The Relative Rates of Ene Reaction of Benzyne with Cyclic Olefins: The Stereochemical Course†

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The benzyne reaction of cyclic olefins, in competition with that of cyclohexene has been studied. The relative reactivities for ene reaction and the stereoselectivity of the reaction with 4-*t*-butylcyclohexene, which afforded *trans*-5-*t*-butyl-3-phenylcyclohexene and *cis*-3-*t*-butyl-6-phenylcyclohexene, are consistent with the stereochemical requirements along the reaction pathway.

The reaction of benzyne with cyclic olefins has been attracting interest in connection with the stereochemical course of the reaction.[1-4]

The addition of benzyne to cyclic dienes falls into three categories: [2+2]-, [2+4]-cycloaddition reactions¸ and ene reaction. The former is believed to be a stepwise reaction and the latter two are mostly concerted reactions.[2] Stephenson has discussed the stereochemistry of the ene reaction, which proceeded in general in a concerned manner, as depicted in Fig. 1.[5]

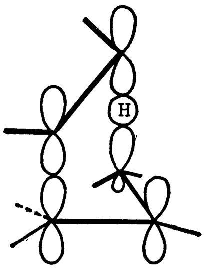

Fig. 1.

As cyclic olefins of medium-sized rings have rather mobile molecular frameworks within the limited conformations, the geometry of approach of benzyne toward cyclic olefins will be, in some cases, somewhat strained, and hence the geometry which can achieve a better overlapping of the correlated molecular orbitals in the transition state will be reflected in the reactivities for the ene reaction.

However, there is no report on the study of relative reactivities for ene reaction of olefins against benzyne, so we investigated the competition reaction of cyclic olefins in the presence of one equivalent of cyclohexene. For cyclic olefins, we chose simple ones: *i.e.*, cyclopentene (**1**), 4-*t*-butylcyclohexene (**2**), cycloheptene (**3**), *cis*-cyclooctene (**4**), and 1,2-cyclononadiene (**5**), to avoid the complexity arising from steric hindrance by substituents.

Identification of Products. *Reaction with (a) Cyclopentene*: From the 1:1 addition mixture, **6** and **7** were detected as products. The fact that **6** showed no olefinic proton signal in the NMR spectrum, in addition to an integral ratio (4:2:6) of aromatic, benzylic, and aliphatic proton signals and to a A_2B_2 symmetry of aromatic signals, supported the [2+2]-structure. The NMR spectrum of **7** indicated that it was a phenyl substituted cyclopentene with two non-equivalent olefinic protons, which defined unequivocally the structure as 3-phenylcyclopentene.

(**6**) *n*=1
(**9**) *n*=3
(**11**) *n*=4

(**7**) *n*=1
(**8**) *n*=2
(**10**) *n*=3
(**12**) *n*=4

Scheme 1.

(b) Cyclohexene: 3-Phenylcyclohexene (**8**)[6] was obtained as the sole product and identified on the basis of IR and NMR spectra.

(c) Cycloheptene: Compounds **9** and **10** were separated using preparative GLC and characterized on the basis of their spectral data. The former was identified with a sample obtained by hydrogenation of a [2+2]-cycloaddition product of benzyne to cycloheptatriene.[7,8]

(d) cis-*Cyclooctene*: Because the 1:1 addition products could not be separated using preparative GLC, the product mixture dissolved in ethyl acetate was hydrogenated over 10% Pd on carbon. GLC analysis of the hydrogenation products allowed us to estimate that the original mixture contained **11** and **12** in a ratio of 1:7.7 by weight;[9] this result was also obtained from the examination of the PMR integral ratio of the original mixture.

