tional Institutes of Health (Grant GM-09251-01) for a postdoctoral fellowship. This is Contribution 294 from the Australian Institute of Marine Science. We thank Dr. F. T. Gillan (Australian Institute of Marine Science) for critical review of the manuscript.

**Registry No.** **1**, 83474-12-8; **2**, 83474-13-9; **4**, 2485-71-4; **6**, 102537-89-3; **6** (nitrile), 102537-88-2; **7**, 102537-91-7; **7** (nitrile), 102573-68-2; **9**, 1119-16-0; **9** (alcohol), 626-89-1; **10**, 52956-93-1; **11**, 21987-21-3; **11** (acid), 2724-57-4; **11** (methyl ester), 5129-58-8; **11** (methanesulfonate), 102537-87-1; **14**, 55695-91-5; **15**, 20194-46-1; (*Z*)-**15** (9-alkene), 58257-54-8; **15** (methanesulfonate), 102537-90-6; **16**, 83474-17-3; **17**, 52715-55-6; $H_3CCH_2CH(CH_3CHO$, 96-17-3; $Br(CH_2)_9OTHP$, 55695-90-4; (*Z*)-$(CH_3)_2CH(CH_2)_2CH{=}CH(CH_2)_6CO_2H$, 102537-86-0; tetradecanoic acid, 544-63-8; 12-methyltetradecanoic acid, 5502-94-3; 14-methylpentadecanoic acid, 4669-02-7; 9-hexadecanoic acid, 2091-29-4; hexadecanoic acid, 57-10-3; 15-methylhexadecanoic acid, 1603-03-8; 14-methylhexadecanoic acid, 5918-29-6; 11-octadecenoic acid, 143-25-9; octadecanoic acid, 57-11-4.

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# Hydrolysis of Mustard Derivatives in Aqueous Acetone–Water and Ethanol–Water Mixtures

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The hydrolyses of two mustard derivatives, 2-chloroethyl ethyl sulfide (CEES) and 2-chloroethyl methyl sulfide (CEMS), were investigated and compared with the hydrolysis of *tert*-butyl chloride (TBC) in aqueous binary mixtures of acetone and ethanol from 0 to 45 °C. The solvent effect on rates and on activation parameters provided further evidence for an $S_N1$ mechanism with anchimeric assistance of the sulfur atom to form a cyclic sulfonium ion as the reaction intermediate. Lower $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of both CEES and CEMS relative to that of TBC reflected the S–C bond formation and the strained structure of the intermediate. A finite and negative $\Delta C_p^{\ddagger}$ was detected. The observed $\Delta H^{\ddagger}$ was corrected for the cosolvent effect by adopting Fagley's model and was consistent with the value in pure water.

Mustard, bis(2-chloroethyl) sulfide, hydrolyzes to form mustard chlorohydrin (2-hydroxylethyl ethyl sulfide) and HCl; the chlorohydrin subsequently hydrolyzes to form another mole of HCl and thiodiglycol. Bartlett and Swain[1] showed that the kinetics of the hydrolysis consisted of two consecutive, first-order reactions at 25 °C and concluded that the hydrolysis proceeded via a sulfonium ion intermediate. Their proposed mechanism was only recently verified. McManus and co-workers[2] monitored the hydrolysis of deuterium-labeled chlorohydrin and observed 100% scrambling of the products by NMR. They also agreed with Bartlett and Swain that nucleophilic solvent attack of the substrate was absent. However, no measurements of the activation energies of mustard hydrolysis were available.[3] In a study on anchimeric-assisted hydrolyses of alkyl halides, Blandamer et al.[4] determined a constant $\Delta C_p^{\ddagger}$ of −71 cal/mol, K between 5 and 50 °C for 2-chloroethyl methyl sulfide (CEMS)—a value consistent with those reported for alkyl halide hydrolyses undergoing an $S_N1$ mechanism.[5] All of the above studies found that it was necessary to measure their rates in the presence of a small amount of acetone, but any solvation effect on kinetics was not examined.

