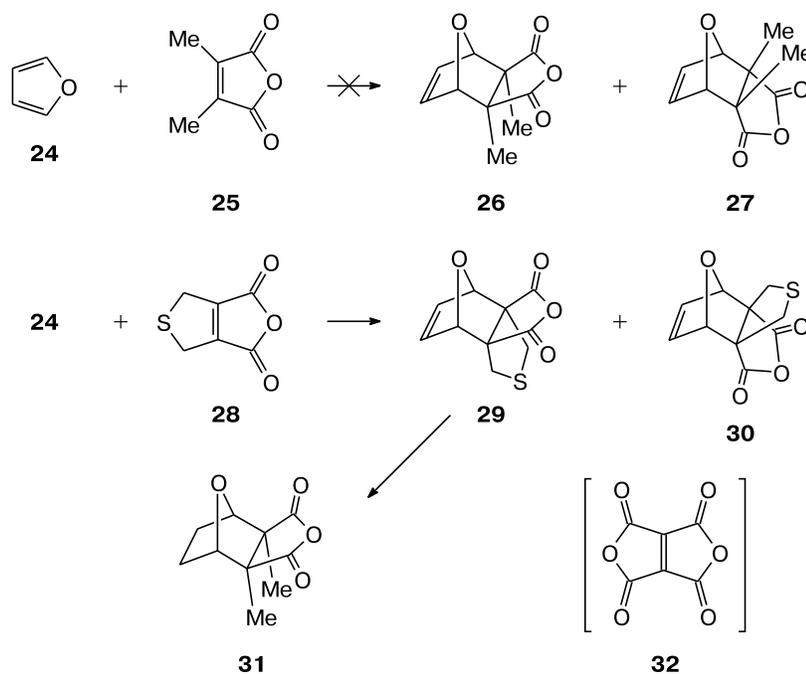
its reactivity in full accord with Eq. (1). For this reason it is impossible to isolate ethylenetetracarboxylic dianhydride (**32**) in the free state, whereas its stable adducts with a number of dienes are formed rather readily.<sup>163,164</sup> Therefore, the rate of reaction **24** + **28** → **29** and stability of product **29** turned out to be rather appropriate for the synthesis of cantharidin (**31**) under milder conditions.<sup>165</sup>

### Naphthalene and thiophene in the Diels–Alder reaction

Equation (1) makes it possible to estimate the rate of accessible and almost inaccessible examples of DARs involving anthracene (**13**), benzene (**33**), naphthalene (**34**), and thiophene (**35**) from the data on *IP* for diene,  $E_A$  for dienophile, and diene geometry ( $R_{C(1)-C(4)}$ ), as well as the data on the heat of hydrogenation calculated from the data on the heat of diene formation (Table 8).

The ionization potentials<sup>167</sup> of dienes **13** (7.45 eV), **33** (9.246 eV), **34** (8.14 eV), and **35** (8.87 eV) and energies of electron affinity<sup>35</sup> for dienophiles **4a** (0.89 eV), **5a** (0.97 eV), and **7** (2.88 eV) are known. The C(1)–C(4) interatomic distance in dienes **33** and **34** and the C(9)–C(10) distance in diene **13** is 2.81 Å, whereas the C(2)–C(5) distance in thiophene (**35**) is 2.52 Å.<sup>167</sup> The values of heats of hydrogenation calculated from the data on the heat of formation in the gas phase of dienes **13** and **33**–**35** and their dihydro derivatives are<sup>168</sup>  $-71 \pm 4$ ,  $+23 \pm 4$ ,  $-8 \pm 4$ , and  $-28 \pm 4$  kJ mol<sup>-1</sup> for compounds **13** and **33**–**35**, respectively. The heat effects of the DAR in 1,4-dioxane of anthracene **13** and dienophiles are also known<sup>35</sup>:  $-106$ ,

Scheme 5



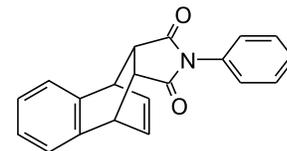
**Table 8.** Calculated parameters of the Diels–Alder reaction for anthracene (**13**), benzene (**33**), naphthalene (**34**), and thiophene (**35**) with *N*-phenylmaleinimide (**4a**), maleic anhydride (**5a**), and tetracyanoethylene (**7**): the enthalpies of the reaction ( $\Delta H_{\text{react}}$ ), rate ( $k_2$ ) and equilibrium ( $K_{\text{eq}}$ ) constants, half-reaction time ( $\tau_{0.5}$ ), and equilibrium conversion ( $\alpha_{\text{eq}}$ ) at 25 °C<sup>166</sup>

