Reaction of Optically Active *exo*- and *endo*-2-Bromonorbornane with Nitronium Tetrafluoroborate in Acetonitrile. Evidence for a Carbenium Ion Pathway

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Received February 22, 1978

Oxidation of both *exo*- and *endo*-2-bromonorbornane with nitronium tetrafluoroborate in acetonitrile afforded *N*-*exo*-2-norbornylacetamide. Optically active *exo*-2-bromonorbornane afforded racemic acetamide, while 5% retention of optical activity was observed with the endo isomer. The data are consistent with a carbenium ion intermediate. A highly stereoselective conversion of optically active norcamphor to *endo*-2-bromonorbornane of known absolute configuration is described. Racemic *endo*-2-chloronorbornane has also been prepared. The ^{13}C NMR spectra of the *exo*- and *endo*-2-bromo- and -chloronorbornanes are compared to their corresponding alcohols.

Although the nitronium ion (NO_2^+) has been utilized extensively in electrophilic addition reactions with aromatic substrates, this potent oxidizing agent has only recently been applied to completely saturated molecules.[2] Olah has reported the nitration of alkanes with NO_2PF_6 in methylene chloride–sulfolane solvent[3] and the oxidation of alkyl methyl ethers with NO_2BF_4 in methylene chloride.[4] In a mechanistic study[5] the reaction of nascent nitronium ion with isobutane has been shown on the basis of kinetic isotope effects to involve rate-limiting hydride abstraction. The nitronium ion has been generated in situ by dehydration of nitric acid with sulfuric acid[5] or by reaction of nitric acid with hydrohalic acid. Under the latter conditions,[6] alkyl iodides and bromides were found to undergo halogen exchange (after being transformed into carbenium ions and subsequently recaptured by chloride or fluoride ion). Heterolytic cleavage of the carbon–halogen bond under these rigorous reaction conditions was supported by the observation that optically active 2-halooctanes afforded only racemic products.[6a]

We have recently found that a variety of alkanes, alkyl halides, and alkyl methyl ethers can be easily and efficiently converted into their corresponding acetamides upon treatment with nitronium tetrafluoroborate in acetonitrile.[7] We postulate that oxidation occurs by electrophilic attack by $NO_2^+BF_4^-$ with abstraction of either hydride, halide, or methoxide ion to form a carbenium ion followed by solvent capture and hydrolysis of the intermediate nitrilium ion.

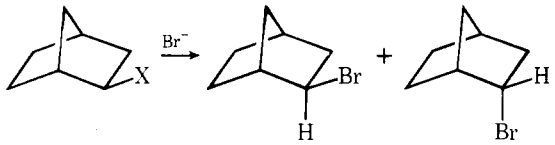
$$R_3CX + NO_2BF_4 \xrightarrow[0\text{–}25\ ^\circ C]{CH_3CN} [R_3CN{\equiv}CCH_3]^+ \xrightarrow{H_2O} R_3CNHC(=O)CH_3 \quad (1)$$

We now report a mechanistic study on the oxidation of optically active diasteromerically related norbornyl bromides that provides convincing evidence for a carbenium ion intermediate in these transformations. We report a stereoselective synthesis of optically active *endo*-2-bromonorbornane of known absolute configuration. Conceptually, this synthetic method may be extended to the preparation of other endo-2-substituted norbornanes.

Results and Discussion

Synthesis of *endo*-2-Bromonorbornane. Our principal goal in this study was to provide a mechanistic probe that would support our contention that alkyl halide oxidation by NO_2^+ involves a discrete carbenium ion intermediate.[7] *exo*- and *endo*-2-norbornyl derivatives have played a key role in carbenium ion chemistry and consequently we have elected to compare the stereochemical results of our oxidative cleavage of a carbon–bromine bond to prior solvolysis studies where carbenium ion behavior has been well established.