The aim of this study is to investigate the effect of an organic cosolvent on the rates and activation parameters of two mustard derivatives CEES and CEMS. These compounds are more common simulants of mustard than chlorohydrin, and each hydrolyzes in one step to form 1 mol of HCl and 1 mol of 2-hydroxylethyl sulfide. We first verified that the reaction rate was independent of the presence of added HCl up to $2 \times 10^{-3}$ M and restricted our substrate concentration below $1 \times 10^{-3}$ M. We also employed a sensitive method[6] to detect whether $\Delta C_p^{\ddagger}$ was constant in a temperature range of 0–45 °C. The solvent systems are in the aqueous regions of both acetone–water and ethanol–water mixtures of mole fractions 0.025–0.20 in the organic cosolvent. These solvent systems have been the subjects of extensive thermodynamic and structural studies. Both acetone and ethanol are "typically aqueous" solutes[7] that promote the structure of water when present in small amounts and were known to affect the kinetics of hydrolysis by revealing large ranges of variations in both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with composition, as observed for TBC hydrolysis.[8] We performed a comparative study of the hydrolyses of CEES and TBC, which has long been used for developing theories of solvent effects on hydrolysis reaction rates and activation parameters, in the same solvent mixtures. Furthermore, we are able to report kinetic data of CEES hydrolysis in pure water and compare these data with cosolvent-corrected enthalpies of activation ($\Delta H^*$)

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(3) Ward, J. R.; Seiders, R. P. *Thermochim. Acta* **1984**, *81*, 343–348. In this study the authors fitted reported kinetic data for mustard hydrolysis in water at different temperatures to a computer program that calculated individual rate coefficients for two consecutive, first-order reactions, because past investigators approximated the kinetics as a single first-order reaction. The results, however, failed to converge, and accurate activation energies could not be obtained. Speculations on the quality of their data were discussed in the article.

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according to Fagley's model.[9]

## Experimental Section

**Materials.** Redistilled CEES and CEMS were obtained from Fairfield Chemical Company, Blythewood, SC. Reagent-grade *tert*-butyl chloride (Eastman Kodak) was used without further treatment. HPLC-grade acetone and ethanol and doubly distilled, deionized water were used for the kinetic runs.

**Equipment.** Kinetic runs were made by following the conductivity of the reaction mixture with a Copenhagen Radiometer conductivity meter (CDM 83) and conductivity cells. Linearity between concentration and conductivity was established in aqueous mixtures up to $1 \times 10^{-3}$ M HCl. Automatic data acquisition was achieved by installing an ouput module (Part 901-090) to the conductivity meter and by using a program that incorporated an ADLAB system[10] for converting the analog signal to digital input with an Apple II+ computer. Two cell sizes of 33 and 55 mL were used for conductivity measurements. These cells were of double walls containing a circulating solution of a methanol–water mixture from a constant temperature bath. Temperature can be controlled to ±0.1 °C. A magnetic stirrer at maximum speed was used in the cell to provide sufficient mixing. It was found that the diffusion of HCl was a limiting factor for rate constants above 0.1 $s^{-1}$.

**Procedure for Kinetic Runs.** Each of the above substrates was first dissolved in pure acetone or ethanol to form a 2% by volume solution before injection into the appropriate solvent in the conductivity cell. The initial concentration was kept below $8 \times 10^{-4}$ M for all kinetic runs. This procedure was found necessary to eliminate a slow dissolution step accompanying direct injection of pure substrate to the solvent mixture. It was observed that this slow dissolution step affected the accuracy of kinetic data even in solvents up to 0.05 mol fraction of acetone at 25 °C. Typical symptoms of the slow dissolution step were an initial induction period and a drifting (increasing) infinity value. Head space was kept to a minimum in the conductivity cells and no $CO_2$ "buffer effect"[11] was observed. To test if chloride ion affected the measured rate coefficients, experiments at various initial chloride ion concentrations ranging from (0.2 to 2.0) $\times 10^{-3}$ M were made. The rate coefficients were identical. Kinetic data from acetone–water mixtures above 35 °C or in 0.10 mol fraction ethanol above 40 °C showed abnormally large values of $k$, presumably because of evaporation of the organic component during temperature-equilibration period were not reported.

