(d), 134.78 (s), 138.06 (s), 142.61 (s), 143.02 (s), 157.75 (s), 158.77 (s). Anal. Calcd for $C_{41}H_{42}N_2O_2$: C, 82.79; H, 7.12; N, 4.71. Found: C, 82.64: H, 7.06: N, 4.61.

General Procedure for Enantioselective Addition of Diethylzinc to Aldehydes. A mixture of diethylzinc (1 M hexane solution, 0.32 mL) and a chiral piperzine 13 (0.16 mmol) in toluene (5 mL) was refluxed for 30 min. Diethylzinc (1 M hexane solution, 4.8 mL) and an aldehyde (3.2 mmol) were added to the mixture at 0 °C. The mixture was stirred for 15–24 h at room temperature. After 1 N HCl (20 mL) was added, the mixture was extracted with CH_2Cl_2. The products, secondary alcohols, were isolated by PTLC (silica gel, hexane–AcOEt).

Bromination of Alkenes in Acetonitrile. A Rate and Product Study

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The reaction of simple alkenes and aryl alkenes with molecular bromine in damp MeCN occurred with solvent incorporation to give 2-bromo-1-(*N*-acetylamino)alkanes, 2-methyloxazolines, 2-acetoxyalkylamine hydrobromides, and 2-(*N*-acetylamino) alcohols. These products arose by the transformation of initially formed 2-bromo-1-(*N*-acetylamino)alkanes obtained by MeCN attack on bromonium or bromocarbonium ions to give nitrilium tribromide salts. These reacted with water to give 2-bromo-1-(*N*-acetylamino)alkanes. The kinetic profile of the reaction showed a very fast initial reaction of the alkene and Br_2 to yield the nitrilium tribromide, followed by a much slower reaction of Br_3^- with the alkene. The incorporation of MeCN was Markovnikov and stereospecifically anti. The degree to which incorporation of solvent occurred depended upon the alkene structure and the initial reagent concentrations. A rationalization for the observed chemoselectivity and its dependence on the reaction conditions is offered.

Introduction

Although the ionic bromination of alkenes[1] by molecular bromine in both aprotic[2] and protic[3] solvents of low polarity and in highly polar protic solvents[4] has been extensively studied, no systematic investigation of the reaction in polar aprotic solvents has been made. The halogenation of alkenes in such nucleophilic solvents can lead to the incorporation of solvent into the products.[5,6] The synthetic potential of such a reaction has been largely overlooked. For example, the reaction of chlorine and bromine with alkenes in MeCN has been reported[7] to give, as minor products, vicinal (*N*-acetylamino)haloalkanes. These arose from MeCN attack on halonium ion intermediates. It was later shown that the yield of such products could be increased if a stoichiometric amount of silver perchlorate was present in the reaction mixture. That additive prevented dibromide formation by scavenging the nucleophilic Br^- ions.[8] On the other hand, compounds that had incorporated MeCN were not observed during the bromination of *cis*- and *trans*-2-butene[3f] or *cis*- and *trans*-stilbene.[9]

To the best of our knowledge, no investigation of the rate of alkene bromination in MeCN has so far appeared in the literature. However, the bromination of *cis*- and *trans*-stilbene in valeronitrile has been reported.[10] This reaction exhibited a very peculiar kinetic course. A fast consumption of halogen was followed by a dramatic slowing of the reaction. No reasonable explanation was given for this behavior.

To obtain a more comprehensive picture of the reaction, we undertook a systematic product and kinetic study of alkene bromination in MeCN. The results showed that the incorporation of MeCN was general, regiospecific, and stereospecifically anti. The degree to which it occurred was markedly affected by both the structure of the alkene and by the reaction conditions.

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Results

Simple Alkenes. When solutions of cyclohexene and bromine in damp (0.05–0.5% water) MeCN[11] were mixed and the resulting solution was immediately examined by UV–vis spectrophotometry, an intense absorption band centered at 270 nm, the λ_{max} typical for the Br_3^- anion,[12] was observed. Furthermore, the solution became strongly acidic and exhibited high electrical conductivity. These observations pointed to the formation of an $H^+Br_3^-$ species.

Additional evidence for the existence of such a species was the disappearance of the typical Br_2 absorption band at λ_{max} = 380 nm, and the concomitant appearance of a new absorption band at λ_{max} = 270 nm ($\epsilon_{max} = 5.7 \times 10^4$ M^{-1} cm^{-1}) observed in the spectra of solutions obtained by mixing 5×10^{-3} to 5×10^{-6} M HBr and Br_2 solutions in MeCN. It was found that there was no dissociation of $H^+Br_3^-$ to HBr and Br_2 on dilution within the previous concentration range. A value of $K \geq 10^7$ M^{-1} was thus calculated for the equilibrium constant of the reaction shown in eq 1. An equilibrium constant, K, of 10^7 M^{-1}

$$HBr + Br_2 \overset{K}{\rightleftharpoons} H^+Br_3^- \quad (1)$$

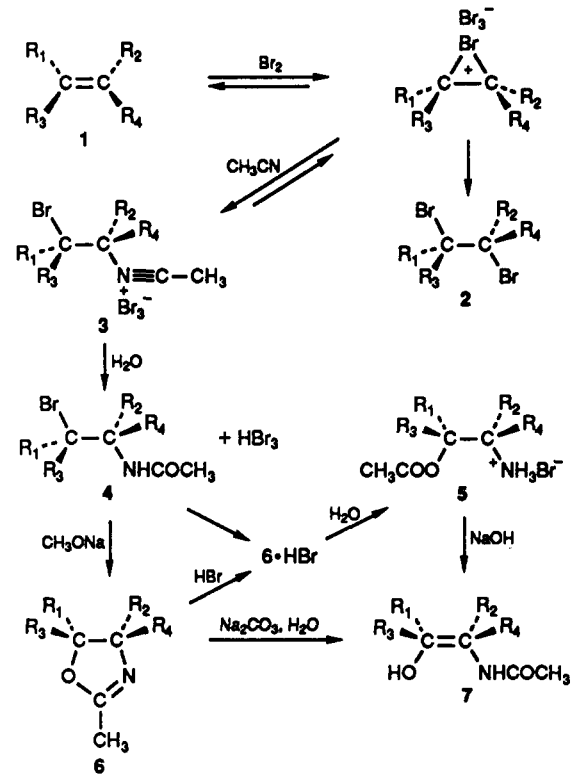
had been determined potentiometrically for the $(C_2H_5)_4N^+Br^-$ + Br_2 system in MeCN.[13,14] These $H^+Br_3^-$ solutions exhibited an electrical conductivity that was a linear function of the concentration up to 5×10^{-3} M. Similar values for the molar conductance were obtained for $H^+Br_3^-$ solutions ($\Lambda^m = 1.40 \times 10^{-1}$ S cm^2 M^{-1}) and for $Bu_4N^+Br_3^-$ solutions ($\Lambda^m = 1.45 \times 10^{-1}$ S cm^2 M^{-1}). A much lower value, $\Lambda^m = 2.4 \times 10^{-2}$ S cm^2 M^{-1}, was found for HBr solutions.

