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Reviews

Diels—Alder reaction Effect of internal and external factors on the reactivity of diene—dienophile systems*

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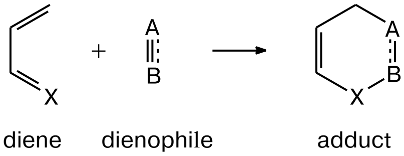
The key factors influencing the Diels—Alder reaction rate at ambient and elevated pressures were elucidated using data on the reactivity of various diene—dienophile systems in usual and Lewis acid-catalyzed Diels—Alder reactions, the reaction enthalpy, complex formation, dissolution, and solvation, and the donor-acceptor properties of the reactants. It was found that taking account of both the orbital interaction energy and the balance of bond rupture and formation energies allows correct prediction of the reaction rate in the absence or in the presence of Lewis acids.

Key words: Diels—Alder reaction, kinetics, catalysis, reaction enthalpy, molecular complexes, activation volumes, reaction volumes.

A key place in organic chemistry is occupied by diene synthesis or the [4+2] cycloaddition in which dienes react with dienophiles to give unsaturated six-membered carbo- and heterocycles (Scheme 1).

This reaction underlies the synthesis of diverse carbo- and heterocyclic compounds (including natural products),

Scheme 1



A, B, X are carbon atoms or heteroatoms

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* The paper is dedicated to the 75-year anniversary of the Diels—Alder reaction.

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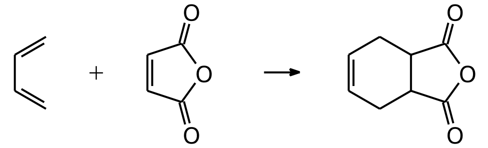
drugs and new types of polymers,[1—3] whose synthesis by other methods is usually difficult or impossible. Considerable attention is devoted to the mechanisms of the Diels—Alder reaction.

The formation of cyclohexene derivatives upon isoprene dimerization under pressure was first suggested by V. N. Ipatiev (1887) and proved by E. E. Wagner (1894); cyclic dimerization of butadiene follows the same route.[1]

The general character of this reaction was established in 1928 by O. Diels and K. Alder, who showed[4] that diene synthesis can proceed not only as cyclodimerization. Butadiene (**1**) reacts with maleic anhydride (**2**) even at room temperature to give adduct **3** in a high yield (Scheme 2).

Scheme 2



1 **2** **3**

Either open or cyclic 1,3-conjugated systems containing a C=C—C=C fragment can be used as dienes, for example, butadiene, cyclopentadiene, anthracene or furan derivatives. Later, the range of 1,3-dienes has markedly extended by covering also heterodienes containing heteroatoms such as O, N, P, S, Se. Dienophiles can be represented by ethylene or acetylene derivatives as well as unsaturated heteroatomic systems containing C=O, C=N, S=O, N=N, N=O, C=S, C=Se, and C=P fragments. Thus it can be seen that cross-combination of dienes with dienophiles can give an enormous number of products.

During the last decade, the Diels—Alder reaction has been studied by chemists in many countries. Among the numerous scientific centers, research groups headed by Sauer,[5—8] Klarner,[9,10] Houk,[11,12] and Sustmann[13,14] can be distinguished.

In most cases, no side reactions are involved; thus, it is possible to obtain reliable quantitative data on the rates of usual and catalyzed processes, equilibria, reaction heats, and the dependence of these characteristics on the properties of substituents, catalysts, solvents, and pressure increase.[15—20] A great body of data on the regio- and stereoselectivity and on the product structures has been accumulated;[21—32] procedures for the preparation of Diels—Alder polyadducts have been developed.[33—39] This review deals with the factors that control the reaction rate, route, and equilibrium in the absence or in the presence of catalysts under ambient and elevated pressures.

1. General views on the Diels—Alder reaction mechanism

The mechanism of the Diels—Alder reaction has been actively discussed for many years, because of the extensive opportunities of experimental verification of any of its versions. R. Woodward and R. Hoffmann have shown[40] that the orbital symmetry is retained in this process on passing from the reactants to the activated complex and then to the adduct. Fukui and coworkers[41] introduced the notion of stabilization energy resulting from interaction of the frontier orbitals. Unlike many organic reactions that are charge-controlled, the Diels—Alder reaction proceeds under orbital control.

Currently, all three variants of the controlling interactions of the frontier orbitals are considered to be possible[14] (Fig. 1).

In the most common version of the reaction (a donor type diene and an acceptor type dienophile, see Fig. 1), the predominant type of interaction is that between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The opposite variant of the controlling interaction between the frontier orbitals (an acceptor type diene and a donor type dienophile, see Fig. 1) was found experimentally[42] in a study of the reactivity of dienophiles toward perchlorocyclopentadiene.

The possibility of intermediate, or "neutral" variant (see Fig. 1, *B*) was first demonstrated experimentally by

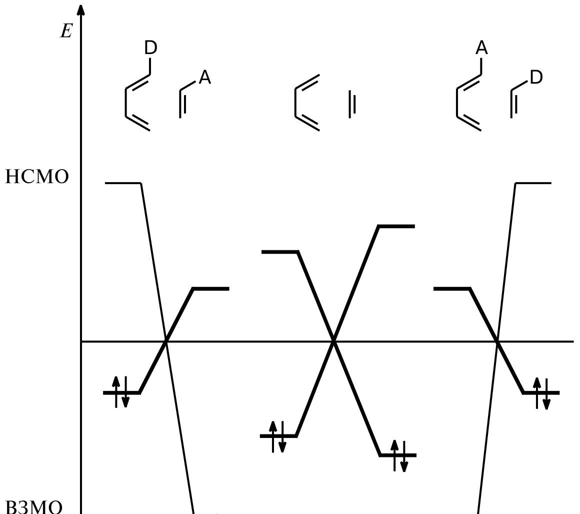


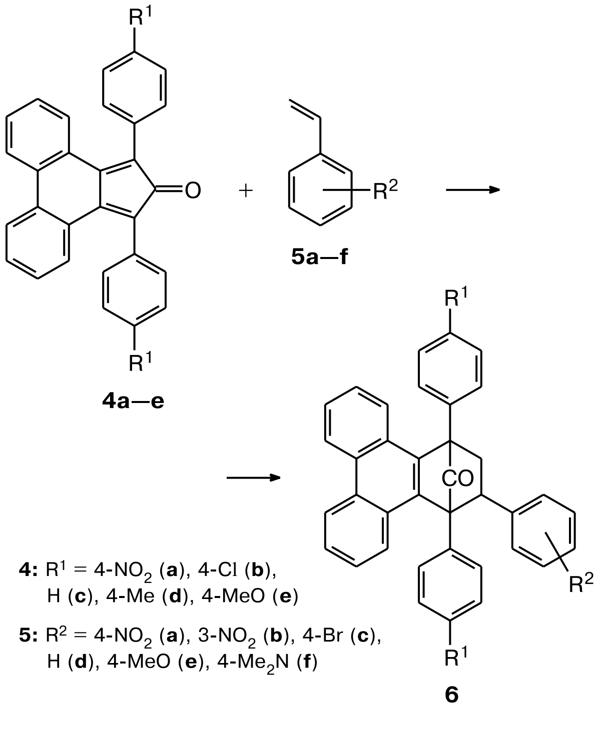
Fig. 1. Three variants of controlling interactions of frontier orbitals in the Diels—Alder reaction: *A* is interaction of a donor diene with a acceptor dienophile, *B* is neutral orbital interaction, *C* is interaction between an acceptor diene and a donor dienophile.

Table 1. Rate constants ($k_2 \cdot 10^3$/L mol^{-1} s^{-1}) of the Diels—Alder reactions of substituted phencyclones **4a—e** with substituted styrenes **5a—f** in toluene at 40 °C [43,44]

Diene	Dienophile					
	5a	**5b**	**5c**	**5d**	**5e**	**5f**
4a	6.12	4.52	8.15	9.40	40.1	710.0
4b	11.70	7.00	8.70	6.00	18.5	112.0
4c	18.20	7.90	7.50	4.40	12.4	74.8
4d	22.00	11.20	9.45	4.10	13.3	45.4
4e	23.20	9.30	7.40	4.60	12.0	54.8

A. I. Konovalov in relation to Diels—Alder reactions involving phencyclones, tetracyclones, and acecyclones.[43—45] The Diels—Alder reactions between substituted phencyclones **4a—e** and substituted styrenes **5a—f** (Scheme 3) were used to embody all three variants of controlling orbital interactions (Table 1). All reactions of substituted styrenes with each substituted phencyclone displayed a neutral type of orbital interactions where electron-donating and electron-withdrawing substituents in styrene both accelerate the reaction (see Table 1).

Scheme 3

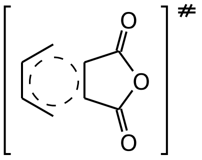


4: R^1 = 4-NO_2 (**a**), 4-Cl (**b**), H (**c**), 4-Me (**d**), 4-MeO (**e**)

5: R^2 = 4-NO_2 (**a**), 3-NO_2 (**b**), 4-Br (**c**), H (**d**), 4-MeO (**e**), 4-Me_2N (**f**)

The rate of reactions of the substituted cyclones **4a—e** with a stronger π-donor, styrene **5f**, is controlled by the interaction of the HOMO of dienophile **5f** with the LUMO of dienes **4a—e**, while in the reaction with a weaker π-donor, styrene **5a**, the interaction between the dienophile LUMO and diene HOMO becomes controlling.[43,44] Recently, the possibility of existence of all three types of controlling interactions between frontier orbitals was also demonstrated for the Diels—Alder reactions between a number of dienes and substituted thioketones (reaction at the C=S bond).[8]

The development of the views on the Diels—Alder reaction mechanism, which is based on extensive experimental material, has been discussed in detail in monographs and reviews.[1—3,5,15—20] Currently, the Diels—Alder reaction is considered to proceed with retention of the orbital symmetry[40,41] on passing to the cyclic activated complex of type **7** and with simultaneous formation of new bonds (one-step process).



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According to the view of concerted consecutive (asymmetric) formation of bonds in the activated complex, the formation of the first and second bonds is somewhat separated in time; in addition, the first bond is formed only provided that the system is ready for closure of the second bond, which rules out the existence of a long-lived intermediate. This two-step mechanism should be expected in most of reactions involving heteroatomic unsaturated compounds because the energies of the incoming bonds are different.[46] The mechanism of concerted cleavage and formation of bonds in the Diels—Alder reaction is confirmed by the retained orientation of the reactant substituents on passing to the adduct (stereospecificity of the addition).[47]

A radical or polar activated complex is currently considered less probable due to the lack of direct experimental evidence.

