methyl)-furan.[17] To a suspension of 6.2 g (0.07 mol) of MnO_2 in 100 mL of CH_2Cl_2 was added 2 g (0.018 mol) of the alcohol with vigorous stirring. After 6 h the reaction mixture was filtered through a small pad of Celite, rinsed with CH_2Cl_2, and concentrated to yield the crude aldehyde. Parts ii–iv were followed to produce **4e**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.25 (1 H, d), 6.18 (1 H, d), 5.8 (1 H, m), 5.2 (1 H, d), 5.1 (1 H, s), 3.65 (2 H, s), 3.17 (2 H, d), 2.00 (3 H, s); MS, *m/e* 168 (M^+), 167, 123, 95.

4,5-Dimethyl-2-[(allylthio)methyl]furan (4f). 2,3-Dimethylfuran[18] was treated as in parts i–iv to produce **4f**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.85 (1 H, s), 5.68 (1 H, m), 5.15 (1 H, d), 5.00 (1 H, m), 3.52 (2 H, s), 3.1 (2 H, d), 2.17 (3 H, s), 1.8 (3 H, s).

4-[(Benzyloxy)methyl]-5-methyl-2-[(allylthio)methyl]-furan (4g). Addition of 3 g (0.027 mol) of 3-(hydroxymethyl)-2-methylfuran[19] to a suspension at 0 °C of 1.6 g (0.04 mol) of NaH (60% in mineral oil) in 100 mL of THF was performed over 15 min. The ice bath was removed and the mixture was stirred at room temperature for 30 min. To this suspension was added 9.2 g (0.054 mol) of benzyl bromide, and the mixture was stirred overnight. Upon completion of the reaction by TLC analysis, the mixture was cooled to 0 °C and quenched via dropwise addition of saturated NH_4Cl solution. The usual workup provided the crude benzyl ether which was distilled prior to use at 82.5–94 °C (0.1–0.08 mm). Parts i–iv were followed to produce **4g**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.3 (5 H, s), 6.04 (1 H, s), 5.68 (1 H, m), 5.17 (1 H, s), 5.00 (1 H, d), 4.46 (2 H, s), 4.25 (2 H, s), 3.55 (2 H, s), 3.1 (2 H, d), 2.23 (3 H, s); HRMS, $C_{17}H_{20}O_2S$ calcd 288.118 29, obsd 288.117 134.

3,5-Dimethyl-2-[(allylthio)methyl]furan (4h). 3,5-Dimethyl-2-(hydroxymethyl)furan[20] was oxidized as in the preparation of **4d**, and the resulting aldehyde was treated as in parts ii–iv to produce **4h**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.65–6.0 (1 H, m), 5.7 (1 H, s), 5.19 (1 H, d), 3.6 (3 H, s), 3.13 (2 H, d), 2.24 (3 H, s), 1.93 (3 H, s); HRMS, $C_{10}H_{14}OS$ calcd 182.076 46, obsd 182.076 158.

3,4-Bis(hydroxymethyl)-2-[(allylthio)methyl]furan (4i). 3,4-Bis(hydroxymethyl)furan[21] was benzylated as above for **4g** using 2 molar equiv of benzyl bromide. The resulting furan was used directly in crude form for parts i–iv to produce **4i**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (11 H, s), 5.68 (1 H, m), 5.15 (1 H, d), 5.00 (1 H, s), 4.64 (2 H, s), 4.48 (4 H, s), 4.4 (4 H, s), 3.1 (2 H, d); HRMS, $C_{24}H_{26}O_3S$ calcd 394.160 12, obsd 394.161 242.

3,4,5-Trimethyl-2-[(allylthio)methyl]furan (4j). 3,4,5-Trimethylfuran[22] was treated as in parts i–iv to produce **4j**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.68 (1 H, m), 5.17 (1 H, d), 5.00 (1 H, s), 3.56 (2 H, s), 3.1 (2 H, d), 2.17 (3 H, s), 1.87 (3 H, s), 1.84 (3 H, s); HRMS, $C_{11}H_{16}OS$, calcd (fragment) $C_8H_{11}O$ 123.080 93, obsd 123.080 869; calcd (fragment) C_4H_7S, calc. 87.02681; exp. 87.026582.