The rate coefficient, $k$, was determined by fitting conductivity at time $t$, $C_t$, to eq 1, where $C_0$ and $C_\infty$ are the conductivity at times

$$C_t = C + (C_0 - C_\infty)\, e^{-kt} \qquad (1)$$

zero and infinity, respectively.[12] Best-fit values of $C_0$, $C_\infty$, and $k$ were obtained for each run. Swain[13] recently provided an excellent discussion of the reasons for finding best-fit values of $C_0$ and $C_\infty$, as well as reasons for avoiding the linear form of eq 1. The standard deviation of each parameter was 2% or less in every run.

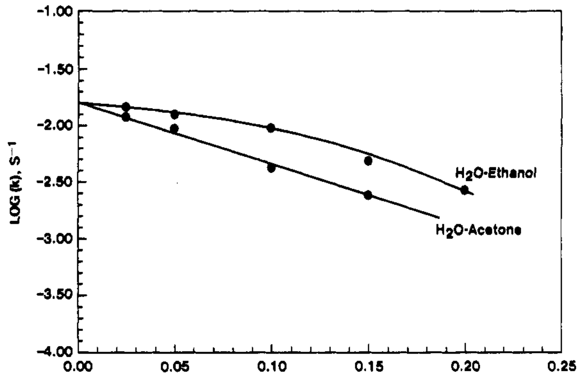

**Figure 1.** Rate coefficients for CEES hydrolysis vs. mole fraction of acetone or ethanol in binary aqueous solvent mixtures.

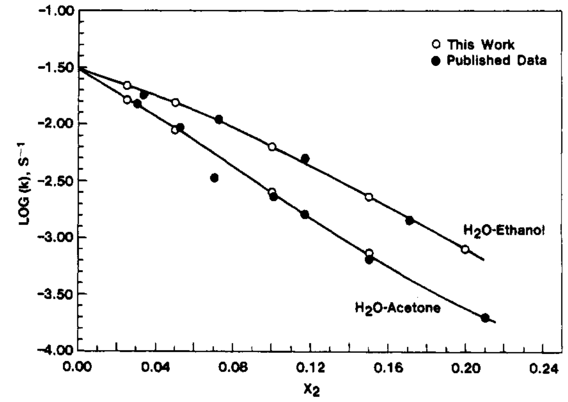

**Figure 2.** Rate coefficients for TBC hydrolysis vs. mole fraction of acetone or ethanol in binary aqueous solvent mixtures.