2. Factors determining the rate of the Diels—Alder reaction

2.1. Effect of the orbital interaction

Orbital interactions responsible for the formation of π,π-molecular complexes[48] make a considerable stabilizing contribution to the formation of the activation barrier in the Diels—Alder reaction. The relations for calculation of the stabilization energy related to orbital interactions proposed in a number of publications[41,48—50] include, as the major component, the difference between the donor HOMO and the acceptor LUMO, $\beta^2/(\varepsilon_D - \varepsilon_A)$, where β is the overlap integral of the reacting p-orbitals. The use of these approaches provides a qualitative explanation for all three variants of orbital interaction (see Fig. 1).

However, neither the principle of orbital symmetry retention[40] nor the controlling interaction of the frontier orbitals[41] allow one to predict the reactivity of particular diene—dienophile systems and to explain numerous substantial abnormal features in the dependence of the reaction rate on the energy of donor—acceptor interaction. It is clear that the stabilization energy characterizes only the decrease in the activation barrier caused by the orbital interaction between the reacting species but not the height of the activation barrier itself. With the assumption that the predominant contribution of the orbital interaction $\beta^2/(\varepsilon_D - \varepsilon_A)$ to the stabilization energy can be expressed by the proportional $\beta^2/(IP_D - E_A)$ value, the activation barrier can be estimated by using the available ionization potential (IP_D) of the diene and the electron affinity (E_A) of the dienophile.

Within an individual structural row of dienes or dienophiles, a rather clear correlation between the ln*k* and $(IP_D - E_A)^{-1}$ values for a constant β^2 value is often observed. The reactivity of compounds of one structural row is often controlled by the change in the orbital interaction energy, because other factors change only slightly. However, the reactivity of compounds in the Diels—Alder reaction is not entirely dictated by the stabilization energy. For example, cyclopentadiene (IP_D = 8.58 eV) and 9,10-dimethylanthracene (**8**) (IP_D = 7.04 eV) behave in different ways with respect to cyanoethylenes (Fig. 2).

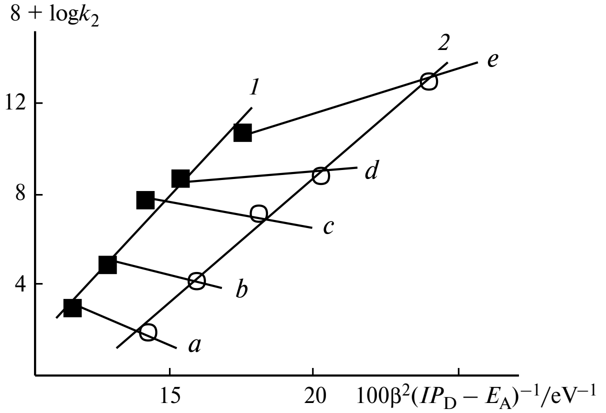


Fig. 2. Logarithm of the rate constants (k_2/L mol^{-1} s^{-1}) of the Diels—Alder reaction of cyanoethylenes with cyclopentadiene (*1*) and with 9,10-dimethylanthracene (*2*) *vs.* donor-acceptor properties of the reactants ($\beta^2(IP_D - E_A)^{-1}$): *a* is cyanoethylene, *b* is 1,2-*trans*-dicyanoethylene, *c* is 1,1-dicyanoethylene, *d* is tricyanoethylene, *e* is tetracyanoethylene.

The rates of reactions of highly electron-withdrawing dienophiles (tetracyanoethylene (**9**) and tricyanoethylene) with 9,10-dimethylanthracene are higher than those with cyclopentadiene. In the case of less electron-withdrawing dienophiles (acrylonitrile, fumarodinitrile, and maleodinitrile), the reaction rate is higher with cyclopentadiene, which is the less conjugated diene. It follows from the data of Table 2 that the kinetic activity of the reactants is not often related unambiguously to the thermodynamic stability of the products.

Table 2. Rate constants of the Diels—Alder reactions (k_2/L mol^{-1} s^{-1}), ionization potentials of dienes (IP_D/eV), electron affinity energies of dienophiles (E_A/eV), and the enthalpies of these reactions in solutions (ΔH_{react}/kJ mol^{-1}) at 25 °C

Reaction	Dienophile	Diene	8 + logk_2	IP_D	E_A	$100/(IP_D - E_A)$	$-\Delta H_{react}$
1	Tetracyanoethylene	1,3-Diphenylisobenzofuran	16.00	7.62	2.88	21.09	69
2	Tetracyanoethylene	9,10-Dimethylanthracene	12.97	7.04	2.88	24.04	88
3	Tetracyanoethylene	9-Methoxyanthracene	11.71	7.17	2.88	23.31	61
4	Tetracyanoethylene	9-Methylanthracene	11.35	7.17	2.88	23.31	85
5	Tetracyanoethylene	9,10-Dimethoxyanthracene	10.94	7.09	2.88	23.75	53
6	Tetracyanoethylene	Anthracene	8.48	7.33	2.88	22.47	77
7	Tetracyanoethylene	9-Chloroanthracene	7.74	7.39	2.88	22.17	66
8	Tetracyanoethylene	2-Methoxy-1,3-butadiene	8.47	8.62	2.88	17.42	159
9	Tetracyanoethylene	2,3-Dimethyl-1,3-butadiene	8.40	8.61	2.88	17.45	176
10	Tetracyanoethylene	*trans*-1-Phenyl-1,3-butadiene	7.81	8.16	2.88	18.94	142
11	Tetracyanoethylene	*trans*-1-Methyl-1,3-butadiene	7.23	8.61	2.88	17.45	163
12	Tetracyanoethylene	*trans,trans*-1,4-Diphenyl-1,3-butadiene	6.87	8.09	2.88	19.19	97
13	Tetracyanoethylene	2-Methyl-1,3-butadiene	6.87	8.89	2.88	16.64	166
14	Tetracyanoethylene	1,3-Butadiene	5.23	9.03	2.88	16.26	154
15	Tetracyanoethylene	Cyclopentadiene	10.63	8.58	2.88	17.54	113
16	Tetracyanoethylene	1,3-Cyclohexadiene	8.14	8.25	2.88	18.62	130
17	Tricyanoethylene	1,3-Diphenylisobenzofuran	12.00	7.62	2.10	18.12	71
18	Tricyanoethylene	9,10-Dimethylanthracene	8.77	7.04	2.10	20.24	90
19	Tricyanoethylene	Cyclopentadiene	8.68	8.58	2.10	15.43	115
20	1,1-Dicyanoethylene	1,3-Diphenylisobenzofuran	11.00	7.62	1.53	16.42	77
21	1,1-Dicyanoethylene	9,10-Dimethylanthracene	7.10	7.04	1.53	18.15	96
22	1,1-Dicyanoethylene	9-Methylanthracene	6.18	7.17	1.53	17.73	93
23	1,1-Dicyanoethylene	Anthracene	4.52	7.33	1.53	17.24	85

(*to be continued*)

Table 2 (*continued*)

Reaction	Dienophile	Diene	$8 + \log k_2$	IP_D	E_A	$100/(IP_D - E_A)$	$-\Delta H_{react}$
24	1,1-Dicyanoethylene	Cyclopentadiene	7.66	8.58	1.53	14.18	121
25	Fumarodinitrile	1,3-Diphenylisobenzofuran	7.49	7.62	0.78	14.62	82
26	Fumarodinitrile	Cyclopentadiene	4.91	8.58	0.78	12.82	126
27	Fumarodinitrile	9,10-Dimethylanthracene	4.14	7.04	0.78	15.97	101
28	Fumarodinitrile	9-Methylanthracene	3.08	7.17	0.78	15.65	98
29	Fumarodinitrile	9-Methoxyanthracene	2.28	7.17	0.78	15.65	74
30	Fumarodinitrile	Anthracene	1.62	7.33	0.78	15.27	90
31	Fumarodinitrile	9,10-Dimethoxyanthracene	1.08	7.09	0.78	15.85	66
32	Acrylonitrile	1,3-Diphenylisobenzofuran	5.34	7.62	0.02	13.16	87
33	Acrylonitrile	Cyclopentadiene	3.02	8.58	0.02	11.68	131
34	Acrylonitrile	9,10-Dimethylanthracene	1.95	7.04	0.02	14.24	106
35	Acrylonitrile	9-Methylanthracene	1.04	7.17	0.02	13.99	103
36	Acrylonitrile	9-Methoxyanthracene	0.70	7.17	0.02	13.99	79
37	Acrylonitrile	Anthracene	−0.07	7.33	0.02	13.68	95
38	Maleic anhydride	1,3-Diphenylisobenzofuran	8.53	7.62	0.97	15.04	85
39	Maleic anhydride	Cyclopentadiene	6.96	8.58	0.97	13.14	129
40	Maleic anhydride	9,10-Dimethylanthracene	6.09	7.04	0.97	16.47	104
41	Maleic anhydride	9-Methylanthracene	4.54	7.17	0.97	16.13	101
42	Maleic anhydride	9-Methoxyanthracene	3.45	7.17	0.97	16.13	77
43	Maleic anhydride	Anthracene	2.78	7.33	0.97	15.72	93
44	Maleic anhydride	9,10-Dimethoxyanthracene	2.49	7.09	0.97	16.33	69
45	Maleic anhydride	9-Chloroanthracene	2.16	7.39	0.97	15.57	82
46	Maleic anhydride	2,3-Dimethyl-1,3-butadiene	4.53	8.61	0.97	13.09	194
47	Maleic anhydride	*trans*-1-Methyl-1,3-butadiene	4.36	8.61	0.97	13.09	179
48	Maleic anhydride	2-Methyl-1,3-butadiene	4.19	8.89	0.97	12.63	182
49	Maleic anhydride	*trans*-1-Phenyl-1,3-butadiene	4.05	8.16	0.97	13.91	158
50	Maleic anhydride	1,3-Butadiene	3.83	9.03	0.97	12.41	170
51	Maleic anhydride	*trans,trans*-1,4-Diphenyl-1,3-butadiene	2.47	8.09	0.97	14.04	113
52	Maleic anhydride	Pentacene	6.13	6.64	0.97	17.64	132
53	Maleic anhydride	Tetracene	4.88	7.01	0.97	16.55	103
54	Maleic anhydride	Hexachlorocyclopentadiene	0.06	8.96	0.97	12.56	58
55	Chloromaleic anhydride	1,3-Diphenylisobenzofuran	8.58	7.62	1.08	15.29	82
56	Chloromaleic anhydride	9,10-Dimethylanthracene	5.81	7.04	1.08	16.78	101
57	Chloromaleic anhydride	9-Methylanthracene	4.35	7.17	1.08	16.42	98
58	Chloromaleic anhydride	Anthracene	2.49	7.33	1.08	16.00	90
59	Chloromaleic anhydride	9-Chloroanthracene	1.83	7.39	1.08	15.85	79
60	Methylmaleic anhydride	9,10-Dimethylanthracene	3.38	7.04	0.83	16.10	103
61	Methylmaleic anhydride	9-Methylanthracene	1.93	7.17	0.83	15.77	100
62	*N*-(*p*-Nitrophenyl)maleimide	1,3-Diphenylisobenzofuran	9.16	7.62	1.01	15.13	96
63	*N*-(*p*-Nitrophenyl)maleimide	Pentacene	7.75	6.64	1.01	17.76	143
64	*N*-(*p*-Nitrophenyl)maleimide	Tetracene	5.96	7.01	1.01	16.67	124
65	*N*-(*p*-Nitrophenyl)maleimide	Cyclopentadiene	7.31	8.58	1.01	13.21	140
66	*N*-(*p*-Nitrophenyl)maleimide	9-Methylanthracene	5.23	7.17	1.01	16.23	112
67	*N*-(*p*-Nitrophenyl)maleimide	Anthracene	3.93	7.33	1.01	15.82	104
68	*N*-(*p*-Nitrophenyl)maleimide	9-Chloroanthracene	2.92	7.39	1.01	15.67	93
69	*N*-Phenylmaleimide	1,3-Diphenylisobenzofuran	8.57	7.62	0.89	14.86	98
70	*N*-Phenylmaleimide	Cyclopentadiene	6.94	8.58	0.89	13.00	142
71	*N*-Phenylmaleimide	9,10-Dimethylanthracene	6.48	7.04	0.89	16.26	117
72	*N*-Phenylmaleimide	9-Methylanthracene	4.71	7.17	0.89	15.92	114
73	*N*-Phenylmaleimide	9-Methoxyanthracene	3.45	7.17	0.89	15.92	90
74	*N*-Phenylmaleimide	Anthracene	2.86	7.33	0.89	15.53	106
75	*N*-Phenylmaleimide	9-Chloroanthracene	1.45	7.39	0.89	15.38	95
76	*N*-Phenylmaleimide	Pentacene	6.98	6.64	0.89	17.39	145
77	*N*-Phenylmaleimide	Tetracene	5.34	7.01	0.89	16.34	126