From the values of ϵ_{max} and Λ^m for the $H^+Br_3^-$ solutions, it was calculated that the reaction mixture obtained by mixing MeCN solutions of Br_2 and cyclohexene in a mole ratio ≥ 2, at $[Br_2] \leq 5 \times 10^{-2}$ M, contained Br_3^- in a concentration comparable to that of the initial alkene. In an attempt to investigate the reaction that formed the Br_3^- ion, 5×10^{-4} M Br_2 and $\geq 2.5 \times 10^{-4}$ M cyclohexene were mixed in a stopped-flow apparatus. The reaction that ensued was monitored in the 350–380 nm range, where the absorption of Br_2 was much less than that of Br_3^-.[12] When the two solutions were mixed, the absorbance attained instantaneously its maximum value, showing that Br_3^- formation was immeasurably fast, even on the stopped-flow time scale. The absorbance remained stable for reactions in which the initial Br_2/cyclohexene mole rato was ≥ 2, but decreased in obedience to a pseudo-first-order rate law when cyclohexene was present in large excess. This behavior appeared to be the consequence of a slower reaction of initially formed Br_3^- with excess alkene. The reaction was second order overall, with $k_2 = 1.70 \pm 0.05$ M^{-1} s^{-1} at 25 °C. The same rate law (eq 2), with $k_2 = 1.55 \pm 0.05$ M^{-1} s^{-1}, was obeyed for the reaction of cyclohexene with $Bu_4N^+Br_3^-$ in MeCN at 25 °C. This reaction gave *trans*-1,2-dibromocyclohexane as the only product.

$$-d[Br_3^-]/dt = k_2[Ol][Br_3^-] \quad (2)$$

A crystalline product was isolated in ca. 90% yield from a reaction performed at initial 5×10^{-2} M Br_2 and 2.5×10^{-2} M cyclohexene (**1a**) in MeCN. It was identified as *trans*-1-(*N*-acetylamino)-2-bromocyclohexane (**4a**) from its ^1H NMR spectrum, which showed signals due to axial protons α to the bromine atom and to the *N*-acetylamino group. That this compound was formed suggested nucleophilic attack of MeCN on a very rapidly formed bromonium ion. This reaction gave an unstable salt of type **3**. Salt **3** then reacted rapidly with the water present in the solvent to give **4a**, with the concomitant release of H^+. The liberation of H^+ was responsible for the acidity developed during the reaction (Scheme I).

Scheme I[a]



[a] Key: a, R_1, R_2 = $(CH_2)_4$, R_3 = R_4 = H; b, R_1, R_2 = $(CH_2)_3$, R_3 = R_4 = H; c, R_1, R_2 = $(CH_2)_5$, R_3 = R_4 = H; d, R_1 = R_2 = R_3 = H, R_4 = *n*-C_4H_9; e, R_1 = R_2 = R_3 = H, R_4 = C_6H_5; f, R_1 = R_4 = C_6H_5, R_2 = R_3 = H.

Heating **4a** with sodium methoxide in methanol yielded the oxazoline **6a**. Treatment of this product with HBr in chloroform gave the protonated species **6**·HBr. Treatment of **6**–HBr with MeCN containing 5% of water yielded *cis*-2-acetoxycyclohexylamine hydrobromide (**5a**). The latter compound was also obtained, presumably by way of the protonated oxazoline, when a solution of **4a** in wet MeCN was refluxed. Deprotonation of **5a** with NaOH induced an acetyl group migration to give *cis*-2-(*N*-acetylamino)cyclohexanol (**7a**). The structures and relative configurations of all these compounds were established by IR and ^1H NMR (Table II).

In order to establish the generality of the reactions described previously, the investigation was extended to include several other alkenes. In contrast to the cyclohexene reaction, those of cyclopentene (**1b**) or cycloheptene (**1c**) and Br_2 performed at initial 2.5×10^{-2} and 5×10^{-2} M reagent concentrations yielded the corresponding *trans*-dibromide as the main product. No product of type **4** was found. However, workup with aqueous $NaHSO_3/NaHCO_3$ gave a low yield of the *cis*-2-acetoxycycloalkylamine hydrobromide **5b** (15%) or **5c** (20%). These were converted to the corresponding *cis*-2-(*N*-acetylamino)cycloalkanols, **7b** and **7c**, by treatment with NaOH.

The regiochemistry of solvent incorporation was investigated with use of 1-hexene (**1d**) as the alkene reactant. 1-Hexene and Br_2 reacted in MeCN at 2.5×10^{-2} and $5 \times$

(11) Bromine is unstable in MeCN over molecular sieves (Fluka, water <0.01%) or in anhydrous MeCN (Aldrich, water <0.005%), and immediately produces Br_3^-.