(e) 1,2-Cyclononadiene: The products were separated using GLC, and were identified as **13** and **14** on the basis of the spectral data.[1]

*(f) 4-*t*-Butylcyclohexene*: The 1:1 addition products were separated into two components, **15** and **16**, in a ratio of 1:1.2; these were carefully investigated. Catalytic hydrogenation (Pd–C) of **15** gave thermodynamically unstable *trans*-3-*t*-butyl-1-phenylcyclohexane, which was transformed to a known *cis*-isomer by treatment with potassium *t*-butoxide in DMSO. Hydrogenation of **16** over PtO_2 gave *cis*-4-*t*-butyl-1 phenylcyclohexane,[10] which was treated under the same conditions of base to give exclusively the known *trans*-isomer. The position of the double bond in **15** and **16** was determined on the basis of their spectral data. The absence of intense absorption bands near 250 nm in UV

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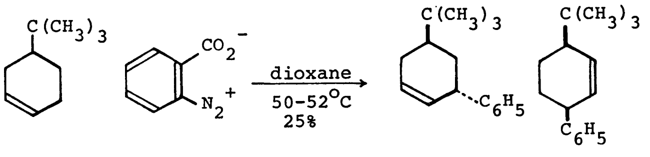
TABLE 1. RELATIVE REACTION RATES OF CYCLIC OLEFINS WITH BENZYNE

Olefins	Relative rates		θ_1	θ_1'	Preferred conformations
	[ene]	[2+2]			
Cyclopentene	1.25[a]	0.19[a]	30°	30°	planar[11]
			17°	40°	envelope[12]
Cyclohexene	1.00	0	4—13°	47—56°	half-chair[12-14]
Cycloheptene	0.62	0.22	32—40°	80—88°	chair[12,15]
cis-Cyclooctene	0.88	0.11	20—56°	64—81°	twist[12,16]
4-*t*-Butyl-cyclohexene	0.89 (0.49+0.40)	0	4—13°	47—56°	half-chair[14]
1,2-Cyclo-nonadiene	7.54 (17.55)[b]	1.63 (4.40)[b]	35°	83°	rigid

a) Dichloromethane was used as solvent. b) Acetonitrile was used as solvent.

spectra of **15** and **16** eliminates phenyl-conjugated cyclohexene structures. That they showed two olefinic proton signals strongly coupled with benzylic proton signals in NMR spectra defined the structures.



(**15**) 1: 1.2 (**16**)

Scheme 2.

Competition Reaction with Cyclohexene. A mixture of an olefin, cyclohexene, and benzenediazonium-*o*-carboxylate in a molar ratio of 1 : 1 : 2 suspended in dioxane was stirred and heated at 50—52 °C. The hydrocarbon products were separated and carefully examined with the use of GLC. The results are collected in Table 1.

TABLE 2.

Cyclic olefins	Ratios of ene/[2+2]	θ_1	θ_2
cis-Cyclononene[18]	∞	0°	0°
Cyclohexene[19]	∞	13°	13°
cis-Cyclooctene[9]	8	0°	34—46°
1,2-Cyclononadiene[1]	6.2	0°	45°
Cycloheptene[7]	2.6	24°	39°
1,3,5-Cycloheptatriene[7]	2.3	36°	36°
trans-Cyclononene[17]	0.9	60°	30°
trans-Cyclooctene[9]	0	55°	65°

Results and Discussion

In 1973, Crews noticed that the product ratio of ene/[2+2] reaction of benzyne for cyclic olefins varies as an angle θ_1 changes (Fig. 2): the ratio and θ_1 values (in parentheses) are ∞ (4°), 3 (5°), 0.8 (33°), 0.07 (37°).[17] We had reached a similar conclusion when we studied the reaction with cycloheptatriene and cycloheptene.[7] Table 2 shows the data[7b] and includes additional values. The dihedral angles (θ_1, θ_1', θ_2, θ_2') between the axis of each *p*-orbital and the corresponding adjacent methylene C–H bonds are taken as shown in

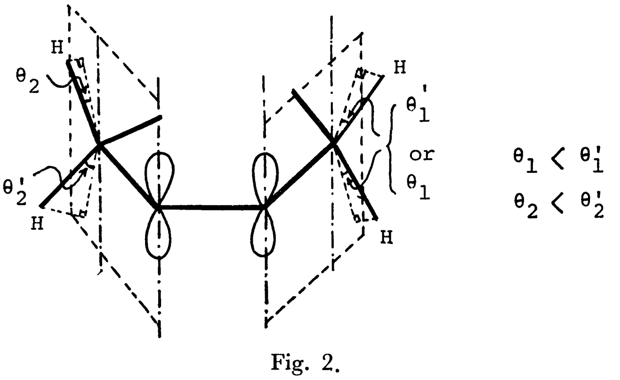


Fig. 2.