(*to be continued*)

Table 2 (*continued*)

Reaction	Dienophile	Diene	8 + logk_2	IP_D	E_A	100/(IP_D − E_A)	−ΔH_{react}
78	*N*-Phenylmaleimide	5,11-Dichlorotetracene	4.43	6.81	0.89	16.89	107
79	Acrolein	1,3-Diphenylisobenzofuran	5.92	7.62	0.15	13.39	78
80	Acrolein	Cyclopentadiene	3.30	8.58	0.15	11.87	122
81	Acrolein	2-Methyl-1,3-butadiene	0.70	8.89	0.15	11.44	175
82	Acrolein	1,3-Butadiene	0.00	9.03	0.15	11.26	163
83	*N*-(*p*-Nitrophenyl)maleimide	1,3-Diphenylisobenzofuran	9.22	7.62	0.99	15.08	95
84	*N*-(*p*-Bromophenyl)maleimide	1,3-Diphenylisobenzofuran	8.87	7.62	0.95	14.99	98
85	*N*-(*p*-Tolyl)maleimide	1,3-Diphenylisobenzofuran	8.56	7.62	0.83	14.73	98
86	*N*-(*p*-Methoxyphenyl)maleimide	1,3-Diphenylisobenzofuran	8.50	7.62	0.81	14.68	99
87	*N*-(*p*-Dimethylaminophenyl)-maleimide	1,3-Diphenylisobenzofuran	8.36	7.62	0.73	14.51	100
88	Maleodinitrile	1,3-Diphenylisobenzofuran	8.12	7.62	0.78	14.62	84
89	Acrylic acid	1,3-Diphenylisobenzofuran	6.18	7.62	0.09	13.28	84
90	Methyl acrylate	1,3-Diphenylisobenzofuran	5.28	7.62	0.19	13.46	85
91	Acrylic acid	Cyclopentadiene	4.77	8.58	0.09	11.78	128
92	Methyl acrylate	Cyclopentadiene	3.51	8.58	0.19	11.91	129
93	Ethylene	1,3-Butadiene	−2.70	9.03	−1.81	9.22	166

Note. The data on the reaction rate constants were taken from Refs. 6,7,15,16,25,51—57; the ionization potentials and electron affinities are from Refs. 6,11,16,48,51,54,58—62, and the reaction enthalpies are from Refs. 16,59,62—65. The enthalpies of reactions *81*, *82*, and *93* were calculated[59] from the data on the heats of formation of the reactants and the adducts.

2.2. Effect of the energy of bond cleavage and formation

In conformity with the Bell—Evans—Polanyi—Semenov principle,[66—68] the energy of bond cleavage plays an important role in the formation of the activation barrier, its "fraction" varying from 0 to 1, depending on the contribution of other factors. With the contribution of other factors remaining constant, a higher activation barrier should be expected for more conjugated systems with a high energy of bond cleavage. Since the difference between the energies of the single C—C bonds in the resulting cycloadducts is insignificant, the change in the activation energy is expected to be proportional to the reaction enthalpy. The reaction enthalpy does not necessarily control the reaction rate but it always influences the activation barrier to one or another extent.

It should be noted that all the Diels—Alder reactions are accompanied by heat evolution and the reaction heat should be greater than −40 kJ mol^{-1} to ensure the possibility of detecting at least traces of the adduct. This is due to the rather constant negative entropy of the process (−150±20 J mol^{-1} K^{-1}). Hence, the equilibrium for a less exothermic process would be shifted appreciably toward the reactants. For this reason, it is almost impossible (see below) to perform this reaction with conjugated dienes such as benzene or naphthalene.

When the energy of conjugation is sharply changed, the dependence of the reaction rate on the stabilization energy can be violated even within a single reaction series.[16] For example, due to the enhanced energy of conjugation, the exothermic effect of the Diels—Alder reaction involving 9-methoxy- or 9,10-dimethoxyanthracene is much lower than that of the reaction with 9-methyl- or 9,10-dimethylanthracene, which are comparable as regards the electron-donating properties (see Table 2). This is responsible for not only the relatively low values of the equilibrium constant but also for lower reaction rate constants.[59,62] Due to the lower energy of conjugation in the row of substituted butadienes, the exothermicity of reactions involving these compounds is much higher than that with substituted anthracenes (see Table 2). Indeed, despite the fact that the π-donor properties of anthracene (IP_D = 7.33 eV) are more pronounced than those of 2,3-dimethylbutadiene (8.40 eV), these compounds exhibit equal reactivities toward a strong π-acceptor, tetracyanoethylene (E_A = 2.88 eV), due to the substantial difference between the enthalpies of these processes (−77 and −176 kJ mol^{-1}, respectively). On passing to a less π-acceptor dienophile, maleic anhydride (E_A = 0.97 eV), the reactivity of anthracene becomes 56 times lower than 2,3-dimethylbutadiene reactivity due to the decrease in the stabilization energy (see Table 2). The difference between the enthalpies of reactions of maleic anhydride with 2,3-dimethylbutadiene (−194 kJ mol^{-1}), *trans*-1-phenylbutadiene (−158 kJ mol^{-1}), and especially *trans,trans*-1,4-diphenylbutadiene (−113 kJ mol^{-1}) is so pronounced that the direction of the change in the reaction rate cannot be predicted based on the orbital properties of the reactants alone; the contributions of bond cleavage and formation energies should also be taken into account (Fig. 3).

Analysis of the whole set of data listed in Table 2 reveals quite a few "violations" of this type. Thus, the usual and "abnormal" patterns of variation of the reactiv-

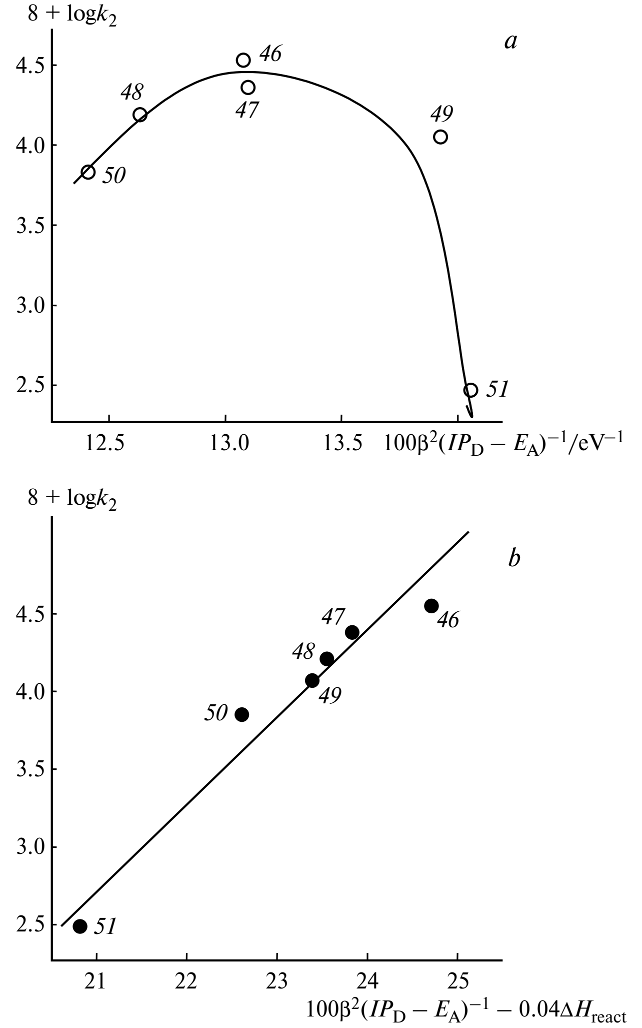


Fig. 3. Logarithm of the rate constants (k_2/L mol^{-1} s^{-1}) of the Diels—Alder reaction of substituted butadienes with maleic anhydride *vs.* donor-acceptor properties of the reactants (($IP_D - E_A$)$^{-1}$/eV^{-1}) without (*a*) and with allowance (*b*) for the reaction enthalpy (ΔH_{react}/kJ mol^{-1}). The numbering of points corresponds to that in Table 2.

ity of compounds of various classes in the Diels—Alder reaction become understandable upon combined consideration of the effects of the intermolecular interaction energy and the reaction enthalpy; this is true not only for comparison of different reaction series but sometimes even within a single reaction series.