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Table I. Reaction of Alkenes with Br_2 in MeCN at 25 °C

alkene	[alkene] (M)	[Br_2] (M)	products[a] (%) 2	4	6
1a	2.5×10^{-1}	2.5×10^{-1}	52	41	
	2.5×10^{-2}	2.5×10^{-2}	40	50	
	2.5×10^{-3}	2.5×10^{-3}	27	62	
	2.5×10^{-1}	5×10^{-1}	41	46	
	2.5×10^{-2}	5×10^{-2}	9	91	
	2.5×10^{-3}	5×10^{-3}	6	92	
1b	2.5×10^{-1}	5×10^{-1}	90		
	2.5×10^{-2}	5×10^{-2}	78		
	2.5×10^{-3}	5×10^{-3}	26		
1c	2.5×10^{-1}	5×10^{-1}	94		
	2.5×10^{-2}	5×10^{-2}	68		
	2.5×10^{-3}	5×10^{-3}	27		
1d	2.5×10^{-1}	5×10^{-1}	64		
	2.5×10^{-2}	5×10^{-2}	46		
	2.5×10^{-3}	5×10^{-3}	20		
1e	2.5×10^{-1}	5×10^{-1}	77		
	2.5×10^{-2}	5×10^{-2}	30		
	2.5×10^{-3}	5×10^{-3}	10		
1f	2.5×10^{-2}	5×10^{-2}	44[b]		50
	2.5×10^{-3}	5×10^{-3}	32[b]		68

[a] Yields were determined by GC for 1a–e and by HPLC and ^1H NMR for 1f. [b] The ratio of *meso*- to *d,l*-dibromide was 75:25.

10^{-2} M initial concentrations, respectively, to give, after workup with $NaHSO_3/NaHCO_3$, a complex mixture of 1,2-dibromohexane, **6d**, **6d**·HBr, and **5d**. It was possible to direct the reaction toward the formation of 2-methyl-4-*n*-butyloxazoline (**6d**) as the only product of solvent incorporation by treating the reaction mixture with aqueous Na_2CO_3 instead of aqueous $NaHCO_3$ after removal of the dibromide by extraction with hexane. In this way, **6d** could be obtained in 40% yield. The structure of **6d** was established from its ^1H NMR spectrum, which showed a splitting of the 2-methyl group proton signal into a doublet (J = 1.3 Hz). This splitting, due to a long-range coupling[15] of the methyl group protons with a C(4) proton through the $H_3C—C=N—C—H$ bonds, clearly showed that the *n*-butyl substituent was at C(4). If, however, the reaction mixture was made alkaline with Na_2CO_3 and then was refluxed, opening of the oxazoline ring occurred, and 2-(*N*-acetylamino)-1-hexanol (**7d**, 33%) was isolated. Thus, incorporation of MeCN occurred regiospecifically at C(2) of 1-hexene.

Arylalkenes. The reaction of styrene (**1e**) and Br_2 in MeCN at 2.5×10^{-2} and 5×10^{-2} M initial concentrations, respectively, gave, besides a small amount of 1,2-dibromo-1-phenylethane, products of solvent incorporation. What these products were depended on the workup conditions. 2-Acetoxy-1-phenylethylamine hydrobromide (**5e**) was isolated in low yield (12%) by recrystallization of the crude product mixture after workup with $NaHCO_3/NaHSO_3$. In contrast, 2-methyl-4-phenyloxazoline (**6e**, 56%) was obtained if the reaction mixture was made alkaline with Na_2CO_3 and then was allowed to stand at room temperature. If, however, the alkaline solution was refluxed, 2-(*N*-acetylamino)-2-phenylethanol (**7e**, 50%), the hydrolysis product of **6e**, was isolated. The structures of all the compounds were established by IR and ^1H NMR (Table II). Furthermore, HPLC analysis of the crude product obtained from the Na_2CO_3 treatment at room temperature showed the presence of only one oxazoline product. This observation confirmed that solvent incorporation was regiospecific at the benzylic carbon.

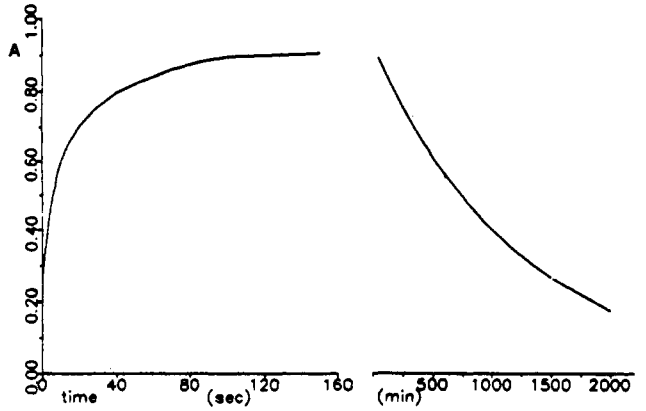

Figure 1. Plots of absorbance (360 nm, 2-cm optical path) vs time for the reaction of Br_2 and *trans*-stilbene at 7.5×10^{-4} and 1.2×10^{-2} M initial concentrations, respectively, in acetonitrile at 25 °C obtained with a stopped-flow apparatus (left side) and a conventional spectrophotometer (right side).

The stereochemistry of MeCN incorporation was next investigated. *trans*-Stilbene (**1f**) served as the alkene reactant. In this case, the reaction was slow enough to follow with the stopped-flow technique the early kinetic event that led to the formation of Br_3^- and that resulted in the appearance of a maximum in the absorbance vs time curves obtained for the reaction with excess alkene (Figure 1). Because the formation of Br_3^- was much faster than its subsequent bromination of the excess alkene, the two reactions could be considered to be completely independent. However, the initial increase in absorbance could not be fitted to a simple kinetic model because the monitored species, Br_3^-, was not the only product of the initial reaction. Dibromide **2f** was concurrently formed. Therefore, the rate law for the attack of free bromine on the alkene was not established.[16] The subsequent consumption of Br_3^- obeyed a second-order rate law (eq 2), with $k_2 = (1.31 \pm 0.10) \times 10^{-3}$ M^{-1} s^{-1} at 25 °C. The same rate law was obeyed, and an identical rate constant, $k_2 = (1.43 \pm 0.08) \times 10^{-3}$ M^{-1} s^{-1} at 25 °C, was calculated for the bromination of *trans*-stilbene by $Bu_4N^+Br_3^-$ in MeCN. The latter reaction yielded *meso*-1,2-dibromo-1,2-diphenylethane as the sole product.