Our first objective was to prepare optically active *exo*- and *endo*-2-bromonorbornane. An examination of the literature revealed a stereoselective synthesis[8] of the *exo*-bromide from (−)-*endo*-2-hydroxynorbornane (1). The *exo*-bromide **2** is formed with partial racemization upon treatment of *endo*-**1** with bromine and triphenylphosphine. Although the racemic *endo*-bromide **3** has been prepared,[9] only a single preparation of optically active *endo*-2-bromonorbornane has been reported.[8] The reaction of (+)-*exo*-2-hydroxynorbornane (**4**) with bromine and triphenylphosphine afforded both diastereomeric 2-bromides with the desired (+)-*endo*-bromide as the minor product. Although the procedure[8] is reproducible, the isolation method is tedious and the desired product is obtained in less than 10% yield. In general, preparation of optically active endo-2-substituted norbornanes by nucleophilic displacement of exo leaving groups is unsatisfactory since this reaction often fails to occur efficiently or is attended by competing solvolysis affording racemic exo products[8] (eq 2). Our alternate route circumvents this problem by employing



major product (racemic) minor product (optically active) (2)

a free-radical pathway which affords a much higher stereoselectivity favoring the endo isomer.

Norcamphor was prepared by hydroboration of norbornene using tetraisopinocamphenyl diborane derived from (+)-α-pinene.[10] Oxidation of the resulting (−)-*exo*-2-norbornanol afforded (+)-norcamphor (**5**), $[\alpha]^{25}_D$ 8.3°, which is 28.4% optically pure based upon a reported rotation of 29.1° for optically pure (1*S*,4*R*)-(+)-**5**.[11]

Bromination of (+)-norcamphor, $[\alpha]^{25}_D$ 8.3°, with phosphorus pentabromide afforded (1*S*,4*R*)-2,2-dibromonorbornane (**6**) (80%), $[\alpha]^{25}_D$ −4.2°. Since the stereospecificity of this process was unknown, the optical purity of **6** was determined by reversion to its precursor, (+)-**5**, by silver-assisted solvolysis in aqueous acetone (Scheme I). The recovered ketone **5** had $[\alpha]^{25}_D$ 8.0° and we conclude that dibromide formation is stereospecific within experimental error. The dibromide darkened on standing and did not give a satisfactory elemental analysis. It was, therefore, quickly utilized after its preparation.

Reduction of the 2,2-dibromide **6**, [α] −4.2°, with tri-*n*-butyltin hydride resulted in a 15 to 85 mixture of *exo*- and *endo*-2-bromonorbornanes. The observed stereoselectivity is consistent with reported k_{exo}/k_{endo} ratios reported for the norbornyl[12] and 2-chloronorbornyl[13] radicals. Attack by the

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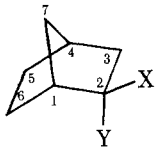
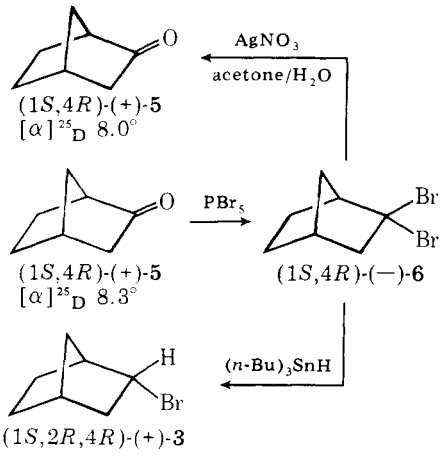
Table I. ^{13}C Chemical Shifts of 2-Substituted Norbornanes[a,b]



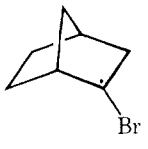
X	Y	C-1	C-2	C-3	C-4	C-5	C-6	C-7
H	H[c]	36.4	29.8	29.8	36.4	29.8	29.8	38.4
Cl	H	46.1	62.2	43.6	35.1	28.2	26.8	36.6
H	Cl	43.7	61.2	41.0	37.1	29.5	22.3	38.1
Br	H	46.6	53.9	43.9	37.1	28.2	27.6	35.5
H	Br	44.0	54.0	41.6	(37.1)[d]	29.5	24.5	(37.7)[d]
OH	H[e]	44.5	74.4	42.4	35.8	28.8	24.9	34.6
H	OH[d]	43.1	72.5	39.6	(37.7)[d]	30.3	20.4	(37.8)[d]

[a] Chemical shifts in ppm from Me_4Si. [b] Chloroform solvent used. [c] See G. S. Poindexter and P. J. Kroop, *J. Org. Chem.*, **41**, 1215 (1976). [d] Parentheses indicate uncertain assignments. [e] See G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 48.

