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Ene Reaction of β-Pinene with 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione: Effects of Temperature, High Pressure, and Solvent Nature

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Abstract—The effects of temperature, solvent nature, and high hydrostatic pressure on the rate of the ene reaction of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione with β-pinene have been studied. The reaction gives only one product and is accompanied by a large heat effect. Comparison of the activation and reaction volumes indicates cyclic structure of the transition state. The reaction rate changes by a factor of 200 in the series of nine examined solvents, but this variation is not determined by solvent polarity.

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Among alkenes and cycloalkenes studied in ene reactions with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**1**), the highest activity was observed for 2,3-dimethylbut-2-ene (k_2 = 200 L mol^{-1} s^{-1} in toluene at 20°C) [1]. Compound **1** showed enhanced reactivity in [4+2]- and [2+2]-cycloadditions and ene reactions in comparison to other dienophiles, including tetracyanoethylene which is the strongest π-acceptor dienophile [1–7]. Triazole **1** reacted at a moderate rate with 9,10-diphenylanthracene in which the reaction centers (C^9 and C^{10}) are completely shielded due to almost orthogonal orientation of the phenyl rings with respect to the plane of the tricyclic fragment [8]. This Diels–Alder reaction proceeds fairly readily, but it involves accessible 1,4-positions [8] rather than 9,10 as presumed previously [9].

β-Pinene **2** reacts with triazole **1** to give adduct **3** as the only product [10]. However, there are no data on quantitative parameters of this ene reaction. In the present work we have determined rate constants of the reaction **1** + **2** → **3** (Scheme 1) in nine solvents at 20, 30, and 40°C and reaction enthalpy, estimated pressure effect on the reaction rate, calculated the activation and reaction volumes, and compared the obtained data with the corresponding parameters of some other ene reactions with compound **1** (Table 1).

The reaction rate in polar solvents such as DMF and acetonitrile was significantly lower than in weakly polar media. The entropy of activation of the reaction **1** + **2** → **3** was close to the entropy of activation of other ene reactions, as well as of [4+2]-cycloaddition, but considerably lower than of [2+2]-cycloaddition reactions (Table 2, Scheme 2).

The ene reaction of **1** with **7** involving C=C bond migration to the bridgehead carbon atom of **7** is forbidden by Bredt's rule due to high strain energy;

Scheme 1.

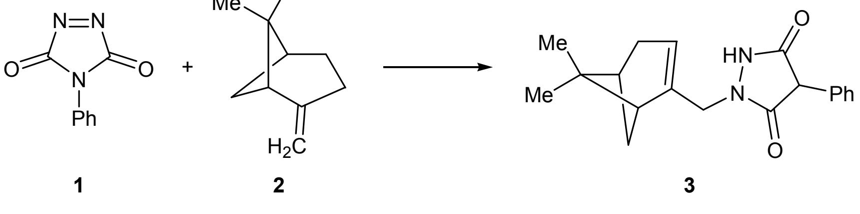

Table 1. Rate constants and enthalpies, entropies, and Gibbs energies of activation of the ene reaction **1** + **2** → **3**

Solvent	ε [11]	k_2, L mol^{-1} s^{-1}			$\Delta H^{\neq}$ (25°C), kJ/mol	$-\Delta S^{\neq}$ (25°C), J mol^{-1} K^{-1}	$\Delta G^{\neq}$ (25°C), kJ/mol
		20°C	30°C	40°C			
DMF[a]	36.7	0.0347	0.0667	0.1226	45.7	117	80.0
Acetone[a]	20.7	0.0506	0.0912	0.153	39.8	134	79.1
Ethyl acetate	6.0	0.0518	0.0941	0.156	39.6	134	78.9
1,4-Dioxane	2.2	0.0990	0.177	0.266	35.3	144	77.5
Acetonitrile	37.5	0.256	0.423	0.637	32.4	146	75.2
Toluene	2.3	0.374	0.606	0.945	32.9	141	74.2
Benzene	2.3	0.563	0.917	1.36	31.3	143	73.2
1,2-Dichloroethane	10.3	2.44	3.38	4.64	22.2	161	69.4
Chloroform	4.6	7.55	10.0	–	20.7	157	66.7

[a] Calculated with a correction for side reaction of **1** with the solvent.

however, the [2+2]-cycloaddition reaction turned out to be less favorable than Wagner–Meerwein rearrangement [5, 13]. The enhanced reactivity of compound **1** as acceptor, even in comparison to tetracyanoethylene, as well as increased stability of adducts obtained from **1** in all the examined reactions (Table 2), enabled [4+2]-cycloaddition of **1** to 9,10-diphenylanthracene **11** with sterically inaccessible positions *9* and *10*. Nevertheless, the reaction **1** + **11** does occur but at the accessible atoms in positions *1* and *4* of **11** [8, 16].