The products from the reaction of *trans*-stilbene (**1f**) and Br_2 performed at initial 2.5×10^{-3} and 5×10^{-3} M reagent concentrations in MeCN were analyzed by HPLC and ^1H NMR. After workup with $NaHCO_3/NaHSO_3$, a 3:1 mixture of *meso*- and *d,l*-1,2-diphenyl-1,2-dibromoethane and a 2-methyl-4,5-diphenyloxazoline (**6f**) were obtained. The oxazoline/dibromide ratio was 7:3. Attempts to isolate the oxazoline by recrystallization of the mixture were unsuccessful and only caused the transformation of the oxazoline into 2-(*N*-acetylamino)-1,2-diphenylethanol (**7f**). The ^1H NMR spectrum of **6f** showed a trans orientation of the phenyl groups, as indicated by the value of the coupling constant (J = 7.6 Hz) between the signals due to the C(4) and C(5) protons, which was typical for a trans arrangement.[17] Because **6f** must have arisen by cyclization of the erythro adduct **4f**, this observation indicated that MeCN incorporation occurred stereospecifically anti. A lower ratio (1:1) of oxazoline **6f** to dibromide was found at the end of reactions performed in the presence of excess alkene, under the conditions

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(16) Measurement of the rate of disappearance of free Br_2 was impracticable because, in MeCN, even at 500 nm the absorption of the Br_3^- formed was far from negligible relative to that of Br_2.

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Table II. Characterization of the Products Obtained from the Reaction of Alkenes 1a–f with Bromine in MeCN

product	mp (°C)	formula	elemental analysis[a] C	H	N	^{1}H NMR[b] (solvent) δ (J (Hz))	IR[c] λ, (cm^{-1})
4a	117–119	$C_8H_{14}NOBr$	43.40	6.55	6.42	(C_6D_6) 0.6–2.1 (8 H), 1.58 (s, CH_3, 3 H), 3.47 (dt, J =	3220–3100,
			(43.65	6.41	6.36)	10.3 and 4.2, CHBr, 1 H), 3.90 (m, W = 33, CHN, 1 H)	1640–1560
5a	224–225	$C_8H_{16}NO_2Br$	40.22	6.67	5.79[d]	(CD_3OD) 1.50–2.10 (8 H), 2.13 (s, CH_3, 3 H), 3.42 (ddd, J =	3100–2500,
			(40.35	6.77	5.88)	10.5, 4.3 and 3.1, CHN, 1 H), 5.12 (m, W = 7, CHO, 1 H)	1740–1250
5b	172–173	$C_7H_{14}NO_2Br$	37.90	6.56	6.23	(CD_3OD) 1.65–2.20 (6 H), 2.12 (s, CH_3, 3 H), 3.65 (dt, J =	3200–2500,
			(37.50	6.25	6.25)	8.2 and 5.3, CHN, 1 H), 5.20 (dt, J = 5.3 and 2.8, CHO, 1 H)	1250, 1740
5c	171–172	$C_9H_{18}NO_2Br$	42.50	7.13	5.45[d]	(CD_3OD) 1.40–2.20 (10 H), 2.13 (s, CH_3, 3 H), 3.55 (m,	3100–2500,
			(42.38	7.19	5.55)	$W_{1/2}$ = 17, CHN, 1 H), 5.20 (m, $W_{1/2}$ = 13, CHO, 1 H)	1745, 1230
5e	162–164	$C_{10}H_{14}NO_2Br$	45.82	5.12	5.57	(CD_3OD)[e] 2.13 (s, CH_3, 3 H), 4.41 (d, J = 7.8, CH_2O, 2	3100–2500,
			(46.18	5.42	5.38)	H), 4.42 (d, J = 4.8, CH_2O, 1 H), 4.66 (dd, J = 7.8 and 4.8, CHN, 1 H), 7.63 (5 H)	1740, 1200
6a	oil	$C_8H_{13}NO$	69.87	9.45	10.30	($CDCl_3$) 1.20–1.70 (8 H), 1.98 (d, J = 1.3, CH_3, 3 H), 3.90	1660, 1438,
			(70.02	9.55	10.20)	(m, $W_{1/2}$ = 24, CHN, 1 H), 4.50 (dt, J = 3.3 and 5.3, CHO, 1 H)	1260
6d	oil	$C_8H_{15}NO$	68.41	10.55	9.79	($CDCl_3$) 0.90 (t, J = 6.5, CH_3, 3 H), 1.20–1.80 (3 CH_2),	1660, 1220
			(68.03	10.71	9.92)	1.98 (d, J = 1.3, CH_3C=N, 3 H), 3.80 (t, J = 7.8, CH_2O, 1 H), 4.00 (m, CHN, 1 H), 4.30 (dd, J = 7.8 and 9.3, CH_2O, 1 H)	
6e	oil	$C_{10}H_{11}NO$	74.82	6.95	8.59	($CDCl_3$) 2.10 (d, J = 1.3, CH_3, 3 H), 4.09 (t, J = 8.4,	1660
			(74.49	6.88	8.69)	CH_2O, 1 H), 4.61 (dd, J = 5.8 and 10.1, CHO, 1 H), 5.18 (m, CHN, 1 H), 7.20–7.40 (5 H)	
7b	94–95	$C_7H_{13}NO_2$	58.43	9.35	9.58	(C_6D_6) 0.80–1.70 (6 H), 1.60 (s, CH_3, 3 H), 3.90 (m, $W_{1/2}$ =	3300, 1625,
			(58.72	9.15	9.78)	11, C*H*OH, 1 H), 4.10 (m, $W_{1/2}$ = 30, C*H*NH, 1 H)	1570
7c	78–81	$C_9H_{17}NO_2$	63.35	10.18	8.05	($CDCl_3$) 1.40–2.00 (10 H), 2.00 (s, CH_3, 3 H), 4.00 (2	3350, 1630,
			(63.13	10.00	8.18)	overlapping m, C*H*(OH) and C*H*(NH))	1530
7d	oil	$C_8H_{17}NO_2$	61.10	10.55	8.50	($CDCl_3$) 0.90 (s, CH_3, 3 H), 1.20–1.70 (3 CH_2), 2.07 (s,	3200, 1650,
			(60.34	10.76	8.79)	CH_3CO, 3 H), 3.50–3.90 (2 overlapping m, CH_2O and CHN)	1560
7f	146–147	$C_{16}H_{17}NO_2$	74.98	6.87	5.28	($CDCl_3$) 1.90 (s, CH_3, 3 H), 4.94 (d, J = 4.7, CHN, 1 H),	3300, 1650,
			(75.26	6.70	5.48)	5.16 (dd, J = 7.9[f] and 4.7, CHO, 1 H), 7.25 (10 H)	1520