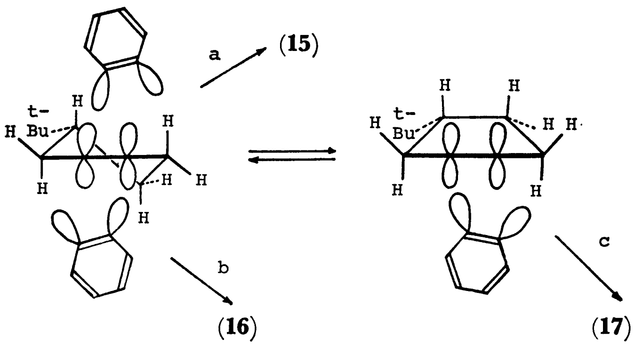
Fig. 2 and measured by the examination of the molecular models. If the molecular model is mobile, θ_2 was obtained after θ_1 was fixed by making it as small as possible. From this table, it is clear that the ene reaction becomes of no account compared to [2+2] cycloaddition when θ_1 (or θ_2) becomes an angle exceeding 55°.

Arnold and co-workers have demonstrated that the hydrogen abstraction occurs regioselectively in the ene reaction of β-pinene with benzyne. This experiment supports the assertion that the reaction proceeds in concerted mechanism.[20]

Accordingly, it is expected that the more close to zero degrees the dihedral angle (θ_1) between a relevant C–H bond and the adjacent olefinic *p*-orbital is (Fig. 2), the more smoothly the ene reaction of benzyne will proceed.

In the case of cyclohexene, however, the ene/[2+2] ratio is reported to be infinite.[6] We could not be convinced either that the [2+2] reaction with benzyne proceeded at similar rates for every olefin or that the ene reaction with cyclohexene advanced at an extraordinary rate. In order to obtain further knowledge about the transition state for the ene reaction of benzyne, we examined the reaction with a cyclohexene having a rather fixed conformation, *i.e.*, 4-*t*-butylcyclohexene. From the knowledge of conformational analysis, we need not consider a conformation of **2** keeping *t*-butyl group in axial position. If the most stable half-chair conformation of cyclohexene ring could easily flip into a half-boat form having an equatorial *t*-butyl group during the reaction (Scheme 3), *cis*-5-*t*-butyl-3-phenylcyclohexene (**17**) might be formed by way of path c. This was not the case. It is clear that the ene reaction involving a quasi-equatorial C–H bond with dihedral angle 47—56°

has not taken place, while the one involving an quasi-axial C–H bond with 4—13° has occurred. These results show undoubtedly that the transition states a and b are practically important.



Scheme 3.

In the competition reaction between 4-*t*-butylcyclohexene and cyclohexene, formation of **15** is somewhat retarded in comparison with the formation of **16**, the rate of which is almost comparable to a half of the formation of 3-phenylcyclohexene from cyclohexene. From this fact, it is assumed that cyclic olefins react with benzyne, with high probabilities, in their most thermodynamically stable conformations, which, except *cis*-cyclooctene,[16)] have a plane or an axis of symmetry intersecting the middle point of the C=C double bond. Therefore, to analyze the ene reaction, it will be enough to compare the conformation of one of the two methylene groups adjacent to the double bond. The angles θ_1 and θ_1' are obtained from measurements on the molecular models.

In the electronic spectra of conjugated ketones with steric hindrance of conjugation, it is claimed that the degree of conjugation is proportional to a directly excited molecular fraction *r*, or a ratio of molecular extinction coefficients of hindered to unhindered ketone, $\varepsilon/\varepsilon_0$, which is approximately given by $\cos^2\theta$ (θ: dihedral angle).[21)] If we suppose that the ene reaction proceeds readily in harmony with the degree of hyperconjugation between an allylic hydrogen and the double bond, the plots of relative rates as a function of $\cos^2\theta_1+\cos^2\theta_1'$ given in Fig. 3 must have some clear feature. (In case of θ_1' 55°, $\cos^2\theta_1'$ is neglected). The approximately linear relationship in them is in line with the stereochemical course of ene reaction discussed above.