For predicting the rates of reactions involving different classes of reactants, it is necessary to take into account all the main factors influencing the reactivity of compounds in this process. It was proposed[16,59] to take into account three main factors, namely, (1) the energies of the diene and dienophile frontier orbitals; (2) the energy balance of bond cleavage and formation; and (3) the change in the overlap coefficients of the orbitals mainly determined by the difference in the C(1)—C(4) interatomic distances in the diene (R_{1-4}). To perform such an extended analysis, data on the enthalpies of all kinetically studied Diels—Alder reactions are required. The results of thermochemical measurements we obtained are summarized in Table 2. It should be noted that heats of the reaction for a series of dienes with any pair of dienophiles differ by an approximately constant value characterizing the difference between the π-bond energies of these dienophiles. A similar feature can be found in reactions of a series of dienophiles with any pair of dienes.[59] This allows one to calculate the heat of reaction between reactants from the heats of other reactions involving each of these reactants.

2.3. Effect of the diene structure

No correlation between the logk_2 and ($IP_D - E_A$)$^{-1}$ values can be followed for the whole array of reactions (see Table 2) between dienes and dienophiles of different structural classes whose rates can differ by almost 20 orders of magnitude.[16,59] If difference between the bond cleavage and formation energies during these reactions, which is determined by the difference between the reaction heats, is additionally taken into account, the whole array of kinetic data (see Table 2) splits into three separate linear dependences (Fig. 4).

It can be noticed that enhanced reactivity of dienophiles is observed in reactions with furan derivatives (see Fig. 4). The interatomic distance (R_{1-4} = 2.19 Å) in furan is shorter than in cyclopentadiene (2.36 Å), anthracene (2.81 Å), or *s-cis*-1,3-butadiene (2.90 Å). With equal values of the 125.7/($IP_D - E_A$) – 0.052ΔH_{react} parameter, the rate constants for the reactions with furan

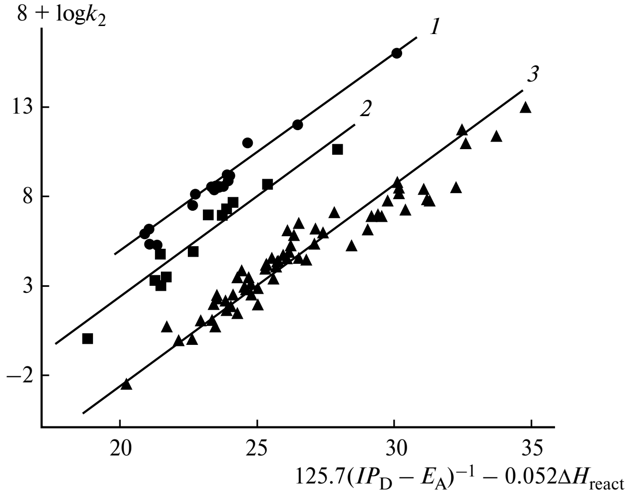


Fig. 4. Logarithm of the rate constants (k_2/L mol^{-1} s^{-1}) of the Diels—Alder reactions of dienophiles with furan (*1*), cyclopentadiene (*2*), anthracene, and butadiene (*3*) derivatives *vs.* donor-acceptor properties of the reactants (($IP_D - E_A$)$^{-1}$/eV^{-1}) and the reaction enthalpy (ΔH_{react}/kJ mol^{-1}) (according to the data of Table 2).

derivatives are two orders of magnitude greater than those with cyclopentadiene derivatives and six to seven orders of magnitude greater than those with anthracene or butadiene derivatives (see Fig. 4). It was shown[13] that an increase in the interatomic distance in the diene (R_{1-4}) entails a linear ($r = 0.999$) decrease in the squared overlap coefficient (β^2) of the reacting p-orbitals

$$\beta^2 = a - bR_{1-4}. \qquad (1)$$

Therefore, the contribution of the stabilization energy with allowance for the diene structure can be expressed by the relation

$$\beta^2/(IP_D - E_A) = a/(IP_D - E_A) - bR_{1-4}/(IP_D - E_A). \qquad (2)$$

Taking account simultaneously of three factors gave (Fig. 5) a general correlation ($r = 0.972$, $N = 93$, $s_0 = 0.9$) for the whole array of reactions

$$\log k_2 = -28.81 + 316.3/(IP_D - E_A) - {} - 69.9R_{1-4}/(IP_D - E_A) - 0.054\Delta H_{\text{react}}, \qquad (3)$$

where the IP_D and E_A values are expressed in eV, R_{1-4} are in Å, and ΔH_{react} are in kJ mol^{-1}.

The influence of the change in enthalpy on the rate ($\log k_2$) of the Diels—Alder reaction (see Fig. 5, Eq. (3)) is commensurable with the contribution of the change in the overlap coefficients of the corresponding reactant orbitals, each of these contributions being twice smaller than the contribution of the difference between the $(IP_D - E_A)^{-1}$ values.

The discovered features allow one to interpret the appearance of usual and "abnormal" relationships between the reactivity and the selectivity and the differences in the ratios of the kinetic activity and thermodynamic stability; to choose deliberately the reactants and conditions needed to prepare particular products, especially when competing processes are involved; and to predict the rates of Diels—Alder reactions between various dienes and dienophiles not yet performed experimentally. For example, it becomes clear that the yield of the adduct formed in the reaction between 9,10-dimethoxyanthracene and tetracyanoethylene cannot be increased by raising the reaction temperature. For the Diels—Alder reaction between benzene and maleic anhydride, relation (3) can be used to estimate the rate constant (~10^{-13} L mol^{-1} s^{-1}) and the equilibrium constant (~10^{-3} L mol^{-1}) at 25 °C. Under ambient conditions, according to the kinetic requirements, the half reaction time for maleic anhydride in benzene equals $>20 \cdot 10^3$ years, and according to thermodynamic requirements, the degree of dienophile conversion cannot exceed 0.1—1.0%.

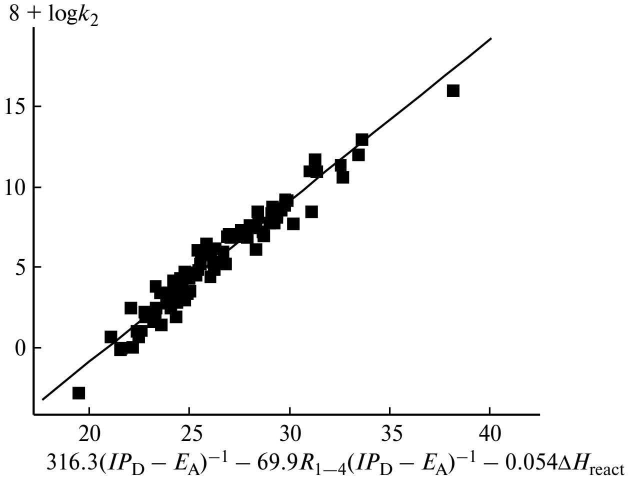


Fig. 5. Logarithm of the rate constants (k_2/L mol^{-1} s^{-1}) of the Diels—Alder reactions *vs.* donor-acceptor properties of the reactants ($(IP_D - E_A)^{-1}$/eV^{-1}), interatomic distance in the dienes (R_{1-4}/Å), and the reaction enthalpies (ΔH_{react}/kJ mol^{-1}) (according to the data of Table 2).

2.4. The "abnormal" relationship between the reactivity and the selectivity

Numerous kinetic data accumulated in organic chemistry for charge-controlled reactions imply that more reactive reagents are less selective and, *vice versa*, less reactive reagents are more selective.[69] It has been shown[15,18,19] that in orbital-controlled processes, in particular, in the Diels—Alder reaction, a more reactive compound can prove to be more selective and, correspondingly, a less reactive compound can be less selective. However, in the case of a great difference between the reaction enthalpies for a particular pair of reactants, the "abnormal" relationship between the reactivity and the selectivity, caused by the controlling contribution of the orbital interaction energy, can switch to the usual one. Analysis of the factors determining the rate of the Diels—Alder reaction (Eq. (3)) shows that the "abnormal" relationship is strictly fulfilled if the following definitions are used: "more donor diene is more selective" and "more acceptor dienophile is more selective."

2.5. The role of molecular complexes in the Diels—Alder reaction

There are numerous examples confirming the formation of molecular complexes between reactants during the Diels—Alder reaction.[15,16,18–20,50,70,71] The effects of the solvent and substituents in the reactant molecules on their donor-acceptor properties induce proportional changes in the rate constant for the Diels—Alder reaction and the equilibrium constant for the formation of π,π-complexes.[51–53,70–76] However, this proportionality does not allow one to elucidate the role of molecular complexes (MC) in the reaction pattern:

$$\mathrm{D + A} \xrightleftharpoons{K_{\text{eq}}} \mathrm{MC} \xrightarrow{k_1} \mathrm{P}, \qquad (4)$$

$$\mathrm{MC} \xrightleftharpoons{K_{\text{eq}}} \mathrm{D + A} \xrightarrow{k_2} \mathrm{P}. \qquad (5)$$