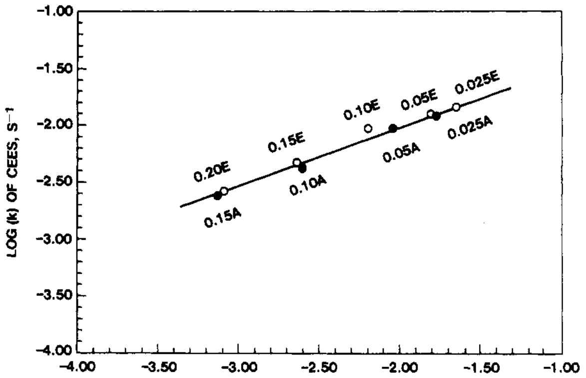

**Figure 3.** Comparison of rate coefficients of hydrolysis of CEES with TBC at 25 °C.

## Results and Discussion

**Rate Constants of Hydrolysis.** The first-order rate coefficients for the hydrolyses of CEES and CEMS were measured at 5-deg intervals between 0 and 35 °C in 0.025 and 0.10 mol fraction acetone–water mixtures. In addition CEES hydrolysis was measured in ethanol–water mixtures with the same mole fractions of organic component at 5-deg intervals between 0 and 45 °C. The hydrolysis of CEES was also monitored at 15, 25, and 35 °C in 0.050 and 0.15 mol fraction acetone–water solutions. Tables 4–6 in the supplementary material list these rate coefficients. The rate coefficients are the mean of these runs at each temperature and solvent; the mean standard deviation is less than 2%. Since the rate of hydrolysis of CEES was too fast relative to the rate of dissolution in pure water at 25 °C, it was impossible to measure the hydrolysis rate directly in our apparatus. The rate was determined by extrapolating the rates in mixed solvent systems at 25 °C to pure water as shown in Figure 1. The extrapolations were made by extending straight lines passing data at $X_2$ = 0.05 and $X_2$ = 0.025 to $X_2$ = 0, while connecting the rest of the data points by smooth curves. A common point was met by the lines drawn from both solvent systems at a rate constant of $1.58 \times 10^{-2}$ $s^{-1}$ for CEES in pure water. As a comparison, rate constants of hydrolysis of TBC at 25 °C in the same binary solvent mixtures were also measured

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**Table I. Rate Coefficients of Hydrolysis for Mustard and Its Derivatives and *tert*-Butyl Chloridate at 25 °C**

| compound | solvent | $k$, s$^{-1}$ |
|---|---|---|
| mustard | 5% acetone[a] | $1.29 \times 10^{-3}$ [b] |
| chlorohydrin | 5% acetone[a] | $4.33 \times 10^{-3}$ [b] |
| | 5% acetone[a] | $4.20 \times 10^{-3}$ [c] |
| CEES | water | $1.58 \times 10^{-2}$ [d] |
| | 0.025 ethanol | $1.46 \times 10^{-2}$ |
| | 0.025 ethanol | $1.22 \times 10^{-2}$ |
| CEMS | water | $1.48 \times 10^{-2}$ [e] |
| | 0.025 acetone | $9.06 \times 10^{-3}$ |
| TBC | water | $3.02 \times 10^{-2}$ [d] |
| | 0.025 ethanol | $2.25 \times 10^{-2}$ |
| | 0.025 acetone | $1.67 \times 10^{-1}$ |

[a] 5% acetone by volume is about 0.015 in mole fraction at 25 °C. [b] Reference 1. Two rate constants corresponding to the following reactions for mustard and chlorohydrin respectively were measured, $k_1$ was divided by two to correct for the two chlorine atoms in mustard. [c] Obtained from ref 3. [d] Determined by extrapolation.

$$(ClC_2H_4)_2S + H_2O \xrightarrow{k_1} ClC_2H_4SC_2H_4OH + HCl \qquad (1)$$

$$ClC_2H_4SC_{24}OH + H_2O \xrightarrow{k_2} (HOC_2H_4)_2S + HCl \qquad (2)$$

[e] Obtained from ref 4, in which a small, unspecified amount of acetone was used to dissolve CEMS.

and listed in Table 7 in the supplementary material. Figure 2 plots the rate constants for TBC vs. mole fraction of the organic component. Our data are shown to be very consistent with those carefully measured by Bentley and Carter[14] for ethanol–water and with those of Tommila et al.[15] for acetone–water mixtures. The extrapolated rate constant was $3.02 \times 10^{-2}$ s$^{-1}$, consistent with those reported in the literature.[7]

All of the reported rate data of CEES at 25 °C were plotted in Figure 3 against those of TBC to see whether the data fitted a Grunwald–Winsteins' linear free energy relationship:[16] $\log k_{\mathrm{CEES}} = m \log k_{\mathrm{TBC}} + \log k_o$. A straight line was observed and tested against a linear regression that calculated a slope ($m$ value) of 0.52 ± 0.03. This showed that CEES hydrolyzed via the same mechanisms as typical alkyl halides in these solvent systems with an $m$ value lower than that of a tertiary carbon but higher than that of a primary carbon and that ethanol–water mixtures had stronger ionizing power than acetone–water mixtures of the same composition.