3-Bromo-2-[(allylthio)methyl]furan (6). 3-Bromo-2-furfuraldehyde[13] was treated as in parts ii–iv to produce **6**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.3 (1 H, d), 6.35 (1 H, d), 5.77 (1 H, m), 5.27 (1 H, s), 5.15 (1 H, d), 3.65 (2 H, s), 3.15 (2 H, d).

Diethyl (3-Methylfurfuryl)allylmalonate (8b). Diethyl (3-methylfurfuryl)malonate was produced in an analogous manner to diethyl furfurylmalonate[23] from 3-methyl-2-furfuraldehyde (see **4e** above) and allylated as in part iv to produce **8b**: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.2 (1 H, d), 6.13 (1 H, d), 5.7 (1 H, m), 5.17 (1 H, br s), 5.04 (1 H, br s), 4.2 (4 H, q), 3.25 (2 H, s), 2.64 (2 H, d), 1.98 (3 H, s), 1.3 (6 H, t); HRMS, $C_{16}H_{22}O_5$ calcd 294.146 59, obsd 294.145 746.

D. Cycloaddition of 4b–j, 6, and 8b. These reactions were performed as for **2a–f**. See Table I and text for yields and ref 10 for methods of analysis.

5b: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 6.25 (2 H, AB q), 3.2 (2 H, AB q), 2.98 (1 H, dd), 2.7 (1 H, t), 2.27 (1 H, ddd), 1.55 (2 H, m), 1.6 (3 H, s).

5c: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.35 (5 H, s), 6.4 (2 H, s), 4.63 (2 H, s), 3.87 (2 H, s), 3.35 (2 H, s), 3.05 (1 H, dd), 2.75 (1 H, t), 2.32 (1 H, m), 1.4–1.7 (2 H, m).

5d: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 4.82 (1 H, s), 4.7 (1 H, d), 3.25 (2 H, AB q), 3.04 (1 H, dd), 2.7 (1 H, t), 2.27 (1 H, m), 1.86 (3 H, d), 1.6–1.8 (1 H, m), 1.45 (1 H, dd).

5e: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.94 (1 H, d), 4.85 (1 H, d), 3.15 (2 H, AB q), 2.98 (1 H, dd), 2.67 (1 H, t), 2.14 (1 H, ddd), 1.81 (3 H, d), 1.75 (1 H, m), 1.48 (1 H, dd).

5f: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.84 (1 H, br s), 3.2 (2 H, AB q), 3.06 (1 H, dd), 2.74 (1 H, t), 2.32 (1 H, m), 1.75 (3 H, d), 1.54 (3 H, s), 1.2–1.7 (2 H, m).

5g: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.35 (5 H, s), 6.2 (1 H, s), 4.5 (2 H, s), 4.1 (2 H, d), 3.23 (2 H, d), 3.04 (1 H, dd), 2.75 (1 H, t), 2.35 (1 H, m), 1.61 (3 H, s), 1.3–1.7 (2 H, m).

5h: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.8 (1 H, d), 3.18 (2 H, AB q), 3.00 (1 H, dd), 2.75 (1 H, t), 2.27 (1 H, m), 1.84 (3 H, d), 1.6 (3 H, s), 1.5–1.7 (2 H, m).

5i: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (10 H, s), 5.00 (1 H, d), 4.47 (4 H, d), 4.15 (4 H, d), 3.34 (2 H, AB q), 3.09 (1 H, dd), 2.72 (1 H, t).

5j: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 3.15 (2 H, AB q), 2.97 (1 H, dd), 2.7 (1 H, t), 2.17 (1 H, m), 1.67 (3 H, s), 1.65 (3 H, s), 1.5 (3 H, s), 1.2–1.7 (2 H, m).

7: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 7.23 (1 H, s), 4.98 (1 H, dd), 3.3 (2 H, AB q), 3.05 (1 H, dd), 2.72 (1 H, t), 2.32 (1 H, m), 1.84 (1 H, dt), 1.6 (1 H, dd).