Scheme I



highly reactive reducing agent, Bu_3SnH, on the incipient radical **7** from the exo direction should afford the desired (1*S*,2*R*,4*R*)-(+)-*endo*-2-bromonorbornane (**3**) with the same optical purity as the starting ketone.



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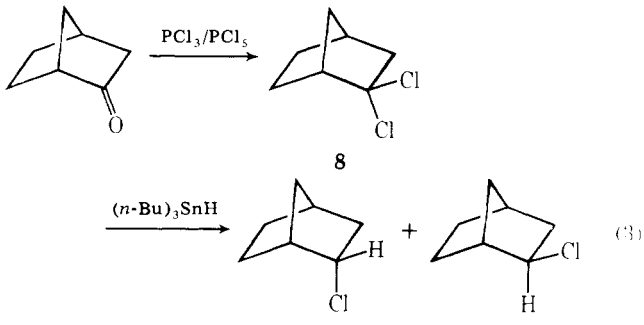
The structure of *endo*-2-bromonorbornane was established by spectroscopic techniques. The compound exhibited the correct molecular ion in its mass spectrum. Its infrared spectrum was distinctly different from the exo isomer. Since the two isomers are not readily separated by gas chromatography, a mixture of exo and endo isomers was synthesized by two independent methods.[8,9b] The ^1H NMR spectrum of the mixture clearly shows the methine absorptions of **2** and **3** at 3.7 and 4.3 ppm, respectively. The most convincing structural evidence comes from ^{13}C NMR since minor contamination of **3** with its exo isomer is not readily discernable by ^1H NMR or infrared spectroscopy. The ^{13}C NMR spectra of both *exo*- and *endo*-2-bromides show seven resonances for the nonequivalent carbon atoms present. The trends noted for the C_1 and C_3 chemical shifts for the isomeric 2-bromides and chlorides are consistent with the assignments given to the corresponding alcohols (Table I). We were able to determine the approximate amount of contamination of endo halides by their exo isomers by averaging the ratios of the carbon resonances.

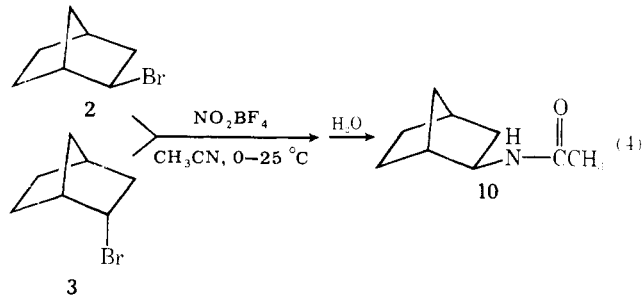
To further test the generality of this stereoselective method of preparing endo-2-substituted norbornanes, we have also synthesized racemic *endo*-2-chloronorbornane (**9**) by a similar procedure. 2,2-Dichloronorbornane was prepared by the reaction of PCl_3/PCl_5 and norcamphor in 65% yield.[14] Subsequent reduction of **8** with $(n\text{-}Bu)_3SnH$, in the presence of a catalytic quantity of benzoyl peroxide, afforded *endo*-2-chloronorbornane (**9**) (42%). Contamination of the product with approximately 13% of the exo isomer was established via ^{13}C NMR (eq 3). We again experienced difficulty in obtaining good separation of the two isomers by gas chromatography.



In general, this overall synthetic procedure allows the preparation of optically active *endo*-2-norbornyl compounds of known absolute configuration from readily available norcamphor. The minor optically active exo isomers can be removed by previously reported methods[8,13] if necessary.