[a] Found and, in parentheses, calculated. [b] Exchangeable protons are not reported. [c] Nujol mulls or neat liquids. [d] After 24 h at 80 °C in vacuo. [e] In DMSO-d_6, the signal due to the proton α to nitrogen is a broad multiplet centered at δ 4.80, due to coupling to the NH_3^+ protons. [f] Due to coupling to the OH proton.

described in Figure 1. Furthermore, in this case, the *meso*-/*d*,*l*-1,2-diphenyl-1,2-dibromoethane ratio changed as the reaction progressed. It increased from 3:1 in the early stages of the reaction to ca. 7:1 at the end. These changes were due to alkene bromination by Br_3^- anion during the latter stages of the reaction, a process that has been shown to lead only to the *meso*-dibromide.

Dependence of the Product Distribution on the Initial Reagent Concentration. Brominations performed under conditions different from those described previously always resulted in changes in the degree of MeCN incorporation. The product yields that were obtained with decreasing initial reagent concentrations are reported in Table I. Table I also shows the dependence of product distribution on the initial reagent ratio for the reaction of cyclohexene at $[Br_2]$:[cyclohexene] = 1:1 and 2:1. A further increase in the reagent ratio did not produce any real change in product distribution. Similar results were obtained with all the other alkenes.

Cyclohexene was the only alkene that gave a stable compound of type 4. With all the other alkenes, the initially formed products 4 could not be detected due to their fast transformation to oxazolines (6) or oxazoline hydrobromides (6·HBr) and then to products of type 5. So, only the dibromide yields could be determined by GC. However, from the results of the preparative experiments described previously, it could be safely assumed that the degree of solvent incorporation could be calculated by difference. In the case of *trans*-stilbene, it was possible to determine the yields of the *meso*- and *d*,*l*-dibromides and 2-methyl-*trans*-4,5-diphenyloxazoline by HPLC and ^{1}H NMR analysis.

Solvent incorporation occurred to the greatest degree when, initially, the ratio $[Br_2]$/[alkene] was ≥2. Under identical reaction conditions, different alkenes gave different amounts of dibromide and, therefore, different amounts of solvent-incorporated products. Furthermore, the dibromide yields always lowered at complete reaction, when the initial reagent concentrations were lower.

The lesser degree of MeCN incorporation that was found with high initial reagent concentrations was tentatively attributed to the lack of a sufficient amount of water in the reaction medium to hydrolyze all the accumulated nitrilium intermediate 3 to amide 4. In the absence of water, 3 could revert to the bromonium ion, which could than collapse to the dibromo adduct 2. In order to test this hypotesis, the bromination of cycloalkenes 1a–c was performed in the presence of up to 5% water. However, no increase in MeCN incorporation was observed. Instead, small amounts (≤10%) of *trans*-bromohydrins were produced.

Discussion

The experimental results showed that the incorporation of MeCN did not occur when Br_3^- was the brominating agent. This fact, together with the observed second-order kinetics and anti stereospecificity observed for the addition to *trans*-stilbene, provided evidence that in MeCN bromination of alkenes by Br_3^- also did not involve the intermediacy of bromonium or bromocarbonium ions, as did the free Br_2 additions.[18] Furthermore, the similar values of the rate constants for the bromination of cyclohexene by $Bu_4N^+Br_3^-$ in MeCN (k_2 = 1.55 ± 0.05 M^{-1} s^{-1}) and in 1,2-dichloroethane (k_2 = 0.72 ± 0.02 M^{-1} s^{-1})[2m] showed that the bulk dielectric constant of the medium had very little effect on the rate of reaction. These observations provided a further evidence against a reaction that proceeded through a strongly polarized transition state like that postulated for the free Br_2 reaction.

The reaction of free Br_2 was much faster in MeCN than in 1,2-dichloroethane[2m,19] and gave both products of solvent

(18) For a discussion of the mechanism of bromination by Br_3^-, see: References 2m–o.

(19) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515.

incorporation and dibromides. The formation of the dibromides was stereospecifically anti from cycloalkenes, but only moderately stereoselectively anti from *trans*-stilbene. These observations were consistent with the involvement of bromonium ions in the former case and of bromocarbonium ions in the latter case. The incorporation of MeCN during the reaction of free Br_2 with *trans*-stilbene was, however, stereospecifically anti, as was also the formation of acetoxy bromides during the reaction of free Br_2 with *cis*- and *trans*-β-methylstyrene in acetic acid.[3e] That these additions were stereospecific has been attributed to the fact that "favorably oriented solvent molecules are always in a position to attack easily from the opposite side to the incoming bromine"[3e] to yield trans adducts. Dimethyl sulfoxide and *N*,*N*-dimethylformamide have also been reported to be incorporated stereospecifically anti during the reaction of stilbenes with *N*-bromosuccinimide.[5,6] On the other hand, the formation of methoxy bromides was reported to be stereospecifically anti from β-methylstyrenes in methanol,[20] but only 70% stereoselectively anti from α-methylstilbenes in methanol.[21]