9b: oil; ^1H NMR (90 MHz, $CDCl_3$) δ 5.73 (1 H, d), 4.76 (1 H, d), 4.14 (4 H, dq), 2.6 (2 H, AB q), 2.45 (1 H, dd), 2.07 (1 H, dd), 1.79 (3 H, d), 1.3–1.8 (3 H, m).

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Chlorination of 1-Hexyne and 3-Hexyne in Acetic Acid and Methanol

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The literature contains conflicting reports concerning the chlorination of aliphatic alkynes in nucleophilic solvents. Hennion et al. found that the chlorination of 1-hexyne (1) occurred in methanol[1] and acetic acid[2] with predominate solvent incorporation; however, a recent study[3] in acetic acid reported only the *Z* dichloride. It is reported that anti addition of chlorine to 1 occurs in methanol[2] and syn addition in acetic acid,[2,3] whereas anti addition of chlorine along with predominate solvent incorporation was found for 3-hexyne (2) in acetic acid.[3,4] Because of our interest in the stability of bridged halonium

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Table I. Products from Chlorination of 1-Hexyne and 3-Hexyne

alkyne and conditns[a]	yields[b] of products: dichloride[c] E	dichloride[c] Z	dichloro[d] ketone	chloro[e] acetate	dichloro[f] ketal
		Acetic Acid			
1, 10% Cl_2	0.5	<0.05	54		
1, 100% Cl_2	0.4	<0.02	50		
1, 10% Cl_2, LiCl	7.2	<0.04	39		
1, 100% Cl_2, LiCl	8.0	<0.04	48		
2, 10% Cl_2	0.6	1.4	6.2	33	
2, 100% Cl_2	0.7	1.0	27	17	
2, 10% Cl_2, LiCl	14	0.7	3.5	24	
2, 100% Cl_2, LiCl	13	0.8	18	15	
		Methanol			
1, 10% Cl_2	1.0		0.8		56
1, 100% Cl_2	3.0	0.01	0.2		52
1, 10% Cl_2, LiCl	3.6	0.04	0.7		51
1, 100% Cl_2, LiCl	4.7	0.02	0.3		48
2, 10% Cl_2	4.6	0.4	0.7		42
2, 100% Cl_2	6.4	0.4	0.7		35
2, 10% Cl_2, LiCl	9.9	0.4	0.9		40
2, 100% Cl_2, LiCl	10.3	0.4	0.9		33
		CH_2Cl_2			
1, 50% Cl_2	16.3	3.1			
2, 50% Cl_2	25.5	2.2			

[a] Percentage of chlorine refers to quantity used to react with 1 mol of the alkyne. LiCl was used at 0.1 M concentration. [b] Moles of dichloroketone and dichloroketal obtained are multiplied by two in calculating the yield. [c] Dichlorides are 1,2-dichloro-(*E*)-1-hexene (3) and 1,2-dichloro-(*Z*)-1-hexene (4) from 1; 3,4-dichloro-(*E*)-3-hexene (5) and 3,4-dichloro-(*Z*)-3-hexene (6) from 2. [d] The dichloro ketone is 1,1-dichloro-2-hexanone (7) from 1 and 4,4-dichloro-3-hexanone (8) from 2. [e] The chloro acetate is 3-chloro-4-acetoxy-(*E*)-3-hexene (9). [f] The dichloro ketals are 1,1-dichloro-2,2-dimethoxyhexane (10) from 1 and 3,3-dichloro-4,4-dimethoxyhexane (11) from 2.

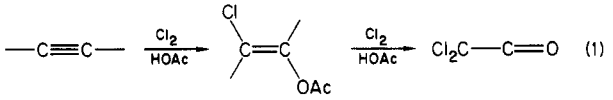
ions, we decided to undertake a product investigation of the chlorination of 1 and 2.

Results

The composition of mixtures of (*E*)- and (*Z*)-dichloroalkenes and other major products obtained from chlorination of 1 and 2 are shown in Table I. Our findings differ sharply from those previously reported. We attributed this to the fact that complex mixtures are obtained and minor products are easily confused. We isolated key compounds from chlorination mixtures by preparative VPC and confirmed their identity by independent synthesis.