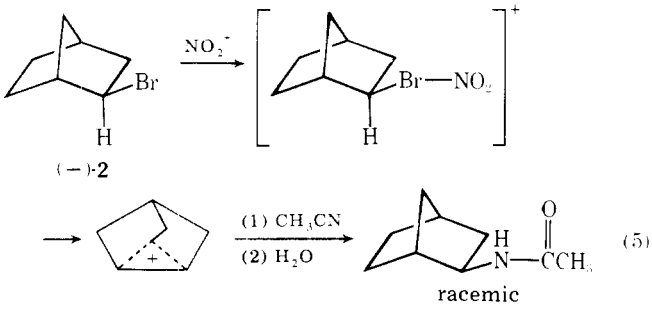
The synthesis of optically active *exo*-2-bromonorbornane utilized the procedure of Shaefer.[8] Accordingly, (1*R*,4*S*)-(−)-norcamphor, $[\alpha]^{25}_D$ −15.8°, was reduced with sodium borohydride in ethanol affording (1*R*,2*S*,4*S*)-(−)-*endo*-2-hydroxynorbornane (**1**), $[\alpha]^{25}_D$ −0.95° (53.4% optically pure).[11] Bromination of (−)-**1** with triphenylphosphine and bromine in benzene afforded (1*R*,2*R*,4*S*)-**2**, $[\alpha]^{25}_D$ −6.4° (ca. 30% optically pure).[8]

Oxidation of *exo*- and *endo*-2-Norbornyl Bromide. The reaction of both *exo*- and *endo*-2-norbornyl bromide with $NO_2^+BF_4^-$ in acetonitrile afforded *N*-(*exo*-2-norbornyl)-acetamide (**10**) (eq 4). The structure of **10** was established by



an independent synthesis involving acetylation of *exo*-2-norbornylamine. The oxidation of optically active **2**, $[\alpha]^{25}_D$ −6.4°, afforded **10** with no detectable optical activity. The comparable reaction of the endo isomer **3**, $[\alpha]^{25}_D$ 4.67° (~27% optically pure), gave *exo*-acetamide **10** with $[\alpha]^{25}_D$ 0.8°. The optical purity of this sample was established by NMR to be between 1.2 and 1.6% using the chiral chemical shift reagent Eu(opt) which achieved a separation (ca. 2 Hz) of the amide methyl signals. Thus, the stereospecificity of the oxidation of the *endo*-bromide was approximately 6% with net inversion of configuration at C-2. This value has been corrected for the 15% of the exo isomer present in the starting bromide which affords racemic *exo*-acetamide. The (1*S*,2*S*,4*R*)-exo contaminate also has a positive sign of rotation of comparable magnitude to that of the endo diasteromer.

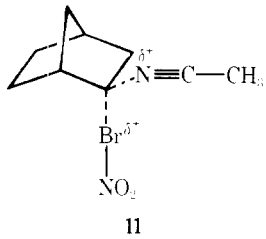
These results suggest a mechanism involving initial complexation of NO_2^+ with the *n* electrons on the bromine. With the exo isomer heterolysis of the carbon–bromine bond occurs in concert with a Wagner–Meerwein rearrangement forming the symmetrical norbornyl cation. Solvent capture of this cation and hydrolysis of the nitrilium ion would necessarily afford a racemic acetamide (eq 5).



(5)

racemic

In contrast, during oxidation of the endo isomer, the C_2–C_6 orbital alignment is not as favorable for rearrangement and some product arises by cation capture on the exo face (**11**) prior to rearrangement resulting in inversion of configuration at C-2.



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Similar results were observed during the solvolysis of optically active *exo*- and *endo*-2-norbornyl brosylate. In these studies,[15] Winstein and Trifan observed that, whereas the solvolysis of optically active *endo*-2-norbornyl brosylate afforded exo products in which 7–8% of the optical activity was retained, a similar reaction with optically active *exo*-2-norbornyl brosylate afforded racemic exo-2-substituted norbornanes.

Our results with the optically active norbornyl bromides provide convincing evidence for a mechanism which proceeds through a nonclassical carbenium ion. In general, we suggest that the oxidation of alkyl bromides involves a mechanism in which a considerable positive charge is formed on the carbon bearing the bromine. Our proposed mechanism is supported by the observation that the comparable oxidation of optically active 2-bromooctane with NO_2^+ occurs with very low stereospecificity and net inversion of configuration.