The smallest difference between the energies of bond cleavage an bond formation, which is reflected in

Scheme 2.

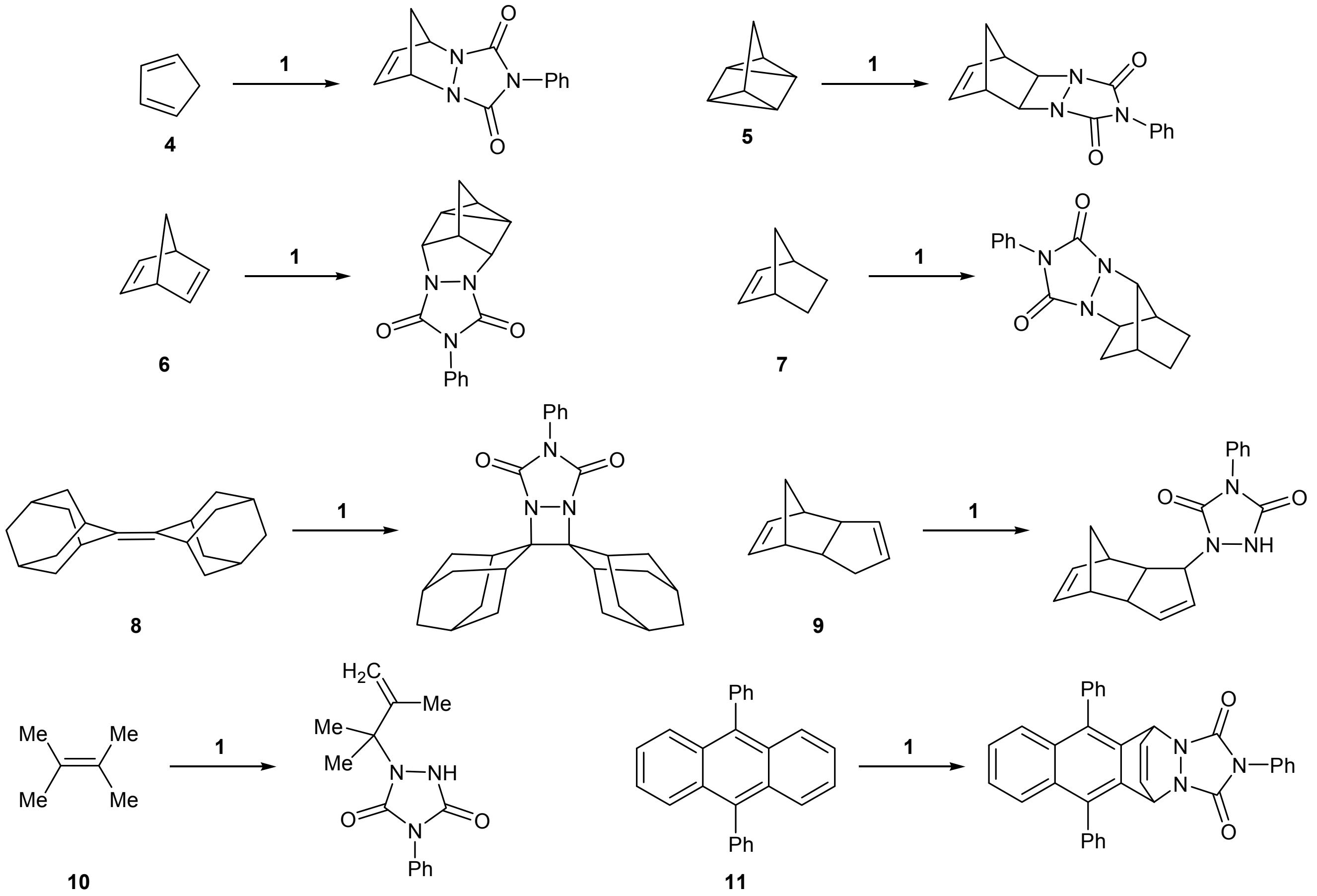

Table 2. Rate constants, enthalpies ($\Delta H^{\neq}$), entropies ($\Delta S^{\neq}$), and volumes of activation ($\Delta V^{\neq}$), and volumes (ΔV_r) and enthalpies (ΔH_r) of some reactions with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**1**) at 25°C