A striking feature of the chlorination of both alkynes is the extremely small quantity of dichlorides which is formed in comparison to solvent-incorporated products. In acetic acid less than 1% of dichloride is obtained from 1 and about 2% from 2. Only small amounts of dichlorides are obtained in methanol also.

The major product from chlorination of 1 in acetic acid is the dichloro ketone (eq 1). The ketone arises by way



(1)

of the chlorovinyl acetate which is one of the minor, unidentified products. Chlorination of 2 to 10% completion gives the chlorovinyl acetate as the major product, whereas at an alkyne to chlorine ratio of 1:1, chlorine is primarily incorporated into the ketone. The difference between 1 and 2 in their reactions in acetic acid can be explained by their considerable difference in reactivity. Yates and Go report[3] that 3-hexyne is 340 times more reactive than 1-hexyne toward chlorine in acetic acid. Hence the intermediate chlorovinyl acetate is consumed more completely in competition with 1-hexyne, whereas it accumulates in competition with the more reactive 3-hexyne.

As reported by Hennion,[1] chlorination of 1 and 2 in methanol gives dichloro ketal as the major product. The chlorovinyl ether intermediates were not isolated but are minor products under all conditions. Gas chromatograms showed no products in amounts exceeding 10% of the ketals. The dichloro ketones are also obtained in small amounts.

Table II. Percentage of Dichloride Obtained from Chlorination of Alkenes and Acetylenes in Acetic Acid

substrate	% dichloride	substrate	% dichloride
$C_4H_9C{\equiv}CH$	0.5	$C_3H_7CH{=}CH_2$	51[6]
$C_2H_5C{\equiv}CC_2H_5$	2.0	(*E*)-$C_2H_5CH{=}CHCH_3$	75[6]
$C_6H_5C{\equiv}CH$	46[5]	(*Z*)-$C_2H_5CH{=}CHCH_3$	52[6]
$C_6H_5C{\equiv}CCH_3$	74[5]		

We also investigated the chlorination of the alkynes in dichloromethane. Chlorination of 2 was complete within a minute, whereas chlorination of 1 required several hours. We found that the product ratios and rates were not affected by oxygen saturation suggesting that the reactions are occurring by an ionic mechanism.

All of the chlorinations of 1 and 2 led to complex product mixtures containing many minor components which were not identified. The gas chromatogram from chlorination of 2 in dichloromethane showed 17 peaks, with six having areas of 10% or more of the main component (*E* dichloride). Chlorination of 2 in acetic acid also gave several unidentified peaks, but none were larger than 10% of the chlorovinyl acetate. Chlorinations of 1 and reactions in methanol gave fewer minor products. Complex mixtures from the alkynes evidently arise from reactive substitution products and rearrangement products such as allenes and dienes.[3]

Discussion

The first point to be noted about the chlorinations of the aliphatic alkynes is the extremely small amount of dichloride formation in the nucleophilic solvents. Under similar conditions the amount of dichloride formed from alkenes[6] is much larger. Arylacetylenes also give large amounts of dichloride in acetic acid.[5] A comparison of the

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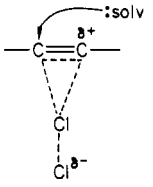
aliphatic acetylenes with alkenes and arylacetylenes for the chlorination in acetic acid is shown in Table II.

A second way in which chlorination of the alkynes differs from alkenes is in the effect of added chloride ion. Added lithium chloride does not increase the amount of dichloride from alkenes,[6] whereas a substantial increase occurred with **1** and **2**. The yield of dichloride from **1** and **2** in acetic acid and 0.1 M LiCl increased from 0.5% to 7.2% and from 2% to 14.7%, respectively.

The above results suggest that the mechanism for chlorination of the aliphatic alkynes is somewhat different from the alkenes and arylalkynes. Perhaps the nucleophile (solvent or added chloride ion) makes an attack at an earlier stage in the mechanism, before cleavage of the chlorine–chlorine bond has progressed to the point that chloride ion is free to migrate to a point of reaction.