It can be shown that for a large excess of one reactant (for example, $c_A >> c_D$), the observed rate constants (k_{exp}) for the above pathways are given by relations (6) and (7), respectively

$$k_{exp} = k_1K_{eq}/(1 + K_{eq}c_A), \qquad (6)$$

$$k_{exp} = k_2/(1 + K_{eq}c_A). \qquad (7)$$

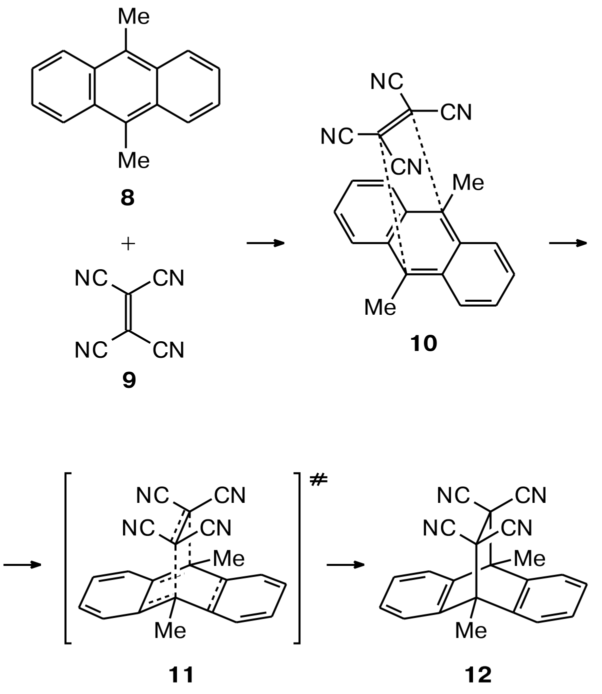
The equilibrium constants (K_{eq}) for processes involving molecular complexes calculated from the dependences of $1/k_{exp}$ on c_A (Eqs. (6) and (7)) are in good agreement with experimental data.[70] It is clear that these results also do not allow one to decide between pathways (4) and (5). Under conditions where the product $K_{eq}c_A$ is appreciably smaller than unity, the experimental values of the activation enthalpy for the two possible routes (4) and (5), respectively, are determined by the relations

$$\Delta H^{\neq}_{exp} = \Delta H^{\neq}_1 + \Delta H^0_{MC}, \qquad (8)$$

$$\Delta H^{\neq}_{exp} = \Delta H^{\neq}_2. \qquad (9)$$

For reactants able to form stable molecular complexes, the $\Delta H^{\neq}_{exp}$ can be negative only in the case of reaction along pathway (4), where $|\Delta H^0_{MC}| > \Delta H^{\neq}_1$ (Eq. (8)). In the Diels—Alder reaction between a strong π-donor, 9,10-dimethylanthracene **8** (IP_D = 7.04 eV), and a strong π-acceptor, tetracyanoethylene **9** (E_A = 2.88 eV), in a number of solvents, the reaction rate constant was found[71] to decrease with an increase in temperature; this gives negative values of the observed activation enthalpy in acetonitrile, dichloromethane, 1,2-dichloroethane, and chloroform (−5.0, −7.5, −7.9, and −11.5 kJ mol^{-1}, respectively). These results indicate that the energy of intermolecular interaction between these reactants exceeds the energy expenditure during redistribution of bonds associated with the formation of the activated complex. It is also noteworthy that this reaction does not require reorientation of the structure of molecular complex **10** for its subsequent transformation into activated complex **11** and reaction product **12** (Scheme 4).[71]

Scheme 4



8 **9** **10** **11** **12**

2.6. Solvation effects in the Diels—Alder reaction

Data on the change in the enthalpy of solvation of reactants and on the activation energy of reactions make it possible to calculate the variation in the enthalpy of solvation of the transition state in a series of solvents.[77—81] It follows from the thermodynamic cycle that the enthalpy of solvation of the transition state ($\delta H_{TS}{}^{solv}$) with respect to that in a reference solvent (S_0) is determined by the relation

$$\delta H_{TS}{}^{solv}(S/S_0) = \delta H^{\neq}(S/S_0) + \delta H_{reag}{}^{solv}(S/S_0). \qquad (10)$$

It was shown that the energy level of the transition state both in noncatalyzed[78—80] and in catalyzed[79,81] processes changes only slightly and randomly. The difference between the activation energies in the solvents studied is largely caused by the change in the energy level of the reactants.[77—81] Weakly associated solvents capable of H-bonding with a dienophile are an exception. Most of Diels—Alder reactions are somewhat accelerated in solvents like chloroform or pentachloroethane due to the enhanced stabilization of the activated complex caused by the increase in the strength of the H-bond between the H-donor solvent and the heteroatom of the activating group of the dienophile.[53]

It is of interest that the change in the enthalpy of solvation of the transition state in the series of solvents (Eq. (10)) found for the forward process coincides with the results found for the retro reaction.[16] The solvation effects involved in catalyzed reactions under normal and enhanced pressure are considered below.

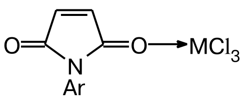
3. Characteristic and specific features of catalytic processes

3.1. Catalysis by Lewis acids

Numerous examples point to slight influence of the solvent polarity on the rate of the Diels—Alder reaction, whereas specific interactions of the reactants with the medium can markedly change the reactivity.[16,71,78,81] Hydrogen bonds usually slightly activate the dienophile. Much stronger interactions occur between dienophiles and Lewis acids. This fact has stimulated extensive research, which gave, during the last two decades, a large array of kinetic data concerning acceleration of Diels—Alder reactions and data on the enthalpy of formation of *n,v*-complexes, the enthalpy of Lewis acid-catalyzed reactions, and on the effect of the medium on the solvation of reactants, *n,v*-complexes, and the transition state.[16,34,37,79,82—93]

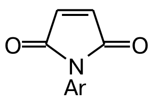
Catalysis by Lewis acids gives a new, more reactive reactant molecule representing an *n,v*-complex of the Lewis acid with the dienophile. The formation of stable *n,v*-complexes entails a sharp (by up to 10^9 times) acceleration of the reaction; thus, the reaction can be carried out with compounds that are highly inert under usual conditions. The increase in the rate of catalyzed Diels—Alder reactions of the "donor diene and acceptor dienophile" type carried out in solvents rather inert toward Lewis acids (benzene, toluene, dichloromethane, dichloroethane) was shown[82,84—93] to be approximately constant. In the case of coordination (to give 1 : 1 complexes) to $SnCl_4$, BBr_3, $GaCl_3$, $AlCl_3$, and $AlBr_3$, the rate usually increases by 1, 3, 4, 5, and 6 orders of magnitude, respectively. In reactions with inverted electronic properties of the reactants, *i.e.*, "an acceptor type diene and a donor type dienophile," the coordination of these Lewis acids to the diene also increases the reaction rate, although in this case, the acceleration is much less pronounced.[16,91,92]

The reason for the observed acceleration of the Diels—Alder reaction on passing from dienophiles to their *n,v*-complexes **13** (with $AlCl_3$) and **14** (with $GaCl_3$) has been studied.[89] It was found[89] that the energy of the maximum of the charge transfer band of the π,π-complexes formed by hexamethylbenzene, a π-donor that does not enter into the Diels—Alder reaction, and *N*-arylmaleimides activated by the formation of the *n,v*-complexes **14a—d** is much lower than that for the π,π-complex of hexamethylbenzene with nonactivated *N*-arylmaleimides **15a—d** (Table 3). For complexes with the same π-donor, the difference between the charge transfer energy corresponds to the difference between the electron affinities of the π-acceptors.[48,50]



13a—c: M = Al

14a—d: M = Ga



15a—d

Ar = *p*-Tol (**a**), Ph (**b**), *p*-BrC_6H_4 (**c**), *p*-$O_2NC_6H_4$ (**d**)

It can be seen from the data of Table 3 that the differences between the charge transfer energy ($E_3 - E_4$) of the π,π-complexes formed by hexamethylbenzene with pure maleimides **15** and with activated maleimides **14a—d** are rather substantial (0.75—1.0 eV) and virtually coincide with the change in the π,π*-transition energy ($E_1 - E_2$) in nonactivated **15a—d** and activated **14a—d** dienophiles.[89] This implies that the decrease in the energy level of the vacant orbital in maleimides **15a—d** upon their transition into complexes **14a—d** plays the crucial role in the observed change in the π,π*-transition energy ($E_1 - E_2$). Comparison of the rate of the Diels—Alder reaction and the charge transfer energy in the π,π-complexes formed by hexamethylbenzene with a series of dienophiles showed[89] a common pattern of dependence for nonactivated and activated maleimides, which is similar to the widely known dependence found for a series of cyanoethylenes (Fig. 6).

Table 3. Energies of the π→π* transitions for *N*-(*p*-RC_6H_4)maleimides **15a—d** (E_1) and their complexes with $GaCl_3$ **14a—d** (E_2), the energies of the absorption maxima for the π,π-complexes formed by hexamethylbenzene with nonactivated (E_3) and activated maleimides (E_4) and the enthalpies of formation (ΔH/kJ mol^{-1}) of complexes of maleimides with $GaCl_3$ in benzene.[89]

R	E_1	E_2	E_3	E_4	$E_1 - E_2$	$E_3 - E_4$	$-\Delta H$
	eV						
Me	4.77	3.63	3.76	2.61	1.14	1.15	57
H	4.79	3.74	3.68	2.64	1.05	1.04	55
Br	4.68	3.82	3.59	2.64	0.86	0.85	53
NO_2	4.49	3.76	3.40	2.67	0.73	0.73	48

The enthalpies of formation of *n,v*-complexes of a Lewis acid with dienophiles and with adducts were found to differ only slightly.[85] This corresponds to a slight dif-

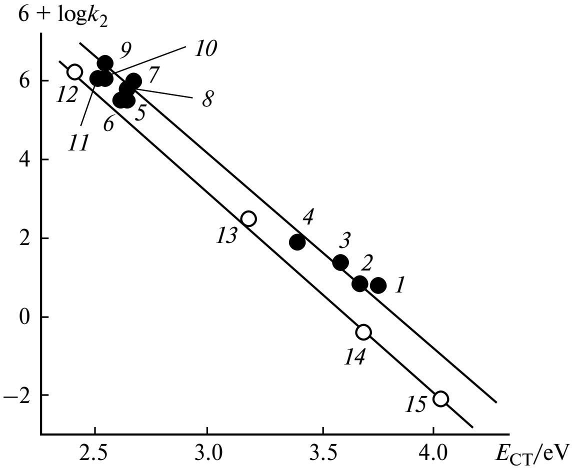
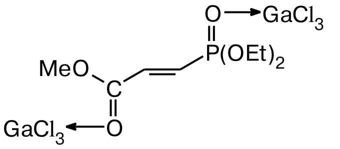


Fig. 6. Logarithm of the rate constants (k_2/L mol^{-1} s^{-1}) of the Diels—Alder reactions of anthracene with a number of dienophiles *vs.* charge transfer energy (E_{CT}) in their π-complexes with hexamethylbenzene: (*1*) *N*-(*p*-tolyl)maleimide (**15a**), (*2*) *N*-phenylmaleimide (**15b**), (*3*) *N*-(*p*-bromophenyl)maleimide (**15c**), (*4*) *N*-(*p*-nitrophenyl)maleimide (**15d**), (*5—8*) *n,v*-complexes with $GaCl_3$ **14a—d**, respectively, (*9—11*) *n,v*-complexes with $AlCl_3$ **13a—c**, respectively; (*12*) tetracyanoethylene, (*13*) 1,1-dicyanoethylene, (*14*) fumarodinitrile, (*15*) acrylonitrile.

ference between the enthalpies of usual and Lewis acid-catalyzed Diels—Alder reactions. With allowance for the change in the electron affinity (E_A) of dienophiles in catalytic processes, Eq. (3) predicts rather accurately the rate of a catalyzed process. This enables deliberate selection of the conditions for conducting the catalyzed reaction. Thus, sharp acceleration of the Diels—Alder reaction in the presence of Lewis acids is due to appreciable enhancement of the orbital interaction between the diene and the activated dienophile. It is of interest that the reaction rate for maleimide as the *n,v*-complex with $GaCl_3$ and, especially, with $AlCl_3$ is close to the reaction rate observed for the most reactive dienophile, tetracyanoethylene (see Fig. 6).