Experimental Section

2,2-Dibromonorbornane (6). To 4.0 g (0.036 mol) of (+)-norcamphor, $[\alpha]^{25}_D$ 8.26° (*c* 1.9 $CHCl_3$), was added 23.3 g (0.054 mol) of phosphorus pentabromide. The solid mixture liquified within 30 min and was stirred at 60–70 °C for 1 h. The excess PBr_5 was destroyed by carefully pouring the reaction mixture into 100 mL of water at 60 °C. The aqueous mixture was extracted with 4 × 25 mL of methylene chloride. The combined organic fractions were washed with 2 × 20 mL of water, dried ($MgSO_4$), and concentrated to afford 7.2 g (80%) of **6**: $[\alpha]^{25}_D$ −4.23° (*c* 2.2, $CHCl_3$); IR (neat) 2950, 2870, 1755, 1455, 1310, 1070 and 670 cm^{-1}; NMR ($CDCl_3$) δ 0.9–3.1 (multiplet), 3.9–4.5 (multiplet).

***endo*-2-Bromonorbornane (3).** To 5.89 g (0.024 mol) of crude 2,2-dibromonorbornane was added dropwise 6.02 g (0.024 mol) of tri-*n*-butyltin hydride at a rate which maintained the temperature between 30 and 40 °C. After stirring at room temperature for 16 h, distillation afforded 2.1 g (50.3%) of **2** and **3** in a ratio of 15:85: bp 30–70 °C (10 mm); IR (neat) 2950, 2880, 1750, 1455, 1320, 1305, 1230, 1190, 900, 765, 755, and 645 cm^{-1}.

When this reaction was repeated with optically active **6**, $[\alpha]^{25}_D$ −4.23° (*c* 2.2, $CHCl_3$), the *exo*- and *endo*-2-bromonorbornanes had $[\alpha]^{25}_D$ 4.67 (*c* 2.57, $CHCl_3$).

***endo*-2-Chloronorbornane (9).** To 8.0 g (0.049 mol) of 2,2-dichloronorbornane[14] and a minute quantity of benzoyl peroxide was added dropwise 14.2 g (0.057 mol) of tri-*n*-butyltin hydride. After heating at 80 °C for 1 h, the mixture was distilled to afford 2.7 g (42%) of **9**: bp 58–60 °C (17 mm) [lit.[14] 51–53 °C (17 mm)]. The infrared spectrum compared favorably to one published by Roberts.[9a] The exo/endo ratio was established by ^{13}C NMR (Table I) to be 13:87.

Oxidation of *exo*-2-Norbornyl Bromide. A solution of 1.77 g (10 mmol) of *exo*-2-bromonorbornane was added to 1.33 g (10 mmol) of nitronium tetrafluoroborate in 30 mL of acetonitrile at 0 °C. After stirring at 0 °C for 1 h, the reaction was warmed to room temperature and allowed to stir an additional 2 h. The oxidation was then quenched and the crude product was purified to afford 0.76 g (50%) of *N*-(*exo*-2-norbornyl)acetamide: mp 141–142 °C (lit.[16] 140–141 °C); IR (Nujol) 3180, 3085, 2920, 2850, 1650, 1550, 1460, 1380 and 715 cm^{-1}; NMR ($CDCl_3$) δ 5.9 (m, 1 H), 3.9 (m, 1 H), 2.15 (m, 2 H), 1.95 (s, 1 H) and 0.9–1.9 (m, 8 H). The infrared and NMR spectra of this amide were identical to those of a sample of *N*-(*exo*-2-norbornyl)acetamide obtained by the reaction of *exo*-norbornylamine with acetic anhydride.