With the unsymmetric alkenes styrene and 1-hexene, MeCN attack showed a completely Markovnikov regiospecificity. This was consistent with the observed regiospecific incorporation of both acetic acid[3e] and methanol[20] during styrene bromination. Such regiospecificity is easily explained in the case of styrene because the proposed intermediate is a benzylic bromocarbonium ion. However, the regio*specificity* observed with 1-hexene was surprising, for only the regio*selective* formation of Markovnikov methoxy bromides occurred during the reaction of 1-hexene with Br_2[22] or BrCl[23] in methanol, and during that of propene with Br_2 in methanol containing 0.2 M NaBr.[24] The regioselectivity that was observed was rationalized in terms of the greater "hardness" of the carbonium ion center at C(2), relative to that at C(1), of the bromonium ion. Thus, if also in MeCN the reaction of Br_2 with 1-hexene involved a bromonium ion intermediate, which seems extremely likely, the difference in the "hardness" of the two carbonium ion centers, that is, the degree to which the positive charge is localized at C(2), appears to be greater in MeCN than in methanol.[25]

The chemoselectivity of the reaction, that is the extent to which the reaction products are distributed between dibromide and the products of solvent incorporation, can be deduced from the data of Table I. First of all, the chemoselectivity that was displayed was markedly dependent on the initial reagent concentrations and ratios. The dependence on the $[Br_2]/[alkene]$ ratio can be easily explained in terms of concurrent reactions of free Br_2 and the Br_3^- anion that was generated by attack of solvent on the initially formed bromonium ion. The fast reaction of Br_2 with alkene and the subsequent reaction of the bromonium ion with solvent that leads to the tribromide salt **3** consume two Br_2 molecules. As a consequence, when, initially, $[Br_2]/[alkene] < 2$, there will not be sufficient free Br_2 available to brominate all the remaining alkene. The alkene will then react slowly with the Br_3^- that was formed. Because of the reaction with Br_3^- leads only to dibromide, larger amounts of dibromide will be produced in reactions performed at $[Br_2]/[alkene] < 2$ than from reactions performed at $[Br_2]/[alkene] \geq 2$.

On the other hand, the dependence of the chemoselectivity on the reagent concentrations when, initially, $[Br_2]/[alkene] = 2$ can be rationalized in terms of a kinetic effect on the competitive attack of the two nucleophiles (Br^{3-} and MeCN) on the bromonium (or bromocarbonium) ion during the product-determining step. In polar MeCN, the ionic intermediates are presumably present mostly as solvent-separated ion pairs, especially at low reagent concentrations. The rate of collapse of these intermediates to dibromide should be proportional to the concentration of both the cation and the anion. On the other hand, the collapse to solvent-incorporated product should depend only on the cation concentration, because the solvent concentration is constant. Thus, if a decrease in reagent concentration is accompanied by a reduced concentration of the ionic intermediates, the rate of formation of dibromide would slow more than that of solvent-incorporated products and an increase in the amount of products of the latter type would be observed.

The data of Table I also show that the chemoselectivity of the reaction with simple alkenes was not what would be expected on the basis of the anticipated charge distribution in the bromonium ion intermediates. Similar amounts of MeCN-incorporated products would be expected to be formed, under comparable reaction conditions, from 1-hexene and the three cycloalkenes **1a–c**. Such was the case in the formation of methoxy bromides from the bromonium ions of 1-hexene and *cis*- and *trans*-2-butene in methanol.[24] In the present case, the degree of MeCN incorporation was greatest for cyclohexene, less for 1-hexene, and least for cyclopentene and cycloheptene. These results suggest that some factor other than charge distribution in the bromonium ion intermediate must be involved in determining the chemoselectivity. One possibility is that the attack of MeCN on the bromonium ion is reversible. If this were so, the relative amounts of dibromide and solvent-incorporated products would be governed by the relative rates of the return of salt **3** to the bromonium ion and of the hydrolysis of **3** to **4**. A fast rate of hydrolysis of **3** and a slow rate of return of the nitrilium salt **3a** would account for the relatively greater degree of MeCN incorporation during, for example, cyclohexene bromination. In the case of cyclohexene, conformational factors may play a part. In the six-membered nitrilium ion **3a**, the bromine atom is not in a favorable position for anti attack on the neighboring carbon atom to displace the nitrilium group. Similar conformational factors may be responsible for the retardation of the cyclization of **4a** to the oxazoline derivative **6a**. Further investigation is required to clear up these points.

Conclusions

The results show that the solvent was incorporated into the reaction products regiospecifically and stereospecifically anti during the bromination of alkenes in MeCN. The degree of solvent incorporation depended on the alkene structure and on the initial reagent concentrations and ratios. The reaction gave a variety of stereoisomerically pure, nitrogen-containing products. When performed under proper experimental conditions, i.e., at sufficiently low initial reagent concentrations and with the initial Br_2 to alkene ratio ≥2, the reaction compares favorably with the Hassner procedure[8] as a method for the preparation of such compounds and, furthermore, does not require the use of silver perchlorate. The peculiar and unexplained kinetic course of the bromination of *cis*- and *trans*-stilbene by Br_2 in valeronitrile, mentioned in the

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(25) The lower nucleophilicity of MeCN relative to MeOH could also contribute to the higher selectivity observed with MeCN.

introduction,[10] can be rationalized by the results of the present study.

Experimental Section

Materials and Methods. Melting points were determined on a Kofler block or in Pyrex capillaries (for **5a–c,e**) and are uncorrected. IR spectra were of Nujol mulls or neat liquids. ^1H NMR spectra were recorded at 200 MHz, with Me_4Si as the internal standard. Electrical conductivities were measured at 25 ± 0.05 °C. Absorbance as a function of time was measured with a stopped-flow apparatus equipped with a 2-cm observation cell or with a conventional UV–vis spectrophotometer. GC analyses were performed with a 2.5 mm i.d. × 2 m glass column packed with 80–100 mesh 10% NPGS on silanized Chromosorb W. HPLC analyses were performed with a diode array detector and a 25 cm × 10 μm particle size Hypersil C18 column. The eluent was 7:3 methanol/water at a flow rate of 1.5 mL min^{-1}. Acetonitrile (Rudi Point HPLC grade, containing 0.05–0.5% of water (determined by Karl Fischer titration)) and bromine (C. Erba >99.5%) were used without further purification. Alkenes **1a–f** were >99% pure commercial products and were distilled immediately before use, with the exception of *trans*-stilbene, which was recrystallized from EtOH. Tetra-*n*-butylammonium bromide (EGA, ca. 99%) was purified by recrystallization from ethyl acetate/toluene. Gaseous HBr (Matheson) was 99.8% pure and was used as received.