The efficiency of the Diels—Alder reaction in the presence of Lewis acids can be clearly seen by examining the rate of reaction of 9,10-dimethylanthracene, which is a π-donor, with the $GaCl_3$ complex formed by an extremely inert dienophile, *O,O*-diethyl β-methoxycarbonylvinylphosphonate (**16**).[87]



16

$\Delta H\,(1:1,\ P{=}O) = -90\ \mathrm{kJ \cdot mol^{-1}}$

$\Delta H\,(2:1,\ P{=}O,\ C{=}O) = -148\ \mathrm{kJ \cdot mol^{-1}}$

Whereas the estimated time for 50% degree of conversion in the absence of $GaCl_3$ at 25 °C is equal to 350 years, the coordination of two $GaCl_3$ molecules to the P=O and C=O groups increases the process rate by a factor of $1.9 \cdot 10^7$, the half-reaction time being less than 10 min.[87]

The enthalpies of formation of *n,v*-complexes were determined by calorimetry.[16,34,37,81,87—93] It was found[16] that the catalytic acceleration of the Diels—Alder reaction $\ln(k_{cat}/k_n)$ is proportional ($r = 0.985$) to the enthalpy of formation of the molecular complex of dienophile with the Lewis acid:

$$\ln(k_{cat}/k_n) = 0.19H_{MC}. \qquad (11)$$

Selection of an appropriate solvent is exceptionally important for a catalyzed reaction. The presence of *n*-donor additives leads to redistribution of the Lewis acid due to its binding to not only the dienophile but also to the competing *n*-donor. Thus it is possible to smoothly modify the catalytic acceleration of the reaction in the presence of Lewis acids from its maximum value to its complete suppression.[79,81,94]

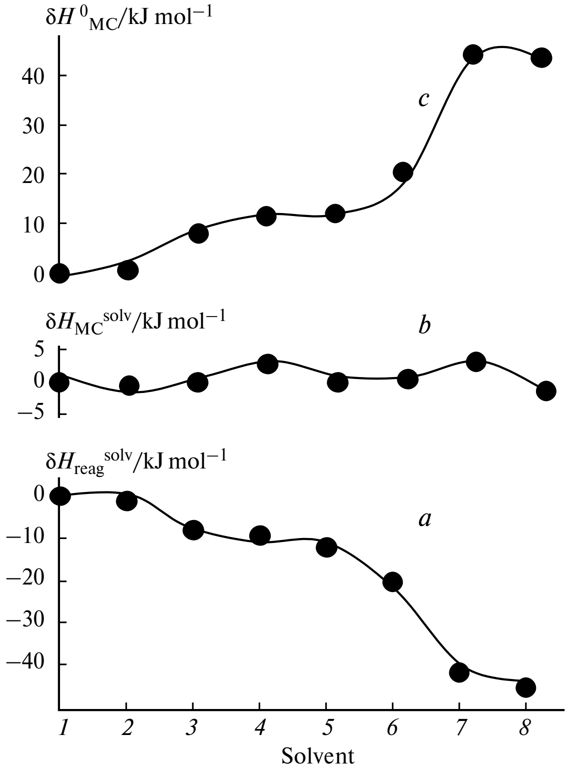


Fig. 7. Change in the enthalpy of solvation of the reactants (*N*-phenylmaleimide and $GaCl_3$) (*a*), *n,v*-complexes they form (*b*), and the enthalpy of formation of this complex (*c*) in chlorobenzene (*1*), benzene (*2*), toluene (*3*), dichloromethane (*4*), *p*-xylene (*5*), mesitylene (*6*), nitromethane (*7*), and nitrobenzene (*8*).

The data of thermochemical measurements[78] were used to determine the changes in the enthalpy of solvation of the *n,v*-complex in various solvents from the difference between the corresponding enthalpies of dissolution of maleimides (δH_{MI}^{solv}) and $GaCl_3$ (δH_{GaCl3}^{solv}) and the enthalpy of formation of the *n,v*-complex (ΔH^0_{MC}) between them in the solution:

$$\delta H_{MC}^{solv} = \Delta H^0_{MC}(S_i) - \Delta H^0_{MC}(S_0) + \delta H_{MI}^{solv} + \delta H_{GaCl_3}^{solv}. \qquad (12)$$

Despite the substantial differences between the enthalpy of dissolution and the enthalpy of formation of the *n,v*-complexes in various solvents, the enthalpies of solvation of the *n,v*-complex are close (Fig. 7).

3.2. Acceleration of the Diels—Alder reaction in the presence of lithium perchlorate

A whole series of compounds (furan and cyclopentadiene derivatives, vinyl ethers) cannot be activated by Lewis acids as they tend to polymerize and/or undergo resinification. Meanwhile, many reactions proceed much faster in a 5*M* solution of lithium perchlorate in diethyl ether,[95—99] and both the reactants and the products are stable under these conditions. Note that this is often accompanied by a decrease in the reactant solubility (salting-out effect).

A possible reason for acceleration of reactions in solutions of $LiClO_4$ might be activation of a reactant (usually dienophile) through the formation of a complex involving the heteroatom of the activating group in the dienophile and the lithium cation. However, this assumption is at variance with some data. Indeed, activation of the same dienophile substantially accelerates some Diels—Alder reactions (for example, between maleimides and cyclopentadiene or furan) and virtually does not accelerate other reactions (for example, between maleimides and substituted anthracenes or isobenzofuran).[99] Conversely, in the presence of aluminum or gallium halides, the acceleration effects are rather persistent for most Diels—Alder reactions. The acceleration observed in the presence of $GaCl_3$ for a reaction carried out in acrylonitrile or ethyl acrylate was found[99] to be $1.9 \cdot 10^4$ and $3.1 \cdot 10^4$, respectively, which virtually coincides with the acceleration in an inert solvent. However, the addition of diethyl ether or acetonitrile entails distribution of $GaCl_3$ between the n-donors due to the competing formation of n,v-complexes; consequently, the acceleration effect sharply decreases. This pattern of $GaCl_3$ distribution was confirmed by the invariability of the calculated ratio of the equilibrium constants of n,v-complexes.[99] A different type of dependence is observed in the presence of lithium perchlorate. The addition of a competing n-donor (diehyl ether) not only does not decrease the reaction rate but even increases it, as has been found in the reaction of cyclopentadiene with acrylonitrile.[99] If the mechanism of $LiClO_4$ activation was the same as with usual Lewis acids, the effect of addition of n-donor solvents would also be the same, at least, in its sign, which is not confirmed experimentally. It is noteworthy that for reversible reactions involving furan in the presence of $LiClO_4$, both rate and equilibrium constants increase, while for reactions with *C,N*-diphenylnitrone, these characteristics decrease (Table 4).[99]

It was found that, unlike the usual salting-out effect of lithium perchlorate observed for a polar compound in diethyl ether, in the case of *C,N*-diphenylnitrone, the solubility in this solvent was found to increase (salting-in effect).[99] Although the reasons for the influence of $LiClO_4$ solutions on the reaction rate and equilibrium are not entirely clear, these solutions have found wide use in organic synthesis.

Calorimetric determination of the enthalpies of dissolution of lithium perchlorate has shown[100,101] that dissolution is exothermic in all solvents, the minimum heat being observed for diethyl ether. Only for diethyl ether and nitromethane, did the heat of dissolution of the salt sharply change in the region of small concentrations. In exactly these solvents, the rates of the Diels—Alder reaction increased more appreciably in the region of small concentrations of lithium perchlorate.[101]

Table 4. Rate constants (k_2) and equilibrium constants (K_{eq}) for the reaction of furan with *N*-phenylmaleimide (reaction *I*), *C,N*-diphenylnitrone with *N*-(4-bromophenyl)maleimide (reaction *II*), and *C,N*-diphenylnitrone with *N*-phenylmaleimide (reaction *III*) in solutions of lithium perchlorate at 25 °C in various solvents[99]

Reaction	Solvent	C_{LiClO_4} /mol L^{-1}	k_2 /L mol^{-1} s^{-1}	K_{eq} /L mol^{-1}
I	Et_2O	0.00	$(6.6\pm0.3) \cdot 10^{-6}$	3.6±0.2
I	Et_2O	0.05	$(5.5\pm0.20) \cdot 10^{-5}$	25.0±1.0
I	Et_2O	4.00	$(5.3\pm0.11) \cdot 10^{-3}$	1180±30
II	Et_2O	0.00	$(6.12\pm0.30) \cdot 10^{-3}$	4500±200
II	Et_2O	3.00	—	100±3
II	Me_2CO	0.00	$(2.41\pm0.10) \cdot 10^{-3}$	2200±160
II	Me_2CO	1.00	$(1.47\pm0.10) \cdot 10^{-3}$	530±13
II	Me_2CO	3.00	$(5.80\pm0.25) \cdot 10^{-4}$	310±18
III	Et_2O	0.00	$(5.30\pm0.30) \cdot 10^{-3}$	913±13
III	Et_2O	4.00	$(5.90\pm0.25) \cdot 10^{-4}$	303±6

Analysis of accumulated data on acceleration of the Diels—Alder reaction in the presence of aluminum, gallium, and boron halides made it possible to establish an enhancement of the orbital interaction. Thus, these salts are more favorable for conducting orbital-controlled processes. In concentrated solutions of $LiClO_4$ in organic solvents, the overall effect on the rates and equilibria of various types of reaction is dictated by charge stabilization and by the difference between salting-in and salting-out of the reactants, products, and transition states.[96—99]