Diene	Dienophile	$\Delta H_{\text{react}}/\text{kJ mol}^{-1}$	$\log(k_2/\text{L mol}^{-1} \text{s}^{-1})$	$\tau_{0.5}/\text{s}$	$\log(K_{\text{eq}}/\text{L mol}^{-1})$	$\alpha_{\text{eq}}(\%)$
<b>13</b>	<b>4a</b>	−106	−5.14	$2.0 \cdot 10^4$	+10.5±1.0	>99.9
<b>13</b>	<b>5a</b>	−93	−5.22	$2.3 \cdot 10^4$	+8.3±1.0	>99.9
<b>13</b>	<b>7</b>	−77	0.48	0.05	+5.5±1.0	>99.9
<b>33</b>	<b>4a</b>	−12±4	−13.7±0.9	$7 \cdot 10^{12}$	−5.6±1.0	$(1-3) \cdot 10^{-3}$
<b>33</b>	<b>5a</b>	+1±4	−13.9±0.9	$1 \cdot 10^{13}$	−7.9±1.0	$6 \cdot 10^{-(6\pm0.5)}$
<b>33</b>	<b>7</b>	+17±4	−10.8±0.9	$9 \cdot 10^9$	−10.7±1.0	$1 \cdot 10^{-(8\pm1)}$
<b>34</b>	<b>4a</b>	−43±4	−9.9±0.9	$1 \cdot 10^9$	−0.3±1.0	70±20
<b>34</b>	<b>5a</b>	−30±4	−10.4±0.9	$3.5 \cdot 10^9$	−2.5±1.0	4±2
<b>34</b>	<b>7</b>	−14±4	−5.2±0.9	$2 \cdot 10^4$	−5.3±1.0	$2 \cdot 10^{-(3\pm0.5)}$
<b>35</b>	<b>4a</b>	−63±4	−7.8±0.9	$8.7 \cdot 10^6$	+3.2±1.0	99.0–99.9
<b>35</b>	<b>5a</b>	−50±4	−8.4±0.9	$3.5 \cdot 10^7$	+0.9±1.0	90–99
<b>35</b>	<b>7</b>	−34±4	−3.6±0.9	690	−1.9±1.0	1.4±2

−93, and −77 kJ mol<sup>−1</sup> for reactions **13** + **4a**, **13** + **5a**, and **13** + **7**, respectively. A comparison of the values of heats of hydrogenation and of the reaction in 1,4-dioxane involving anthracene makes it possible to calculate the heats of the reactions of dienophiles **7**, **5a**, and **4a** with benzene (+17±4, +1±4, and −12±4 kJ mol<sup>−1</sup>, respectively), naphthalene (−14±4, −30±4, and −43±4 kJ mol<sup>−1</sup>, respectively), and thiophene (−34±4, −50±4, and −63±4 kJ mol<sup>−1</sup>, respectively). Accepting that the values of entropy of these DARs are the same and equal to −150 J mol<sup>−1</sup> K<sup>−1</sup>, one can estimate the equilibrium constants ( $K_{\text{eq}}$ ) (see Table 8).<sup>35</sup> The half reaction time ( $\tau_{0.5}$ ) was calculated for the reactants with the initial concentrations 0.5 and 5 mol L<sup>−1</sup>. The maximum conversion of the reactant with the initial concentration 0.5 mol L<sup>−1</sup> was also calculated for these concentrations.

It follows from the data obtained (see Table 8) that the reactions of these dienophiles with benzene are impossible for kinetic and thermodynamic reasons, since the half reaction time of the reactants is more than 300 years and the equilibrium concentration of the adduct is lower than 10<sup>−3</sup>%. The actually high yield of the adduct should be

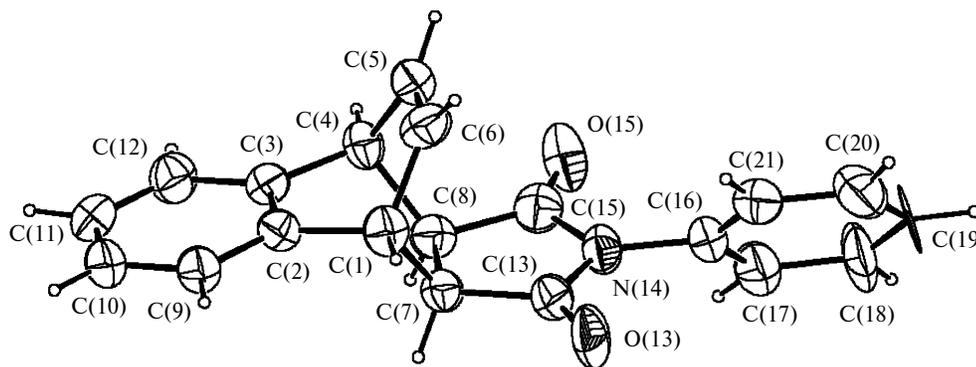
expected in the reaction of naphthalene (**34**) and *N*-phenylmaleinimide (**4a**). This reaction does not occur at normal temperature and pressure because of the very low rate ( $\tau_{1/2} \approx 30$  years), but in the presence of gallium chloride is occurs successfully within a week at ambient temperature.<sup>169</sup> The reaction of naphthalene with maleic anhydride at 100 °C and under 12 kbar in chloroform gave two adducts with m.p. 161 and 172 °C (both with decomposition) assigned to the *endo*- and *exo*-isomers, respectively, according to the <sup>1</sup>H and <sup>13</sup>C NMR spectral data.<sup>162</sup> Catalyzed reaction