The intervention of the nucleophile at any early stage with the aliphatic alkynes may result from the presence of the highly unstable vinyl carbocation intermediate. The extent of charge is suggested by Yate's and Go's comparative study of the chlorination and bromination of dialkylacetylenes.[3] The ρ value for chlorination of the dialkylacetylenes was more negative than the similar value for bromination, suggesting a strong electron demand in the transition state for chlorination. The rate constants for the chlorination of monoalkylacetylenes did not show a correlation with those for the dialkylacetylenes in contrast to bromination where good correlation for both groups of alkynes was observed.

Finally, the stereochemistry of the dichloride formation seems worthy of comment. The dichloride formation is at least 90% anti for the chlorination of **1** in acetic acid and methanol and for **2** in methanol, but the *Z* dichloride is formed primarily from **2** in acetic acid. Anti addition in three of the above cases suggests that bridged chloronium ions are intermediates. If open cations were involved, we see no reason why *Z* dichlorides would not predominate in all cases. We have no explanation for the fact that syn addition predominates for **2** in acetic acid.

Because the quantity of dichloride is so small, we were concerned that it might be formed by a competing radical mechanism. This seems unlikely since neither the yield of dichloride nor the stereochemistry was changed by oxygen saturation.[6]

Experimental Section

General Methods. NMR spectra (CCl_4) were obtained with a Varian EM-360A instrument, and IR spectra (CCl_4) were obtained with a Perkin-Elmer Model 710B spectrophotometer. GC–MS data were obtained on a Hewlett Packard 5985 spectrometer. Acetic acid was purified by distillation from P_2O_5. High purity commercial methanol was used without purification. Alkynes were obtained from Farchan and distilled before use.

General Reaction Conditions. Chlorinations were accomplished by addition of chlorine in carbon tetrachloride solution to dilute solutions of the alkyne (0.3 M) in the solvent. Reactions were done at 25 °C and were protected from light. Product mixtures were obtained after water workup. In a typical chlorination of 1 to 10% completion, 0.20 mL (1.7 mmol) of **1** in 5.6 mL (33 mmol) of anhydrous acetic acid was treated with 0.16 mL (0.17 mmol) of 1.09 M chlorine in CCl_4.

Products from 1-Hexyne. Samples of the dichlorides **3** and **4** were obtained by VPC collection from the reaction of **1** with NCl_3.[7] The dichlorides had the following properties which agreed well with literature values.[9] **3**: bp 50–55 °C (20 mm) [lit.[4] bp 168 °C (760 mm), bp(calcd) 60 °C (20 mm)]; NMR δ 2.53 (t, CH_2), 6.13 (s, HC=C) [lit.[4] δ 2.54 (CH_2), 6.15 (HC=C)]. **4**: NMR δ 2.41 (t, CH_2), 6.12 (s, HC=C) [lit.[4] δ 2.42 (t, CH_2), 6.18 (s, HC=C)]. The *E* dichloride **3** was isolated from the reaction of **1** with Cl_2 in acetic acid and methanol by VPC collection. The dichloro ketone **7** was isolated from the reaction of **1** in acetic acid by distillation: bp 76–80 °C (25 mm) [lit.[10] 72 °C (17 mm)]; NMR δ 2.82 (t, CH_2CO), 5.75 (s, $HCCl_2$) [lit.[10] δ 5.85–5.75 ($HCCl_2$)]; IR 1740 cm^{-1} (C=O) [lit.[10] 1742 cm^{-1} (C=O)]. An authentic sample of **7** was also prepared according to the method of Reed[10] by hydrolysis of the ketal **10**.

The ketal **10** was obtained by distillation of the product from reaction of **1** with chlorine in methanol: bp 102–107 °C (25 mm) [lit.[10] 57 °C (1 mm)]; NMR δ 3.30 (s, CH_3O), 5.66 (s, $HCCl_2$) [lit.[10] δ 3.45–3.24 (CH_3O), 5.85–5.66 ($HCCl_2$)].

The presence of the *E* and *Z* dichlorides in the mixture from reaction of **1** with chlorine in dichloromethane was proved by VPC collection followed by NMR and IR.