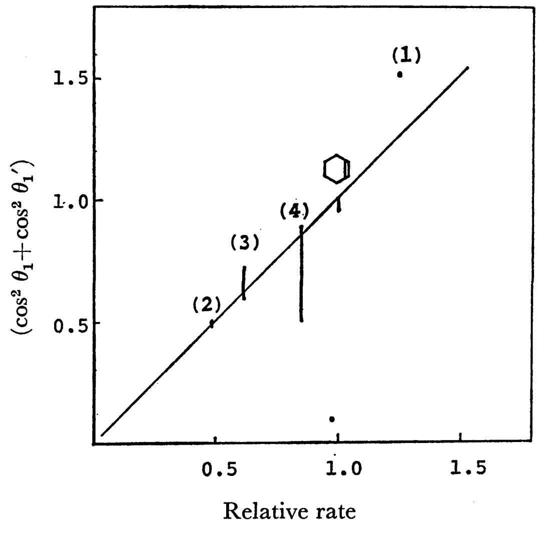


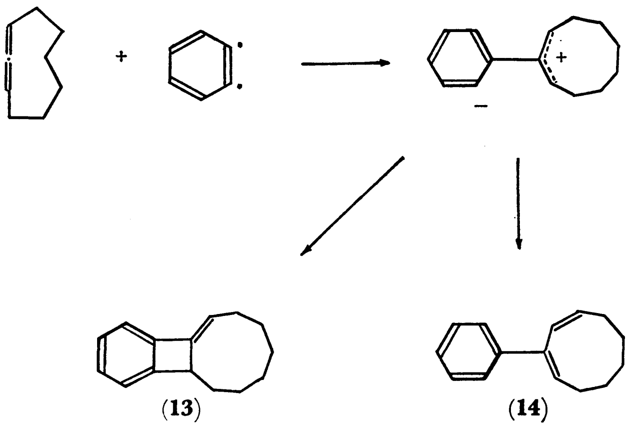
Fig. 3. Plot of relative rates against $\cos^2\theta_1+\cos^2\theta_1'$ for ene reaction of benzyne.

In the case of cyclopentene, if we were to choose either a planar[11)] or an envelope conformation,[12)] the plots deviate above the line.

In the case of *cis*-cyclooctene, the molecular framework is so labile that there are some preferable conformations,[12,16)] of which the one with the smallest θ_1 satisfies the linearity.

On the other hand, at first sight, it seemed that there is no regularity between the reactivities of [2+2]-cycloaddition and the conformations of cyclic olefins. But it is interesting to note that the [2+2]-reaction proceeded in similar rates for cyclopentene and cycloheptene, while the relative rate for *cis*-cyclooctene fell to approximately a half of that for cycloheptene. This suggests that either above or below the sp^2-sp^2 plane of cyclooctene happens to be blocked from any attack of benzyne with the intramolecular methylene group, owing to the mobility of the molecular structure. We could not find any reason to justify the absence of the [2+2] product when cyclohexene was used as a substrate.

The relative rates for both ene and [2+2] reaction with 1,2-cyclononadiene are exceptional, as compared with the other olefins. The extraordinary enhancement of both reaction rates suggests a process of a different mechanism, that is, the ionic process[22)] shown in Scheme 4, in addition to the ring strain. This seems to be supported by an increase in relative reactivities when the reaction was carried out in a more polar solvent such as acetonitrile. Further studies on the reactivities of allenes are now in progress.



Scheme 4.

Experimental

The NMR spectra were obtained on a JEOL Model PS-100 spectrometer with carbon tetrachloride as a solvent and TMS as an internal standard. The chemical shifts are expressed in ppm from TMS. The IR was recorded on a JASCO Model

IRE spectrometer. GLC analysis was carried out on a Varian Aerograph Model 90P gas chromatograph under quoted conditions.