**36**

**34** + **4a** at ambient temperature and under normal pressure afforded<sup>169,170</sup> only one adduct with m.p. 206–208 °C (decomp.), which corresponds, according to the X-ray diffraction data (Fig. 4), to *exo*-isomer **36**. Under more drastic conditions<sup>170</sup> (8 kbar, 100 °C, 80 h), reaction **34** + **4a** gives a mixture of *exo*- and *endo*-isomers in a ratio of 3 : 7.

It can be expected that the adducts of the DARs involving thiophene would exhibit high biological activity



**Fig. 4.** ORTEP structure of *exo*-adduct **36** of naphthalene with *N*-phenylmaleinimide.

similarly to cantharidin (**31**) and other DAR adducts involving furan.<sup>171</sup> It is known<sup>6</sup> that thiophene cannot be introduced into the DAR. It is noteworthy that the conjugation energy in thiophene is noticeably lower than those in benzene and naphthalene and its conversion should expectedly be high (see Table 8). At equal concentrations of the reactants ( $c_{35} = c_{5a} = c_{4a} = 0.1 \text{ mol L}^{-1}$ ) at 25 °C the half reaction time is ~30–60 years. Raising the temperature increases the reaction rate but decreases the equilibrium constant and conversion. Similarly to the reaction with naphthalene, a sharp increase in the reactivity of dienophile in an  $n,\nu$ -complex with a Lewis acid could solve the problem. However, if diene also forms an  $n,\nu$ -complex with a Lewis acid, its  $\pi$ -donor properties decrease considerably, due to which the rate of the reaction with  $\pi$ -acceptor dienophiles is usually retarded.<sup>35</sup> The possibility of gallium chloride redistribution between reactants **5a** and **35** was testified. The calorimetric measurements showed<sup>166</sup> a strong exothermic effect ( $-100 \pm 6 \text{ kJ mol}^{-1}$ ) and the formation of a polymer product upon the dissolution of gallium chloride in a solution of thiophene in toluene. Unlike the reaction with naphthalene (**34**), which forms no strong complex with gallium chloride, the catalyzed reactions of dienophiles **4a** and **5a** with thiophene and 2,5-dimethylthiophene did not occur because of polymerization and Lewis acid redistribution between the complexes with diene and dienophile. Under conditions of high pressure, the rate and equilibrium constants of the DAR usually increase and, hence, the reaction can be carried out at elevated temperature.<sup>35,162,166,170–175</sup> In this case, the total acceleration of the reaction is determined by the product of both effects ( $k_{T=100}/k_{T=25} \cdot (k_{P=8000}/k_{P=1})$ ) and can be 4–5 orders of magnitude, and the decrease in the equilibrium constant with the temperature rise to ~100 °C is completely compensated by its increase with the pressure increase to ~8 kbar. It is clear that the maximum favorable condition for the reaction is the use of high concentrations of reactants, *i.e.*, the reaction of maleic anhydride with thiophene without a solvent. The X-ray diffraction data for the isolated crystals confirm the formation of *exo*-adduct **37** (Fig. 5) in 25% yield.

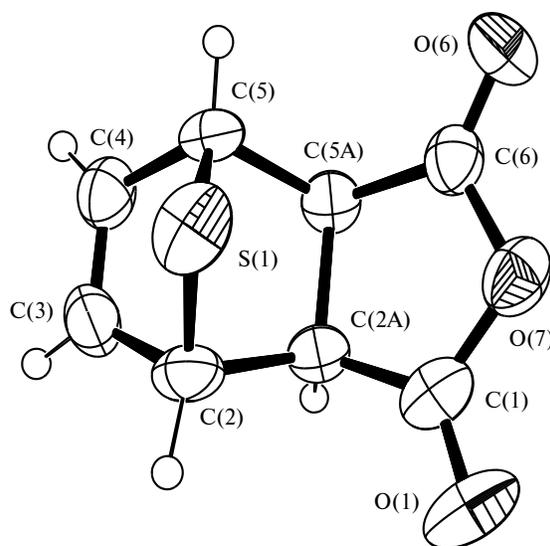
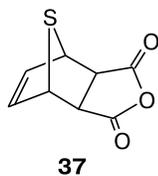


Fig. 5. ORTEP structure of *exo*-adduct **37** of thiophene with maleic anhydride.

lish a series of regularities that control the rate and equilibrium of the normal and catalyzed processes under standard and nonstandard conditions. The regularities observed allow deeper understanding of specific features of other processes in organic chemistry to be achieved.

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