As reported by previous investigators[17,18] that there was backside attack of water molecules in forming the carbonium ion intermediate for TBC hydrolysis and that the bulkier *l*-adamantyl halides were better $S_N1$ models, we believe water molecules also were present in the formation of the sulfonium intermediate and agree with the structure proposed by Blandamer et al. for CEMS hydrolysis.[4] The presence of water molecules may have stabilized the sulfonium ion and replaced the alcohol or acetone species that originally solvated the ground-state substrate at the same sites. This proposed structure is consistent with the model we used to correlate $\Delta H^{\ddagger}$ with $X_2$ in the next section.

Table I is a comparison of the $k$ values of a series of chlorinated sulfides at 25 °C. It shows that the hydrolysis rates are mustard < chlorohydrin < CEMS < CEES. This trend can be rationalized in terms of the relative stabilities of the sulfonium ion intermediates formed during the transition state. When the substituent is more electron-donating, the sulfonium ion becomes more stable, and the reaction rate is faster.

**Table II. Enthalpies of Activation vs. Mole Fraction of Solvent System at 25 °C**

| solvent $X_2$ | $\Delta H^{\ddagger}$, kcal/mol | $\varphi L_2$,[a] kcal/mol | $\Delta H^{\ddagger} - n\varphi L_2$, kcal/mol | $n$ |
|---|---|---|---|---|
| | | CEES | | |
| acetone | | | | |
| 0.025 | 17.7 | −1.9 | 19.6 | 1 |
| 0.050 | 16.7 | −1.7 | 20.1 | 2 |
| 0.100 | 16.8 | −1.5 | 19.8 | 2 |
| 0.150 | 17.3 | −1.2 | 19.9 | 2 |
| | | | 19.9 ± 0.03[b] | |
| ethanol | | | | |
| 0.025 | 20.2 | −2.2 | 20.2 | 0 |
| 0.050 | 19.2 | −2.1 | 19.2 | 0 |
| 0.100 | 19.0 | −1.6 | 19.0 | 0 |
| 0.150 | 17.1 | −1.2 | 19.5 | 2 |
| 0.200 | 17.5 | −0.9 | 19.3 | 2 |
| | | | 19.4 ± 0.08[b] | |
| | | CEMS | | |
| acetone | | | | |
| 0.025 | 17.7 | −1.9 | 19.6 | 1 |
| 0.100 | 14.5 | −1.5 | 19.0 | 3 |
| | | | 19.3 ± 0.03[b] | |

[a] $\varphi L_2 = \Delta H^{\mathrm{E}}\ \mathrm{MIX}/X_2$, where $\Delta H^{\mathrm{E}}$ MIX data were obtained from ref 20 and from ref 21 for ethanol–water mixtures. [b] Average.

**Activation Parameters.** To determine the activation parameters, we used a method recommended by Blandamer et al.[6] which assumes that $\Delta C_p^{\ddagger}$ is constant. At a fixed temperature, $T_o$, and $k$ value, $k_o$, both parameters $\Delta H_o^{\ddagger}$ and $\Delta C_{p_o}^{\ddagger}$ were determined by fitting the rest of the $k$–$T$ data to the following equation by a nonlinear least-squares computer fit (eq 2). The process was repeated

$$k = \frac{k_o T}{T_o} \exp\left(\frac{\Delta H_o^{\ddagger}}{R}\left(\frac{1}{T_o} - \frac{1}{T}\right) + \frac{\Delta C_{p_o}^{\ddagger}}{R}\left(\ln\left(\frac{1}{T_o}\right) + \left(\frac{T_o}{T}\right) - 1\right)\right) \qquad (2)$$

until each value of $T$ in the data set had been used at $T_o$. The subsequent values of $\Delta C_p^{\ddagger}$ were examined to see if the temperature dependence of $\Delta C_p^{\ddagger}$ was zero, constant, or variable. The results based on the above method are summarized in Table 8 of the supplementary material.