Reaction of Optically Active *exo*-2-Bromonorbornane with Nitronium Tetrafluoroborate in Acetonitrile. To a solution of 0.174 g (1 mmol) of *exo*-2-bromonorbornane, $[\alpha]^{25}_D$ −6.4° (*c* 1.82, $CHCl_3$), in 2 mL of acetonitrile was added 0.133 g (1 mmol) of nitronium tetrafluoroborate. After stirring at 0 °C for 1 h, the solution was warmed to room temperature and stirred an additional 2 h. The reaction was quenched and afforded 0.62 g (41%) of *N*-(*exo*-2-norbornyl)acetamide which had $[\alpha]^{25}_D$ 0.0° (*c* 5.5, $CHCl_3$). A duplicate experiment afforded 0.58 g (38%) of the amide having $[\alpha]^{25}_D$ 0.0° (*c* 3.95, $CHCl_3$), mp 140–141 °C.

Oxidation of Optically Active *endo*-2-Norbornyl Bromide with Nitronium Tetrafluoroborate in Acetonitrile. To 0.266 g (2 mmol) of nitronium tetrafluoroborate in 4 mL of acetonitrile at 0 °C was added 0.348 g (2 mmol) of *endo*-2-norbornyl bromide, $[\alpha]^{25}_D$ 4.67° (*c* 2.57, $CHCl_3$). After stirring at 0 °C for 1 h, the reaction was warmed to room temperature and allowed to stir an additional 3 h. The oxidation was quenched with water and the acetamide was isolated in the usual manner to afford 0.183 g (60%) of *N*-(*exo*-2-norbornyl)acetamide having $[\alpha]^{25}_D$ 0.81° (*c* 2.7, $CHCl_3$). A duplicate experiment afforded 0.178 g (58%) of the amide having $[\alpha]^{25}_D$ 0.71° (*c* 2.9, $CHCl_3$). The gas chromatography retention time and infrared spectrum of these samples were identical to an authentic sample of *N*-(*exo*-2-norbornyl)acetamide.

Acknowledgement. We wish to acknowledge support of this research by the National Science Foundation (CHE 76 21992).

Registry No.—(1*R*,2*S*,4*S*)-(−)-*endo*-**1**, 36779-79-0; (1*R*,2*R*,4*S*)-(−)-*exo*-**2**, 2566-14-5; (+)-*exo*-**2**, 67815-05-8; (1*S*,2*R*,4*R*)-(+)-*endo*-**3**, 67844-23-9; (+)-*endo*-**3**, 67815-06-9; (1*S*,4*R*)-(−)-**6**, 67815-07-0; (+)-**6**, 67844-24-0; (+)-**8**, 67844-25-1; (+)-*endo*-**9**, 67844,26-2; (+)-exo-**9**, 67844-27-3; (1*S*,2*S*,4*R*)-(+)-*exo*-**10**, 67844-28-4; (+)-*exo*-**10**, 67815-08-1; (+)-norcamphor, 2630-41-3; phosphorus pentabromide, 7789-69-7.

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Kinetics of the Reactions of Phenylketene Dimethyl Acetal with Azocarboxylate Esters

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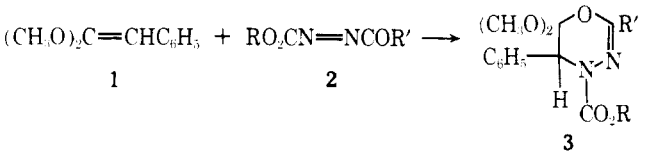
Received January 4, 1978

The kinetics of the reaction of phenylketene dimethyl acetal with diethyl azodicarboxylate, dimethyl azodicarboxylate, and ethyl benzoylazocarboxylate to give 5,6-dihydrooxadiazines have been determined. The relative rates in benzene at 40 °C are 1:3.22:29.1. The reactions are accelerated slightly by polar solvents. The relative rates in benzene and acetonitrile are 1:13.4 and 1:3.4 for diethyl azodicarboxylate and ethyl benzoylazocarboxylate, respectively. The enthalpies of activation were highly negative (−36 to −46 cal deg^{-1} mol^{-1}), typical of other $2\pi + 4\pi$ cycloaddition reactions. The question of the involvement of a 1,4-dipolar intermediate vs. a concerted cycloaddition is discussed.