Reaction	Solvent	k_2, L mol^{-1} s^{-1}	$\Delta H^{\neq}$, kJ/mol	$-\Delta S^{\neq}$, J mol^{-1} K^{-1}	$-\Delta V^{\neq}/-\Delta V_r$, cm^3/mol	$-\Delta H_r$, kJ/mol
1+**2**, ene	Ethyl acetate	0.070	39.8	134	36.0/30.4	159.1, dichloroethane
1+**4**, [4π+2π]	Toluene	1.6×10^5 [6]	–	–	–	134 [6]
1+**5**, [2π+2σ+2σ]	Toluene	0.282 [11]	39.6	123	25.4/20.9 [11]	255 [11]
1+**6**, [2π+2π+2π]	Toluene	3.95×10^{-3} [12], dichloroethane	50.9	121	25.1/30.9 [12]	218 [12]
1+**7**, with Wagner–Meerwein rearrangement	Toluene	1.28×10^{-4} [5, 13]	55.3	134	26.6/24.6 [5, 13]	170 [5, 13], dichloroethane
1+**8**, [2π+2π]	Toluene	0.0175 [14]	24	198	50.8/37.6 [14]	86.4 [14], dichloroethane
1+**9**, ene	Toluene	0.027 [15]	46	125	27.6/20.6 [15]	172 [15]
1+**10**, ene	Dichloroethane	335 [1]	20	144	–	150 [1]
1+**11**, [4π+2π]	Toluene	2.74×10^{-3} [8, 16]	58.6	97	17.5/15.4	50.2 [8, 16]

the reaction, was observed for the reactions **1** + **8** and **1** + **11**, and the largest reaction enthalpies were found for the reaction **1** + **6** with non-conjugated norbornadiene, as well as for the reaction **1** + **5** involving two cyclopropane rings of **5**. However, the data in Table 2 show that high exothermicity is not the main factor determining the reaction rate.

The enthalpy of the reaction **1** + **2** → **3** was determined from the data of three successive dissolutions of a crystalline sample of **1** in a solution of donor **2** in 1,2-dichloroethane at 25°C. With correction for the heat of dissolution of **1** in 1,2-dichloroethane (21.9 kJ/mol), we obtained the following heats of the reaction: –157.5, –160.5, and –159.4 kJ/mol, the average value being ΔH_r(av.) = –(159.1±1.1 kJ/mol. The high exothermicity of the reaction **1** + **2** → **3** makes it almost irreversible.

The activation volume of the reaction **1** + **2** → **3** was determined in ethyl acetate at 25°C on the basis of the rate constants under normal pressure (1 bar) and at a pressure of 1000 bar [Eqs. (9, 10); see Experimental). From the ratio $k_{1000\,\text{bar}}/k_{1\,\text{bar}} = 3.92$ we calculated the value $\Delta V^{\neq}_{\text{exp}} = -39.0\pm1.5$ cm^3/mol. With account taken of variation of the reactant concentration due to compressibility of the solvent, the corrected activation volume was $\Delta V^{\neq}_{\text{cor}} = -(36.0\pm1.5)$ cm^3/mol.

The reaction volume ΔV_r was determined in two ways. The dependence of the density of the reaction mixture on the concentration of adduct **3** [Eq. (11); see Experimental) was measured two times ($c_{01} = c_{02} = 5.00$ mM).

$$d^{-1} = -(0.0346118\pm0.00039)\,c_3 + (1.1178038\pm0.00000087),$$
$$R^2 = 0.9979;\ \Delta V_r = -30.9\pm0.5\ \text{cm}^3/\text{mol};$$

$$d^{-1} = -(0.0331679\pm0.000279)\,c_3 + (1.1177995\pm0.00000066),$$
$$R^2 = 0.9985;\ \Delta V_r = -(29.8\pm0.3)\ \text{cm}^3/\text{mol};$$

$$\Delta V_r = V_3 - V_1 - V_2 = 257.17 - 128.98 - 158.84 = -30.65\ \text{cm}^3/\text{mol};$$
$$\Delta V_r\ (\text{av.}) = -(30.4\pm0.5)\ \text{cm}^3/\text{mol}.$$

The ratio $\Delta V^{\neq}_{\text{cor}}/\Delta V_r$ is equal to 1.18. All studied ene reactions are characterized by a $\Delta V^{\neq}_{\text{cor}}/\Delta V_r$ ratio of larger than unity [1, 6, 15]. This may be rationalized assuming cyclic structure of the transition state which is thus more compact than the acyclic adduct [17].