Reaction of Cyclopentene with Benzyne. Solid benzenediazonium-*o*-carboxylate, prepared from 20 mmol of anthranilic acid,[23] was suspended in dichloromethane (100 ml) containing cyclopentene (1.36 g, 20 mmol) and stirred at 37 °C for 3 h. The resulting solution was washed successively with water, aq sodium bicarbonate, and water, then dried (anhyd sodium sulfate). The residue (2.06 g) from the organic layer, dissolved in benzene, was chromatographed on Silicic Acid (Mallinckrodt, 100 g) and eluted with the same solvent. The hydrocarbon fraction (1.33 g, light brown liquid) from the eluate was rechromatographed on Silicic Acid (50 g). Fraction 1—10 (417 mg) contained **6** and **7** in a ratio of 0.26: 1 and fractions 11—20 (225 mg) contained **7**. GLC separation of the samples (see below) gave pure samples of them. The physical data of **6** and **7**: **6** NMR δ: 1.1—2.1 (6H, m), 3.78 (2H, broad d), 6.75—7.2 (4H, A_2B_2 type). Found: C, 91.63; H, 8.49%. IR ν(liq. film): 3060, 2930, 2850, 1460, 1350, 1290, 1205, 1112, 1003, 997, 820, 763, 743. **7** NMR δ: 1.5—2.0 (1H, m), 2.2—2.4 (3H, m), 3.68—4.0 (1H, m), 5.6—6.0 (2H, m), 6.9—7.4 (5H, m). IR ν(liq. film): 3060, 2940, 2850, 1602, 1496, 1455, 1360, 1080, 1032, 1012, 917, 760, 730, 700. Found: C, 91.57; H, 8.46%. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39%.

*Reaction of 4-*t*-Butyl-1-cyclohexene with Benzyne.* Solid benzenediazonium-*o*-carboxylate, prepared from 20 mmol of anthranilic acid,[23] was suspended in dioxane (100 ml) containing 4-*t*-butyl-1-cyclohexene (2.76 g, 20 mmol) and stirred under heating at 50—52 °C for 3 h. The solvent was evaporated and the residue, taken in dichloromethane, was washed successively with 5% aq sodium bicarbonate and water. After drying the organic solution, the residue, taken in benzene, was chromatographed on Silicic Acid (50 g). The yellow liquid obtained by elution with benzene was rechromatographed on Silicic Acid (50 g) with hexane–ether (90: 10 v/v) as solvent. The 1: 1 addition products (1.07 g, 25% yield) were obtained as a pale yellow oil, which was separated using preparative GLC [10% Silicone DC-QF-1 on Chromosorb WAW; 1/4 inch × 3 m; Helium flow rate, 20 ml/min; column temperature, 150 °C; retention times: **15**, 15.3 min; **16**, 19.7 min]. Physical data: **15** NMR δ: 0.76 (9H, s), 0.9—2.3 (5H, m); 3.54 (1H, broad S), 5.6—6.1 (2H, m), 7.0—7.3 (5H, m); IR (liq. film) ν: 3020, 2945, 2870, 1600, 1498, 1480, 1452, 1400, 1370, 1238, 1078, 1032, 880, 785, 760, 720, 702. **16** NMR δ: 0.96 (9H, s), 1.1—2.1 (5H, m), 2.06 (s, impurity), 3.2—3.5 (1H, m), 5.6—6.1 (2H, m), 7.0—7.3 (5H, m). IR (liq. film) ν: 3020, 2940, 2860, 1600, 1495, 1480, 1452, 1398, 1370, 1226, 1075, 1032, 1020, 990, 890, 850, 818, 767, 756, 730, 700.

*Characterization of **15**.* **15** (60 mg), dissolved in ethyl acetate (5 ml) was hydrogenated over 10% Pd–C as a catalyst to give *trans*-1-*t*-butyl-3-phenylcyclohexane (**18**) (54 mg) as the sole product. **18** NMR δ: 0.87 (9H, s), 0.9—2.0 (7H, m), 2.0—2.5 (2H, m), 2.95—3.3 (1H, broad s), 6.9—7.4 (5H, m). IR (liq. film) ν: 2930, 2850, 1600, 1500, 1470—1480, 1450, 1400, 1370, 1230, 1030, 780, 757, 728, 700.