Although there are many reports on the cycloaddition reactions of azocarboxylate esters, there have been only a few kinetic studies. Rodgman and Wright[1] examined the Diels–Alder reactions of dimethyl and diethyl azodicarboxylates with cyclopentadiene. They reported that the rate of reaction with the methyl ester was increased slightly as the solvent was changed from petroleum ether to benzene to dioxane (relative rate, 1:3.3:4.6). Activation parameters calculated from their data on the ethyl esters indicate the normal low enthalpy of activation (11.6 kcal/mol) and highly negative entropy of activation (−33 eu) commonly observed in Diels–Alder reactions. Gustorf and Kim[2] examined the kinetics of the reaction of indene with diethyl azodicarboxylate under the assumption that the product was a 1,2-diazetidine. The product was later shown to be a 5,6-dihydrooxadiazine.[3,4] The reaction was reported to be somewhat faster in polar solvents (relative rate, 1:1.5:5.2:6.2:8.6 in ethyl acetate, benzene, acetic anhydride, acetonitrile, and indene, respectively). The activation parameters were similar to those reported for the reaction with cyclopentadiene, except that the entropy of activation was much more negative ($\Delta H^* = 12.8$ kcal/mol; $\Delta S^* = -44$ eu in indene). Gustorf and co-workers[3] also reported the kinetics of the reaction of diethyl azodicarboxylate with ethyl vinyl ether; in this case the product is a 1,2-diazetidine. Here also, the reaction is accelerated slightly in the more polar solvents (relative rate, 1:1.3:1.7:5.7 in ethyl vinyl ether, ethyl acetate, benzene, acetic anhydride, and acetonitrile). The activation parameters of this $\pi^2 + \pi^2$ reaction were remarkably similar ($\Delta H^* = 11.0$; $\Delta S^* = -46$ in ethyl acetate) to those of the π^2s + π^4s Diels–Alder reaction above. However, in spite of the similarity, a stepwise mechanism was postulated based on a study of secondary isotope effects at the reaction centers.[6,7]

In a study of the reactions of ketene acetals with azocarboxylate esters, it has been shown that the initial products are 5,6-dihydrooxadiazines.[8] In this paper, the kinetics of the reaction of phenylketene dimethyl acetal with dimethyl and diethyl azodicarboxylates and with ethyl benzoylazocarboxylate are reported. The kinetics were monitored by following



a, R = CH_3; R′ = OCH_3
b, R = C_2H_5; R′ = OC_2H_5
c, R = C_2H_5; R′ = C_6H_5

the rate of disappearance of the colored azo compound spectrophotometrically. The reactions were carried out under pseudo-first-order conditions using a 10–40-fold molar excess of phenylketene dimethyl acetal. The first-order plots were linear over 5 half-lives. The rate constants are given in Table I. The second-order rate constants were calculated by dividing k_{obsd} by the phenylketene dimethyl acetal concentration.

The relative rates at 40 °C of diethyl azodicarboxylate, dimethyl azodicarboxylate, and ethyl benzoylazocarboxylate, calculated from the data in Table I, are 1:3.22:29.1. The slower rate for the diethyl ester compared with the dimethyl ester is consistent with the Diels–Alder reactions of these compounds with cyclopentadiene, where the relative rates are 1:5.3 in benzene at 23.5 °C.[1] It is also in agreement with the qualitative observation of Firl and Sommer that the dimethyl ester reacts faster than the diethyl ester in its reaction with phenyl vinyl ether; however, in this case the products are mixtures of a 1,2-diazetidine and a 5,6-dihydrooxadiazine in 77:23 and 65:35 ratios for the dimethyl and diethyl esters, respectively.[9]

The increased rate of reaction of ethyl benzoylazocarboxylate over that of the azodicarboxylate esters was not expected, since the reaction of azodibenzoyl with vinyl ethers to give 5,6-dihydrooxadiazines is apparently rather slow.[10] The reaction of ethyl benzoylazocarboxylate with phenylketene dimethyl acetal is regiospecific, giving only **3c**.[8b] Apparently it also reacts with phenyl vinyl ether regiospecifically,[10] although details were not given.

The rates of reaction of both diethyl azodicarboxylate and

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