Spectrophotometric and Conductimetric Measurements. Working-strength solutions of $H^+Br_3^-$ and of $Bu_4N^+Br_3^-$ were prepared by mixing neat MeCN and aliquots of stock solutions of Br_2 and HBr or $Bu_4N^+Br^-$ in MeCN. The limiting value of the formation constant of the tribromide ion (eq 1) was calculated from the UV spectra recorded in the 250–350 nm range (300–350 nm for the most concentrated solutions). The Lambert–Beer law was rigorously obeyed by solutions obtained by mixing equimolar reagent solutions in the 5×10^{-3}–5×10^{-6} M range. Thus, no appreciable dissociation of the tribromide ion occurred with dilution.

The conductivity of MeCN solutions of $H^+Br_3^-$, $Bu_4N^+Br_3^-$, and HBr in the 1×10^{-2}–2×10^{-4} M range were measured at 25 °C.

Rate Measurements. Runs with Br_2 as reactant were performed at 25 °C with the stopped-flow apparatus in the case of the reaction with cyclohexene and with both the stopped-flow apparatus and the UV–vis spectrophotometer in the case of the reaction with *trans*-stilbene. The 350–380-nm wavelength range was monitored. Second-order rate constants, k_2, for the descending part of the absorbance vs time curves obtained from the reactions in which a large excess of alkene was initially present were derived from the pseudo-first-order rate constants calculated by the usual least-squares fitting of the absorbance vs time data to the integrated pseudo-first-order rate equation.

The reactions of $Bu_4N^+Br_3^-$ were monitored with the stopped-flow apparatus in the case of cyclohexene and with the UV–vis spectrophotometer in the case of *trans*-stilbene. At least a 10-fold excess of alkene was employed. The rate of disappearence of Br_3^- was monitored in the 350–400-nm range and was followed for more than three half-lives. Absorbance as a function of time was again fitted to the integrated pseudo-first-order rate equation, and the k_2 values were calculated in the usual way.

Determination of the Products from the Bromination of 1a–f in MeCN. An aliquot (2 mL) of a MeCN solution (5×10^{-1}–5×10^{-3} M) of alkene **1a–f** was added to an equal volume of Br_2 solution ($(1–5) \times 10^{-3}$ M) in MeCN. The initial reagent concentrations are given in Table I. After 20 min at room temperature, the mixture was treated with saturated aqueous $NaHSO_3/NaHCO_3$. The solution was then analyzed by GC (for the reaction of **1a–e**) or HPLC (for the reaction of **1f**) after the introduction of an appropriate amount of internal standard. The following internal standards and column temperatures were used: 1,2-dibromocyclohexane and 110 °C for the products from **1b**; 1,2-dibromocycloheptane and 140 °C for the products from **1a**, **1d**, and **1e**; 1,2-dibromocyclopentane and 150 °C for the products from **1c**. *erythro*-1,2-Dibromo-1-phenylpropane was the internal standard for the HPLC analysis of the products from **1f**. The products from **1f** were also analyzed by ^1H NMR (see the following text). The product yields are reported in Table I.

Synthetic Scale Bromination and Product Isolation. In a typical experiment, 200 mL of a 5×10^{-2} M MeCN solution of alkene **1a–e** or 200 mL of a 5×10^{-3} M solution of **1f** was slowly added to 200 mL of a freshly prepared 1×10^{-1} M solution of Br_2 (1×10^{-2} M for the reaction of **1f**) in MeCN. After 20 min at room temperature in the dark, the reaction mixture was worked up in one of the two ways (A or B). The physical properties of the isolated products are reported in Table II.

Workup A. The bromination mixture was treated with saturated aqueous $NaHSO_3/NaHCO_3$ and was then repeatedly extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was washed with hexane to remove the dibromide and then was treated as described in the following text.

1a. The residue (2.1 g) was recrystallized from chloroform/hexane to give pure **4a** (1.95 g, 90% yield), mp 117–119 °C (lit.[7] mp 109–110 °C).

1b. The residue (500 mg) was recrystallized from chloroform to give pure **5b** (350 mg, 15% yield).

1c. The residue (570 mg) was recrystallized from chloroform to give pure **5c** (500 mg, 20% yield).

1d. The residue (900 mg) was a 3:3:4 mixture of **6d**, **6d**·HBr, and **5d** as determined by integration of the respective methyl group proton signals at δ 1.98 (d, J = 1.3 Hz), 2.62 (s), and 2.20 (s) in the ^1H NMR ($CDCl_3$) spectrum of the residue. Attempts to isolate pure products from the mixture by recrystallization failed.

1e. The residue was repeatedly recrystallized from chloroform to give pure **5e** (290 mg, 12% yield).

1f. The residue (250 mg) was a 70:22:8 mixture of **6f** and *meso*- and *d,l*-1,2-dibromo-1,2-diphenylethane (**2f**) as determined by HPLC analysis. The respective retention times were 8, 15, and 17 min. The ^1H NMR ($CDCl_3$) spectrum of the mixture showed signals at δ 2.20 (d, J = 1.4 Hz, CH_3 of **6f**), 5.00 (dq, J = 7.6 and 1.4 Hz, CHN of **6f**), 5.20 (d, J = 7.6 Hz, CHO of **6f**), 5.49 (s, CHBr of *d,l*-**2f**), 5.50 (s, CHBr of *meso*-**2f**), and 7.20–7.60 (aromatic protons). The IR spectrum showed absorptions at 1660, and 1260 cm^{-1}. Integration of the ^1H NMR signals confirmed the results of HPLC analysis. Attempts to isolate **6f** by recrystallization of the mixture from $CHCl_3$ gave pure **7f** (150 mg).

Workup B. The bromination mixture was treated with saturated aqueous $NaHSO_3$ and then was repeatedly extracted with hexane to remove the dibromides. The two liquid phases were separated and the aqueous phase was made alkaline with saturated aqueous Na_2CO_3. After 24 h at room temperature, the solution was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The residue was treated as described in the following text.