18 (20 mg), dissolved in DMSO (6 ml), was treated with potassium *t*-butoxide (100 mg) at 120—130 °C for 1.5 h under nitrogen atmosphere to give *cis*-isomer[10] of **18** (5 mg). An authentic *cis*-isomer was synthesized from 4-*t*-butyl-2-phenyl-1-cyclohexanone by Wolff-Kischner reduction (KOH–hydrazine hydrate in diethylene glycol) in 74% yield and identified. *cis*-1-*t*-Butyl-3-phenylcyclohexane NMR δ: 0.89 (9H, s), 0.9—2.1 (9H, m), 2.2—2.8 (1H, m), 6.9—7.3 ((5H, m). IR (liq. film) ν: 3030, 2930, 2850, 1602, 1500, 1480, 1450, 1400, 1370, 1240, 1072, 1032, 762, 701. Found: C, 88.89; H, 11.39%. Calcd for $C_{16}H_{24}$; C, 88.82; H, 11.18%.

*Characterization of **16**.* Catalytic hydrogenation of **16** (20 mg) over platinum oxide (5 mg), dissolved in ethyl acetate, gave *cis*-1-*t*-butyl-4-phenylcyclohexane (**19**) as a colorless liquid. **19** NMR δ: 0.81 (9H, s), 0.9—2.0 (7H, m), 2.0—2.42 (2H, broad d), 3.02 (1H, broad s), 6.95—7.4 (5H, m). IR (liq. film) ν: 2930, 2850, 1602, 1500, 1480, 1452, 1400, 1370, 1028, 802, 760, 730, 700. Found: C, 88.89; H, 11.29%. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18%.

When 10% Pd–C was used as a catalyst in place of platium oxide, some *trans*-1-*t*-butyl-4-phenylcyclohexane was formed along with **19**. Isomerization of **19** to the *trans*-isomer was carried out (DMSO/*t*-butoxide) as described above for that of **18**.[10] *trans*-Isomer of **19**: mp 40.5—41 °C. NMR δ: 0.87 (9H, s), 0.9—2.1 (9H, m), 2.1—2.6 (1H, m), 6.9—7.3 (5H, m). IR (liq film) ν: 2930, 2840, 1600, 1498, 1480, 1450, 1400, 1370, 1230, 1018, 898, 760, 700. This compound was identified with an authentic sample.[10]

A Competitive Benzyne Reaction of a Representative Olefin with Cyclohexene. Solid benzenediazonium-*o*-carboxylate, prepared from 20 mmol of anthranilic acid,[23] suspended in dioxane (100 ml) containing 10 mmol each of cyclohexane and an olefin, was stirred under heating at 50—52 °C until the gas evolution had ceased. After the usual work-up (see above experiment on 4-*t*-butylcyclohexene), the product mixture was roughly chromatographed on Silicic Acid (100 g) using benzene as solvent. The hydrocarbon fraction was rechromatographed on Silicic Acid (50 g) with the use of hexane as solvent. The products were estimated and separated into their components with use of GLC. For GLC separation, two kinds of columns, *i.e.*, a 10% polyethylene glycol succinate on Chromosorb WAW, 1/4 inch × 2 m (Column 1), and a 10% silicone DC-QF-1 on Chromosorb WAW, 1/4 inch × 3 m (Column 2), were used. The retention times are: On column 1: (column temp 140 °C; Helium flow rate, 30 ml/min) **6**, 2.68; **7**, 3.6; **8**, 6.0 min; (column temp 130 °C; He, 20 ml/min) **9**, 12.4, **10**, 14.9 min; (column temp 150 °C; He, 20 ml/min) **12**, 12.4; **8**, 4.95 min. On column 2: (column temp 180 °C; He, 20 ml/min) **14**, 9.5; **13**, 11.3 min; (column temp 150 °C; He, 20 ml/min) **15**, 6.2; **16**, 7.5; **8**, 3.45 min.

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