Product ratios and yields were obtained by VPC. Retention times on SE-30 (80–100 Chromosorb W, 8 ft × 6 mm glass, 70 °C) are as follows (min): **3**, 1.76; **4**, 2.25; **7**, 2.69; **10**, 12.63. Runs from acetic acid were also analyzed on OV-17 (2.5% on 80–100 Chromosorb W, 15 ft × 0.125 in. programmed 80–140 °C) are as follows (min): **3**, 6.20; **4**, 8.61; **7**, 10.49; **10**, 17.95.

Products from 3-Hexyne. An authentic sample of **5** was obtained from the reaction of **2** with NCl_3, and **6** was obtained from the reaction of **2** with $MoCl_5$.[11] Properties of the dichlorides are the following: **5**, NMR δ 1.15 (t, CH_3), 2.58 (q, CH_2) [lit.[4] δ 1.12 (CH_3), 2.58 (CH_2)]; **6**; NMR δ 1.17 (t, CH_3), 2.47 (q, CH_2) [lit.[4] δ 1.15 (CH_3), 2.45 (CH_2)].

Products from the reaction of **2** with chlorine in acetic acid were identified as follows. Samples of **5**, **8**, and **9** were obtained by VPC collection from reaction mixtures and identified by NMR and IR.[12] **8**: NMR δ 1.18 (t, CH_3), 2.34 (q, CH_2CO), 2.97 (q, CH_2CCl_2) [lit.[13] δ 1.17 (CH_3), 2.38 (CH_2), 3.01 (CH_2)]; IR 1740 cm^{-1} (C=O) [lit.[13] 1740 cm^{-1}]. **9**: NMR δ 1.00 and 1.07 (overlapping t, CH_3), 2.12 (s, CH_3CO), 1.7–2.7 (m, CH_2) [lit.[3] δ 1.00 and 1.07 (CH_3), 2.12 (CH_3CO), 2.0–2.60 (CH_2)]; IR 1760 cm^{-1} (C=O). A sample of **8** was also obtained by hydrolysis of the ketal **11**:[10] bp 50–51 °C (20 mm) [lit.[10] 55 °C (16 mm)]. The presence of the *Z* dichloride **6** in the reaction product from acetic acid was proved by GC–MS: MS, *m/e* 152, 154, 156 (M^+, 2-chlorine pattern), 117, 119 (M^+ – Cl, 100 and 29), 81 (M^+ – HCl_2, 69).

Products from the reaction of **2** with chlorine in methanol were identified as follows. The *E* dichloride was obtained by VPC collection. The ketal **11** was obtained by distillation: bp 90–100 °C (20 mm) [lit.[10] 59 °C (1 mm)]; NMR δ 1.06 and 1.28 (overlapping triplets, CH_3), 1.92–2.39 (overlapping quartets, CH_2), 3.47 (s, CH_3O).

In the reaction of **2** with chlorine in dichloromethane, the identity of **5** was proved by VPC collection and NMR and the presence of **6** was proved by GC–MS.

Product ratios and yields were obtained by VPC: 2.5% OV-17 on 80–100 Chromosorb W, 15 ft × 0.125 in., programmed 80–140 °C. Retention times are as follows (min): **5**, 5.19; **8**, 7.67; **6**, 7.97; **9**, 10.91; **11**, 16.06.

(7) A mixture of the *E* and *Z* dichlorides (ca. 10:1) is obtained with less impurities than by direct chlorination. Trichloramine evidently reacts by a radical mechanism.[8]

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(9) The properties of the *Z* dichloride agree with those previously reported. The NMR constants reported[3] by Yates and Go for the *Z* dichloride are in close agreement with constants which we found for the dichloro ketone **7**. The NMR spectra of the dichloride and the ketone are very similar but differ significantly in chemical shift values.

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Accurate Kinetic Studies by High-Performance Liquid Chromatography

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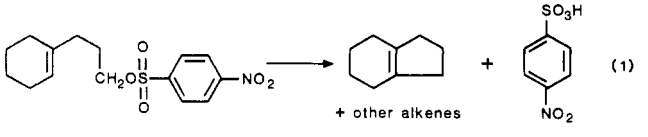
High-performance liquid chromatography (HPLC) is applied routinely in organic chemistry to quantitative analyses of products and to semiquantitative studies of reactions in progress.[2] We now report that good quality rate constants can be obtained with standard equipment by direct analysis of microaliquots (<2 μL) and without addition of an internal standard.