1d. The residue (550 mg, 40% yield), was purified by Kugelrohr short-path distillation to give pure **6d**.

In another experiment, the alkaline aqueous phase was refluxed for 2 h. The cooled solution was then extracted with dichloromethane. Evaporation of the solvent from the dried extract gave **7d** (530 mg, 33% yield).

1e. The residue was purified by Kugelrohr short-path distillation to give **6e** (900 mg, 56% yield).

In another experiment, the alkaline aqueous phase was refluxed for 2 h. The cooled solution was then extracted with dichloromethane. Evaporation of solvent from the dried extract gave 900 mg (50% yield) of **7e**, identical with the product obtained from the reaction of **5e** with NaOH.

***cis*-2-Acetoxycyclohexylamine Hydrobromide (5a).** A solution of **4a** (900 mg, 4.1 mmol) in MeCN containing 5% water (5 mL) was refluxed for 3 h. The solution was evaporated under reduced pressure. The residue was recrystallized from chloroform/hexane to give pure **5a** (750 mg, 48% yield).

3a,4,5,6,7,7a-Hexahydro-2-methylbenzoxazole (6a). A methanolic solution of **4a** (3.8 g, 17 mmol) that also contained an equimolar amount of sodium methoxide was refluxed for 2 h. After being cooled, the solution was evaporated to dryness. The residue was dissolved in dichloromethane and the solution was extracted with water. The organic phase then was dried, and the solvent was evaporated. The residue was distilled to give the pure oxazoline **6a** (2 g, 84% yield).

Gaseous HBr was bubbled through a chloroform solution of **6a**. Evaporation of the solvent under reduced pressure gave

6a·HBr as an oil: ^{1}H NMR ($CDCl_3$) δ 1.20–1.80 (8 H), 2.62 (s, CH_3, 3 H), 4.70 (m, CHN, 1 H), 5.50 (m, CHO, 1 H).

Compound **6a**·HBr was dissolved in 95:5 MeCN/H_2O, and the solution was allowed to stand at room temperature for 30 min. Evaporation of the solvent gave **5a**.

Conversion of Compounds 5 to 7. A solution of **5** (0.8 mmol) in dichloromethane was shaken with 0.1 N aqueous NaOH. The two liquid layers were separated, and the organic layer was dried ($MgSO_4$). Evaporation of the solvent gave, in quantitative yield, the following: **7a**, mp 144–146 °C (benzene) (lit.[26] mp 145–146 °C). **7b**, recrystallized from $CHCl_3$. **7c**, recrystallized from $CHCl_3$. **7e**, mp 122–123 °C ($CHCl_3$) (lit.[26] mp 123–124 °C).

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Dissociation and Aromatization of a Semibenzene. Reactions of Triphenylmethyl and Methyl Isobutyryl Radicals

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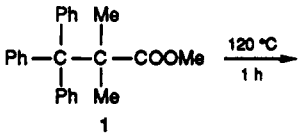
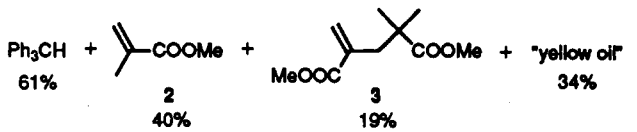
Semibenzene **4**, which can be regarded as the recombination product of triphenylmethyl and methyl isobutyryl radicals (**5**), affords exactly these intermediates on thermolysis or inefficiently on direct photolysis. Recombination and disproportionation of these dissimilar radicals proceeds with a much lower barrier than the dimerization of triphenylmethyl. Whereas thiophenol or triplet 9-fluorenone aromatize **4**, thermolysis in the presence of 1,4-cyclohexadiene allows trapping of **5** and oligomeric radical **13**. From the measured heat of aromatization (22.0 kcal/mol), the C–H bond dissociation enthalpy of **4** and its analogue lacking the side chain ("*p*-isotriphenylmethane") is calculated to be 54 kcal/mol, the lowest value known for any closed-shell, neutral hydrocarbon. Exposure of **4** to the atmosphere causes rapid autoxidation to hydroperoxide **19**, which thermolyzes in the GC to aromatic ketones and phenols instead of undergoing a 1,2-aryl shift.

In 1953, McElvain and Aldridge reported the following reaction in the absence of solvent:[1] As in the case of

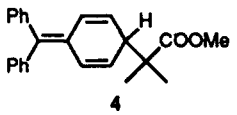


1



2 40% **3** 19%

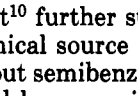
hexaphenylethane itself,[2] the actual structure of starting material **1** was later found to be the semibenzene methyl 7,7-diphenyl-*p*-mentha-1(7),2,5-triene-8-carboxylate, **4**.[3]



4

McElvain and Aldridge tried to deduce the decomposition mechanism by thermolyzing **4** in various solvents thought to be capable of trapping any intermediate radicals or ions. For example, heating **4** in methyl methacrylate failed to initiate polymerization, and toluene as solvent left the product composition unchanged except that **3** was supposedly absent. On the basis of such trapping reactions (and the wrong structure **1**), these early workers proposed an unlikely looking concerted cleavage of **1** to Ph_3CH plus **2**. Another dubious concerted process via a "six-membered cyclic complex" of **1** and **2** was offered to account for **3**.

Since **4** can be regarded as a recombination product of triphenylmethyl (trityl) and methyl isobutyryl radicals (**5**), our interest in compounds containing weak bonds[4-6] and the paucity of data on radical cross reactions[7-9] prompted us to reexamine its decomposition. The comment that



5

4 was sensitive to light[10] further suggested to us that it might be a photochemical source of free radicals. The present knowledge about semibenzenes coupled with the results to be presented here provide overwhelming evidence that thermolysis of **4** is also a radical reaction. Kinetic and thermodynamic measurements on **4** have allowed us to construct an energy diagram for its thermolysis and to demonstrate that its allylic C–H bond is the weakest on record for this type of compound.

Kinetics and Thermochemistry of 4. A sample of **4** was prepared in our laboratory from triphenylmethyl fluoroborate and dimethylketene methyl trimethylsilyl

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