4. Diels—Alder reactions at elevated pressure

Any cycloaddition reaction is accompanied by a decrease in the volume on passing from the reactants to the activated complex and then to the products. The dependence of the rate and equilibrium constants of the reaction on the external pressure (p) is described by the relations

$$(\partial \ln k/\partial p)_T = -\frac{(\partial G^{\neq}/\partial p)_T}{RT} = -\frac{\Delta V^{\neq}}{RT}, \tag{13}$$

$$(\partial \ln K/\partial p)_T = -\frac{(\partial G_0/\partial p)_T}{RT} = -\frac{\Delta V_0}{RT}, \tag{14}$$

where $\Delta V^{\neq}$ and ΔV_0 are the activation and reaction volumes, respectively. Thus it follows that the rates and equilibrium constants increase when the process is carried out under an elevated hydrostatic pressure.[102,103]

4.1. Reactions without a catalyst

Study of the effect of solvation on the change in the molar volumes of the reactants, the activated complex, and the products is a key problem in elucidating the reasons for the change in the rate and equilibrium positions of the reactions under elevated pressure. The volume of a dilute solution can be represented by the relation

$$V = V_A N_A + V_S N_S + (V^*_S - V_S) n N_A, \qquad (15)$$

where V_A, V_S, and V^*_S are the molar volumes of the solute, the free solvent, and the solvent in the solvation shell; n is the number of the solvent molecules in the solvation shell; N_A and N_S are the numbers of moles of the solute and the solvent, respectively. Thus it follows that the partial molar volume of a substance (V_A) in a dilute solution is determined by the relation

$$\partial V/\partial N_A = V_A + n(V^*_S - V_S). \qquad (16)$$

In the absence of specific interactions in the solution ($V^*_S - V_S = 0$), the partial molar volume of the solute can be calculated from the data on solution density and even using an additive pattern with atom or bond increments.[104] If the interaction of the solute with the medium is significant, the additivity rule does not hold due to a large contribution of the change of the volume of the solvent as it passes to the solvation shell. In these cases, the calculated partial molar volumes are often negative.[105] Evidently, this problem is also faced for infinitely dilute solutions.

Since separate experimental determination of the $n(V^*_S - V_S)$ and V_A values is impossible, all the changes of these values are attributed to the molar volume of the solute (V_A). The experimental values of the activation or reaction volume reflect the change in the volume of the whole reacting system as it has reached the activated complex or the reaction products. Therefore, the difference between the partial molar volumes of the reactants and the products corresponds to the true reaction volume. The activation volume can be calculated only from the dependence of the reaction rate constant on the external pressure (Eq. (13)). The reaction volume can be determined from the dependence of the equilibrium constant on the external pressure (Eq. (14)) and from the difference between the partial molar volumes of the products and the reactants. This allows one to verify the presence or absence of complications in determination of the volume parameters from the dependence of the equilibrium constant on the external pressure.

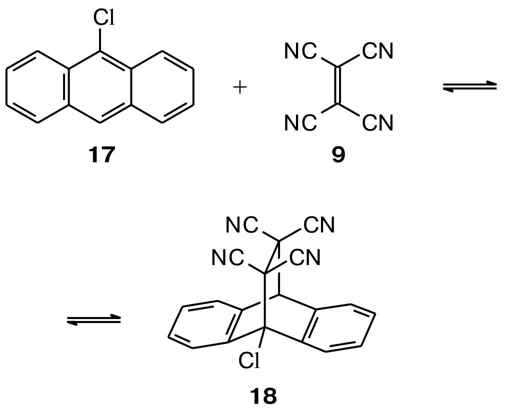
A highly reactive π-acceptor dienophile, tetracyanoethylene, forms complexes with many solvents.[50,71,106] The partial molar volumes of tetracyanoethylene determined from the density of dilute solutions are listed in Table 5.[107—111] Comparison of the presented data shows that the changes in the enthalpy of solvation of tetracyanoethylene in alkylbenzenes have qualitatively the same effect on its partial molar volume, the enthalpy and the free energy of formation of its π,π-complexes with the solvent, and on the rate of the Diels—Alder reaction (see Table 5).[107—111]

There exist a great deal of data[102,103] concerning the influence of the elevated pressure on the rate of the forward Diels—Alder reaction; however, no data on direct measurements of the effect of the pressure on the process equilibrium have been reported. Only direct spectrophotometric monitoring of the reaction in a high-pressure cell[112,113] can provide a complete cycle of independent measurements of the influence of the pressure on the reaction rate and equilibrium. The reversible reaction between 9-chloroanthracene (**17**) and tetracyanoethylene (TCNE) (**9**) in 1,2-dichloroethane proved to be convenient for such measurements (Scheme 5).

Table 5. Partial molar volumes of tetracyanoethylene (V_{TCNE}), ionization potentials of the solvents (IP), dissolution (ΔH_{sol}) and solvation (ΔH_{solv}) enthalpies, free energies (ΔG_0) of the formation of tetracyanoethylene complexes with alkylbenzenes, and rate constants (k_2) for the Diels—Alder reaction of tetracyanoethylene with anthracene at 25 °C in various solvents[107—111]

Solvent	IP /eV	V_{TCNE} /cm^3 mol^{-1}	ΔH_{sol}	$-\Delta H_{solv}$	$-\Delta G_0$	k_2 /L mol^{-1} s^{-1}
			kJ mol^{-1}			
Chlorobenzene	9.10	109.23	23.1	58.1	−0.65	1.82
Benzene	9.25	108.40	14.9	66.3	1.72	0.38
Toluene	8.82	104.56	9.7	71.5	3.24	0.13
o-Xylene	8.58	102.06	1.4	79.8	4.81	0.061
p-Xylene	8.48	101.46	0.0	81.2	5.04	—
Mesitylene	8.14	98.07	−2.7	83.9	7.07	0.010
Acetonitrile	12.12	109.97	15.2	66.0	—	2.18
Ethyl acetate	9.54	112.09	9.2	72.0	—	0.24
Cyclohexanone	9.14	110.42	7.6	73.6	—	0.20
1,4-Dioxane	9.13	105.72	4.3	76.9	—	0.34
1,2-Dichloroethane	11.12	107.81	21.3	59.9	—	3.82
Dichloromethane	11.35	107.50	23.4	57.8	—	4.28

Scheme 5



The volume of this reaction was determined[114–118] by three independent methods. First, the volume V_0, equal to -20.6 ± 1.5 cm^3 mol^{-1}, was calculated from the effect of pressure on the equilibrium constant. Second, the reaction volume was determined from the difference between the partial molar volumes of the adduct **18** (255.5 cm^3 mol^{-1}) and the reactants **17** and **9** (170.7 and 107.8 cm^3 mol^{-1}, respectively); this gave V_0 equal to -23.2 ± 2.0 cm^3 mol^{-1}. Finally, the difference between the activation volumes for the forward (-28.5 cm^3 mol^{-1}) and back (-6.5 cm^3 mol^{-1}) reactions also provides a similar value for the reaction volume (-22.0 ± 1.5 cm^3 mol^{-1}). Thus, it can be concluded that the activation and reaction volume parameters based on the effect of pressure on the Diels—Alder reaction rate and equilibrium are correctly defined by relations (13) and (14).

It is of interest that activation during decomposition of adduct **18** is also accompanied by a decrease in volume. This fact was explained[118] by assuming that the decrease in volume caused by flattening of the sterically branched structure of the adduct after the transition state has been reached is more pronounced than the volume increase caused by loosening of two C—C bonds.

In the absence of strong specific interactions of the reactants with the solvent, the solvent exerts an insignificant effect on the activation volume of the Diels—Alder reaction.[102,103] The contribution of the energy of specific interactions of tetracyanoethylene with the solvent sharply decreases on passing to the activated complex and, especially, to the adduct.[110,111] It was shown for these reactions that an increase in the process exothermicity in a series of solvents entails an increase in the negative values of the actvation and reaction volumes.[110,111,119] Therefore, for the greatest and favorable change in the rate and equilibrium of these reactions under conditions of high pressure, the most inert solvent should be used.[110]

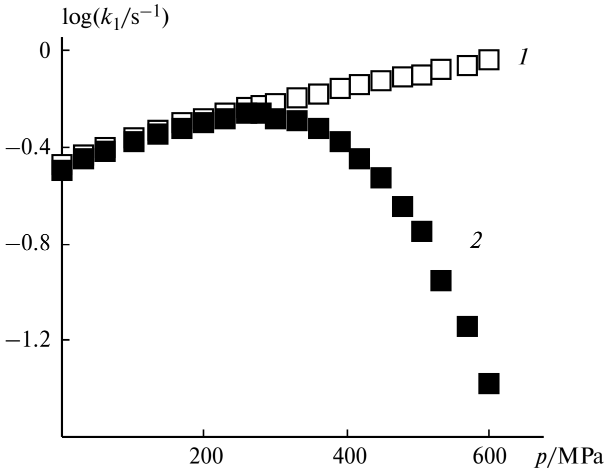
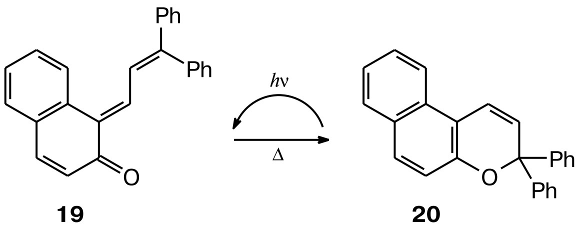


Fig. 8. Rate of thermal intramolecular Diels—Alder reaction **19** → **20** (see Scheme 6) *vs.* external pressure in methylcyclohexane (*1*) and 2-methyl-2,4-dicyclohexylpentane (*2*).