We have studied rates and products of the cyclization of 3-(cyclohex-1-enyl)propyl *p*-nitrobenzenesulfonate (I) in hexafluoroisopropyl alcohol (HFIP) containing added buffers and salts. In anticipation of a requirement for kinetic studies in the presence of an excess of substituted pyridines as buffers, we have developed an alternative to the usual spectrophotometric method.[3] A direct method based on HPLC proved to be surprisingly accurate. As reversed-phase HPLC is a very versatile and reproducible analytical method,[2] it seems likely that there will be many other suitable applications.

Results

Peak areas for both appearance of the sulfonic acid (eq 1) and disappearance of the ester I were obtained, after



(1)

I

direct injection of quenched aliquots of *only 1.8 μL* of the HFIP solution into the HPLC loop-injection valve. Rate constants for these two almost independent measurements agree well (Table I)—the average discrepancy between appropriate pairs of values is only 2.4%. More detailed inspection showed, as might have been expected, that a primary source of experimental uncertainty was slight variation (often <1%) in the volume of solution injected. Correction of these small errors was based on the linear relationship between peak areas for acid and ester (Table II). Our best estimates of the rate constants are the normalized values (Table I), and a brief, general explanation of the normalization procedure will now be given.

The symbols S and P will refer to observed peak areas (integrator counts) of the *s*tarting material and *p*roduct, respectively. Also the peak areas corresponding to the initial concentration of starting material and the final concentration of product are S_0 and P_∞, respectively. When a constant volume is injected and the combined concentrations of starting material and product are unchanged, then eq 2 applies (see also Table II). Corrected

$$P + (P_\infty/S_0)S = P_\infty \quad (2)$$

values of S and P, referred to as S' and P', can be obtained from eq 2 (with $P = P'$, $S = S'$, and the appropriate P_∞ and S_0 values given in Table II) and eq 3, which assumes that the ratio of peak areas (P/S) is accurate.

$$P/S = P'/S' \quad (3)$$

From these two equations it can be shown that each pair of values of P and S needs to be multiplied by an individually calculated scaling factor, given by $P_\infty/\{P + (P_\infty/S_0)S\}$, to obtain the corresponding corrected values P' and S'. In practice only one set of calculations is required (correcting independently each value of either P or S), because both sets of values (P' or S') lead to the same value of the rate constant (see the normalised values in the final column in Table I).[5]

Discussion

The normalized values of the rate constants (Table I) are close to, but different from, the averages of the corresponding rate constants obtained from acid and ester peaks. The statistical uncertainty in the normalized values varies from only ±1.3 to ±2.4% of k. The high reproducibility of the chromatography is shown by the very good agreement between the relative response ratios P_∞/S_0 (Table II), even for wide variations in the acidity or basicity of the solutions and the nature of added buffers or salts. Only for run 2 is the value of P_∞/S_0 significantly higher than the other values, and the normalized rate constant quoted for run 2 (Table I) probably includes a small systematic error decreasing the calculated rate constant by 3–5%. This conclusion is based on trial calculations of the effect of incorrect values of P_∞/S_0[6] and on a plot of rate constants vs molar concentration of triethylamine (runs 1–5). An independent kinetic run, duplicating closely the conditions of run 2 but 5 months later, gave the expected value of P_∞/S_0 (2.76 ± 0.07) and a significantly higher rate constant ((1.65 ± 0.05) × 10^{-4} s^{-1}, based on 20 HPLC injections). Thus, from the slightly high value of P_∞/S_0 for the original run 2, it can be correctly predicted that the rate constant is slightly too low.

As well as providing a good guide to the reliability of the data, the plots of P vs. S (eq 2, Table II) provide a means in future work to establish a reliable rate constant from relatively few (10–15) HPLC injections for each kinetic run. For most of the work reported here, we made about 40

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(6) For run 6, normalised values of 10^4k calculated from different values of P_∞/S_0 are as follows: 2.326 (Table I), 2.711 (Table II), 2.277, 2.811; 2.237, 2.911.

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