In the examined solvent series (Table 1) the reaction rate changes by two orders of magnitude; however, the differences are not related to the solvent polarity. Analogous activation of dienophiles in proton-donor media is well known for other reaction types. We previously [11, 14] examined solvent effect on the rate of a number of reactions with dienophile **1**. These data allowed us to consider solvent effect on the rate of the ene reaction **1** + **2** → **3** in comparison with the [2π+2σ+2σ] reaction of **1** with quadricyclane **5** [11], ene reaction with 2-methylbut-2-ene **12** [18], [2π+2π] cycloaddition with 2-chloroethyl vinyl ether

13 [19], addition and rearrangement in the reaction with norbornene **7** [5, 13], ene reaction with *trans*-hex-3-ene **14** [7], [4π+2π]-cycloaddition with anthracene **15** [1], [2π+2π] reaction with biadamantylidene **8** [14] with account taken of the enthalpy of dissolution (ΔH_r) of compound **1** in the given solvents [20]:

$$\ln k_{1+5} = (0.8192\pm0.1397)\ln k_{1+2} + (0.1293\pm0.2856); \quad R^2 = 0.8515, N = 8; \tag{1}$$

$$\ln k_{1+12} = (0.9912\pm0.0272)\ln k_{1+2} + (0.6748\pm0.0590); \quad R^2 = 0.9912, N = 9; \tag{2}$$

$$\ln k_{1+13} = (0.5192\pm0.0345)\ln k_{1+2} + (2.6474\pm0.0763); \quad R^2 = 0.9869, N = 5; \tag{3}$$

$$\ln k_{1+7} = (0.4592\pm0.0069)\ln k_{1+2} - (6.7253\pm0.0137); \quad R^2 = 0.9995, N = 4; \tag{4}$$

$$\ln k_{1+14} = (0.8764\pm0.1816)\ln k_{1+2} - (2.5507\pm0.3543); \quad R^2 = 0.9588, N = 3; \tag{5}$$

$$\ln k_{1+15} = (0.8848\pm0.03561)\ln k_{1+2} - (0.1990\pm0.0633); \quad R^2 = 0.9919, N = 7; \tag{6}$$

$$\ln k_{1+8} = (1.0730\pm0.2603)\ln k_{1+2} - (2.2136\pm0.5648); \quad R^2 = 0.7081, N = 9; \tag{7}$$

$$\ln k_{1+2} = (0.2632\pm0.0423)\Delta H_{\mathrm{sol\,1}} - (5.1619\pm0.7499); \quad R^2 = 0.8854, N = 7. \tag{8}$$

A significant difference in the solvent effect on the reaction rate was observed only with the [2π+2π]-cycloaddition of **1** with biadamantylidene (**1**+**8**, R^2 = 0.7081. A high degree of proportionality was found with the ene reactions **1**+**12** and **1**+**14** and Diels–Alder reaction **1**+**15**, and the slope is close to unity.

Similarity in the solvent effects on different reactions implies a small difference in the effect of the medium on the transition state level. The reaction **1**+**7** accompanied by Wagner–Meerwein rearrangement cannot be regarded as a concerted one-step process [5]. The formation of intermediate aziridinium imide complex was proved experimentally [3–5]. It follows from correlations (1)–(8) that assumingly dipolar or diradical nature of this intermediate should be low sensitive to the solvent polarity. The available data allow us to conclude that new bonds are formed most rapidly and easily in the Diels–Alder reactions of **1** with 1,3-dienes; next follow ene reactions, including that accompanied by Wagner–Meerwein rearangement, and [2+2]-cycloadditions are least favorable. There are no other more favorable versions of the addition of **1** to biadamantylidene; therefore, the formation of cyclobutane adduct in the [2+2]-cycloaddition **1**+**8** involves increased steric hindrances and is characterized by lower exothermicity than the other reactions (Table 2).