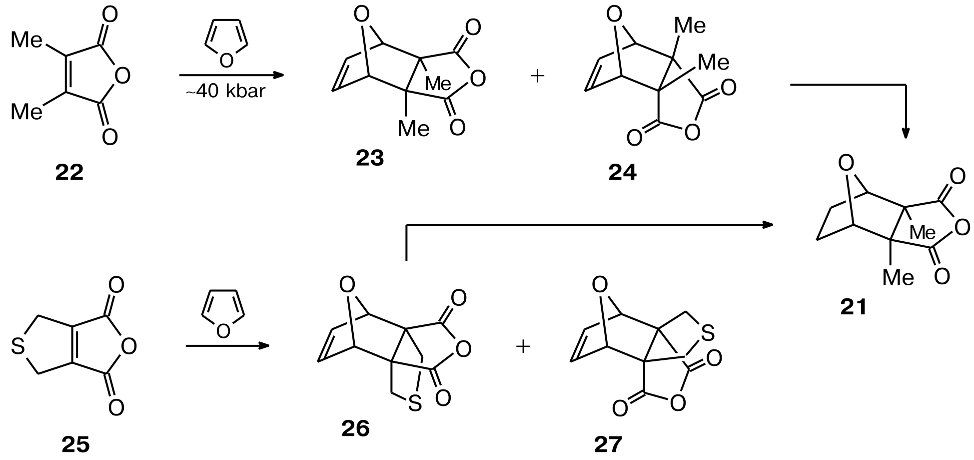
The substantial change in the activation volume for reactions with a polar transition state in solvent differing in polarity is usually due to different compressibility coefficients of the medium.[102,103] However, with an increase in pressure, the reaction rate can additionally change due to the change in the solvent properties (for example, an increase in the density, dielectric constant, and viscosity). It was shown[116–118] that for reactions with polar or ionic activated complexes, a pressure increase results in an increase in the rate constant due to both the $p\Delta V^{\neq}$ contribution and the increase in the dielectric constant. It is worth noting that after subtraction of the latter term, the activation volume for these reactions depends only slightly on the solvent properties.[116–118] Higher temperature and higher pressure usually entail opposite changes in the properties of the medium. Therefore, the use of elevated pressures is quite useful not only for practical purposes but also for elucidating some theoretical aspects. For example, it was found[120] that the thermal intramolecular Diels—Alder reaction **19** → **20** (Scheme 6) carried out in a low-viscosity solvent is markedly accelerated when the pressure is increased to 6 kbar, like other reactions of this type.[103] In a high-viscosity solvent (Fig. 8), this type of dependence is observed only up to 3 kbar. The solvent viscosity is known to increase exponentially with an increase in pressure.

Scheme 6



When the pressure and, hence, viscosity is further increased, the reduced thermal fluctuations of solvent mol-

Scheme 7



ecules do not provide any longer the necessary activation upon collision with reactant **19** (dynamic effect of the solvent).[120]

A great deal of data on the activation and reaction volumes for the Diels—Alder reaction have been accumulated to date. It is noteworthy that these volume parameters are originated not only due to the change in the intrinsic volumes of the reactants (change in the van der Waals volume $V_{\text{v.d.w}}$) on passing to the activated complex or to the adduct, but also due to the change in the volume of voids during the reaction in solution. The latter contribution often exceeds in magnitude the change in the van der Waals volume, which is rather constant for the Diels—Alder reaction, being equal only to $-(8—10)$ cm^3 mol^{-1}.[9,10] The change in the volume of intermolecular voids during the reaction is determined by the difference between the packing coefficients ($\eta = V_{\text{v.d.w}}/V$) of the reactants, the activated complex, and the reaction products. The change in the packing coefficients during the reaction is usually higher for small reactant molecules than for large molecules.[9,10] For this reason, the activation and reaction volumes are more negative for reactions involving reactants with small molecules. Thus for reactions of dienophiles with cyclopentadiene and alkylbutadienes, the activation and reaction volumes are $-(35—40)$ cm^3 mol^{-1}, whereas for reactions with anthracene derivatives, these parameters are only $-(20—25)$ cm^3 mol^{-1}. When the pressure increases, the volume of the intermolecular voids decreases. For this reason, the activation and reaction volumes also decrease in magnitude with an increase in pressure. El´yanov and coworkers[121,122] obtained valuable semiempirical relations for determining the volume parameters of the reactions at different temperatures and pressures, which allow one to predict much more precisely the change in the rate and the equilibrium for processes upon an increase in pressure. All the foregoing should be taken into account in interpreting the reaction mechanism using data on the reaction and activation volumes.[9,10,110—124]

Much experience has been accumulated in the successful use of elevated pressures for the synthesis of a large number of products difficult to prepare.[125,126] A typical example is the synthesis of cantharidin (**21**), a compound actively used for treating benign tumors.[126] The seemingly simple route for its synthesis according to the Diels—Alder reaction between furan and dimethylmaleic anhydride (**22**) to give *exo*- (**23**) and *endo*-adducts (**24**) (Scheme 7) followed by hydrogenation cannot be implemented without using high pressure. The reason is that the rate of formation of adducts **23** and **24** is exceptionally low (k_2 ~ 10^{-10} L mol^{-1} s^{-1} at 25 °C).[93] The traditional ways of increasing the reactivity are inapplicable in this case because at higher temperature, the equilibrium shifts toward the reactants and because furan tends to polymerize in the presence of Lewis acids. Due to the substantial decrease in the real activation volume,[122] the process acceleration at a pressure of 40 kbar proved to be much lower than predicted by relation (13) and product **21** was obtained only in a low yield.[126]

A more convenient procedure for cantharidin synthesis involves the Diels—Alder reaction between furan and strained bicyclic dienophile **25** (see Scheme 7).* Here the rate of the reaction between furan and anhydride **25** and the stability of adducts **26** and **27** were suitable for convenient synthesis of cantharidin **21** at lower pressures.[126]

4.2. Catalysis at elevated pressure

The conduction of catalyzed processes at elevated pressures is of special interest. Since catalysts cannot influ-

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* The strain of the double bond in bicyclic dienophiles of this type sharply increases, which results in an enhanced ease of its cleavage. For this reason, dianhydride of ethylenetetracarboxylic acid cannot be isolated in a pure state, whereas its stable adducts with a number of dienes are formed rather easily.[127,128]

ence the reaction equilibrium, this combined action is fairly desirable for slow reversible reactions.

The very high sensitivity of the rate of a catalytic reaction to the change in the bond energy in the *n,v*-complex (Eq. (11)) makes it the most convenient model for testing the possible changes in the bond energy in this *n,v*-complex at elevated pressures.

If the energy of dienophile bonding to the Lewis acid increases with an increase in pressure, the increase in the reaction rate will be due not only to the contribution of $p\Delta V^{\neq}$, as in the reaction without a Lewis acid, but to the increase in the dienophile activity. It follows from relations (11) and (13) that, if the bond energy in the complex increases by only 1.0 kJ mol^{-1} at an external pressure of 1 kbar, the additional change in the rate of the catalyzed reaction under pressure ($\ln k_{cat}(p = 1000)/k_{cat}(p = 1)$) is equivalent to an additional decrease in the activation volume ($\Delta V^{\neq}$) by 5 cm^3 mol^{-1}. By using modern barostats with direct monitoring of the reaction rate under pressure, one can determine the activation volume with an error of not more than (1—2) cm^3 mol^{-1}.[103,112,113] The results of these measurements allow one to draw conclusions concerning the change or retention of the type of bonds in the activated complex under elevated external pressure.

Study of the rates of catalyzed reactions in *n*-donor solvents (*e.g.*, acetonitrile, diethyl ether) is faced with problems in interpretation of the results due to catalyst redistribution between the *n*-donor solvent and the dienophile. Recently, it was shown[94] that the addition of only 0.5% (v/v) of dibutyl ether to a solution of reactants in 1,2-dichloroethane can suppress almost completely the $AlCl_3$-catalyzed Diels—Alder reaction between 9,10-dimethylanthracene and maleic anhydride. This is due to the fact that the catalyst is bound almost entirely into a complex with the ether, which is a stronger *n*-donor.

Data on the influence of π- and *n*-donor solvents on the properties of π- and *v*-acceptors have been reported.[129]

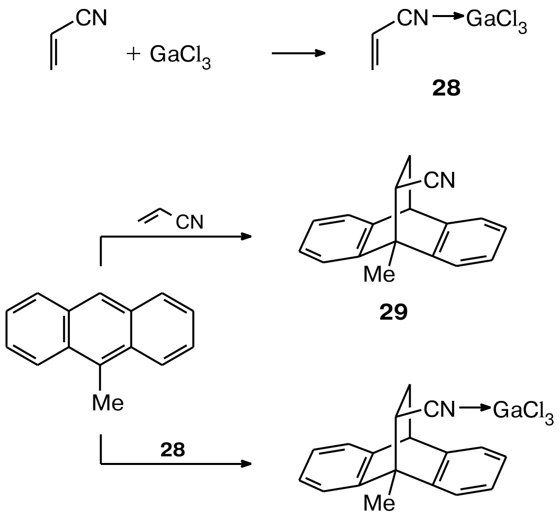
The data listed in Table 6 indicate that $GaCl_3$, unlike tetracyanoethylene, interacts much more efficiently with *n*-donor than with π-donor solvents and reacts only slightly with benzene, toluene, and 1,2-dichloroethane.

Table 6. Partial molar volume (V) and heat of dissolution (ΔH_{sol}) of $GaCl_3$ and tetracyanoethylene (TCNE) in various solvents[129]

Solvent	V/cm^3 mol^{-1}		ΔH_{sol}/kJ mol^{-1}	
	$GaCl_3$	TCNE	$GaCl_3$	TCNE
Benzene	74.8±0.1	108.4	9.6	15.1
Toluene	68.7±0.1	104.4	2.50	9.6
o-Xylene	67.1±0.1	102.2	−0.8	1.4
Mesitylene	64.8±0.4	98.1	−7.1	−2.7
1,2-Dichloroethane	73.4±0.4	107.8	5.1	21.3
Ethyl acetate	60.7±0.3	112.8	−65.7	9.2
Acetonitrile	61.9±0.3	109.8	−71.1	15.1
1,4-Dioxane	61.5±0.5	106.1	−74.0	4.2

The effect of pressure on the rate of the catalyzed Diels—Alder reaction between acrylonitrile and 9-methylanthracene in the presence of $GaCl_3$ in toluene has also been studied[130—133] (Scheme 8). Due to substantial reaction acceleration in the presence of $GaCl_3$ (when complex **28** is the real dienophile), the contribution of the noncatalyzed reaction between acrylonitrile and 9-methylanthracene to give adduct **29** to the overall reaction rate does not exceed 0.1%. The calculated activation volume for the catalyzed reaction is −16.9±1.0 cm^3 mol^{-1}.[130—133] The activation volume for the non-catalyzed reaction of acrylonitrile with 9,10-dimethylanthracene is −18.0±1.1 cm^3 mol^{-1}.[134]

Scheme 8



The equal activation volumes for the usual and catalyzed processes imply[130—133] that an increase in the pressure does not lead to bond strengthening in the *n,v*-complex formed by dienophile and gallium chloride. The results show that in the transition state, the character of bonds also does not change or changes only slightly upon a pressure increase (at least, when the pressure increases up to 1 kbar).

* * *

The series of studies into the Diels—Alder reactions identified the main factors that control the reactivity of various diene—dienophile systems. Quantitative relationships between the reaction rate and experimentally available characteristics of the above-mentioned factors were established. This made it possible to elucidate the reasons for many "abnormal features" in the Diels—Alder reaction in the absence and in the presence of catalysts under typical and atypical reaction conditions.

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