It is known [21] that the heat effect in the hydrogenation of 1-methylcyclohexene is smaller by 19 kJ/mol than in the hydrogenation of methylidenecyclohexane. Therefore, it may be presumed that the exocyclic C=C double bond in β-pinene **1** should be more reactive than the endocyclic double bond in α-pinene. In fact, the rate constant of the reaction **1**+**2** in 1,4-dioxane at 25°C is higher by a factor of 26.5 than that of the reaction of **1** with α-pinene.

EXPERIMENTAL

Commercial β-pinene (**2**, 6,6-dimethyl-2-methylidenebicyclo[3.1.1]heptane; 99%, Sigma–Aldrich) was used without additional purification. 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**1**; 97%, Aldrich) was additionally purified by sublimation at 100°C under reduced pressure (100 Pa), mp 165–170°C (decomp.) [2]. The purity of **1** was checked by UV spectrophotometry with account taken of the reported molar absorption coefficient [6]. Adduct **3** was obtained in quantitative yield and was recrystallized from hexane–ethanol (5:1), mp 136–137°C; published data [10]: mp 137–139°C. The ^{1}H and ^{13}C NMR spectra of **3** completely coincided with those given in [10]. All solvents were purified by known methods [22].

Kinetic measurements under atmospheric pressure. The reaction rate was monitored by spectrophotometry, following the absorbance of alkene **2** in the region λ 530–550 nm with a Hitachi U-2900 spectrophotometer. The temperature of the reaction solution in a quartz cell capped with a ground stopper was maintained with an accuracy of ±0.1°C. The stability of triazole **1** in all solvents used was checked by measuring its absorbance over a period corresponding to the reaction time. The relative standard error in the determination of the rate constants was ±3%, and the enthalpies and entropies of activation were determined with accuracies of ±2 kJ/mol and ±6 $\mathrm{J\,mol^{-1}\,K^{-1}}$, respectively.

Kinetic measurements at elevated pressure. The effect of pressure on the rate of the reaction **1** + **2** → **3** was studied in ethyl acetate at 25°C with the aid of an HP-500 pressure multiplier, a PCI-500 variable-volume quartz cell, and a programmed SCINCO spectrophotometer. The observed activation volume $\Delta V^{\neq}_{\mathrm{exp}}$ for the reaction **1** + **2** → **3** was calculated from the rate constants at 1 and 1000 bar using correlation (9) proposed in [23]:

$$(\partial \ln k_p/\partial p)_{1\,\text{bar}} = (1.15\pm0.03)\times10^{-3}\ln(k_{1000\,\text{bar}}/k_{1\,\text{bar}}). \quad (9)$$

The $\Delta V^{\neq}_{\text{exp}}$ value was corrected for the compressibility of the solvent:

$$\Delta V^{\neq}_{\text{cor}} = \Delta V^{\neq}_{\text{exp}} + \beta_T RT, \quad (10)$$

where $\beta_T = 1.20\times10^{-4}$ bar^{-1} is the isothermal compressibility coefficient of ethyl acetate [24].

Reaction volume. The reaction volume ($\Delta V_{\text{r.}}$) was determined in two ways. The kinetic method allows determination of reaction volume from correlation (11) between the density of the reaction solution and concentration of adduct **3**. Reaction volume can also be determined from the difference in the partial molar volumes of the product and initial reactants [Eq. (12)]:

$$1/d_\tau = 1/d_0 + c_{3,\tau}\,\Delta V_r/1000\,d_0; \quad (11)$$

$$\Delta V_r = V_3 - V_2 - V_1. \quad (12)$$

Here, d_0 and d_τ are, respectively, the densities of the reaction solution at the initial moment and at a time τ; $c_{3,\tau}$ is the current concentration of adduct **3**; and V_1, V_2, and V_3 are the partial molar volumes of compounds **1**–**3**, respectively. The current concentration of **3** was calculated from the kinetic data. The density of the reaction mixtures was measured at 25±0.002°C with an Anton Paar DSA 5000M precision densitometer with an accuracy of $\pm2\times10^{-6}$ g/cm^3. The V_1, V_2, and V_3 values were calculated from the densities of solutions and the solvent.

Heat of reaction. The enthalpy of the reaction **1** + **2** → **3** was determined in 1,2-dichloroethane at 25°C using a differential calorimeter according to the procedure described in [1, 6]. A weighted amount of crystalline compound **1** was added to a solution of β-pinene taken in excess.

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