For CEES in 0.10 acetone, $\Delta C_p^{\ddagger}$ was zero in the 0–35 °C range, but $\Delta C_p^{\ddagger}$ was finite, negative, and varied with temperature in other solvent mixtures. Negative and temperature-dependent $\Delta C_p^{\ddagger}$'s were also found for CEMS hydrolysis in acetone–water mixtures. Since eq 2 was derived on the basis of a constant $\Delta C_p^{\ddagger}$, the values of $\Delta H^{\ddagger}$ or $\Delta C_p^{\ddagger}$ in the above tables are not thermodynamically correct. Blandamer et al.[4] reported that CEMS had a constant $\Delta C_p^{\ddagger}$ of −71 cal/mol in pure water from 5 to 50 °C. Our analysis indicated this negative $\Delta C_p^{\ddagger}$ was not constant with temperature, in agreement with those reported by Wold.[19] To obtain $\Delta H^{\ddagger}$ at 25 °C as a function of mole fraction, the $k$ values at 15 and 35 °C were used, and it was assumed that $\Delta H^{\ddagger}$ was constant over this temperature range. The values of $\Delta H^{\ddagger}$ are listed in Table II for CEES in acetone–water and ethanol–water and for CEMS in acetone–water mixtures. In all three cases, $\Delta H^{\ddagger}$ varied with mole fraction of the cosolvent. The enthalpy

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of activation was reduced as the mole fraction of the cosolvent increased but passed through a minimum as the mole fraction of cosolvent increased further, which is analogous to TBC.[8]

Fagley and his co-workers[9] have proposed that the reorganization of the solvent at the transition state required some of the cosolvent molecules to leave the solvation shells of the ground-state substrate in order for water molecules to subsequently react with the substrate. They proposed that the unmixing of the solvent pair contributed to the measured $\Delta H^{\ddagger}$ in terms of heats of mixing or the relative partial molal enthalpies of the solvent components. Based on their model, the apparent relative partial molal enthalpy of the cosolvent, $\varphi L_2$, representing an enthalpy contribution from the unmixing of all the polymeric cosolvent species that solvated the substrate, was related to the net enthalpy of activation, $\Delta H^{*}$, in pure water, and observed $\Delta H^{\ddagger}$ according to eq 3, where $\Delta H^{*}$ is the corrected enthalpy of activation from a binary aqueous solvent mixture to pure water, $\Delta H^{\ddagger}$ is the measured enthalpy of activation in binary solvent mixtures, $\varphi L_2$ is the apparent relative partial molal enthalpy of solvent component two (acetone or ethanol), and $n$ is the number of cosolvent molecules leaving the solvation shell at the transition state as an $n$-mer. The above correlations were examined in Table II for both CEES and CEMS using published data on the relative partial molal enthalpies of the solvent systems.[20,21] The corrected $\Delta H^{*}$ for CEES hydrolysis in pure water from acetone–water was very close to that from ethanol–water mixtures at 19.4 ± 0.8 kcal/mol. This was also consistent with $\Delta H^{\ddagger} = 19.5$ kcal/mol at 25 °C determined from the extrapolated $k$ values of $5.01 \times 10^{-3}$ and $4.90 \times 10^{-2}$ s$^{-1}$ at 15 and 35 °C, respectively, for pure water. The corrected $\Delta H^{\ddagger}$ for CEMS hydrolysis was 19.3 ± 0.03 kcal/mol, consistent with the 19.7 ± 0.05 kcal/mol value reported by Blandamer et al.[4]

$$\Delta H^{*} = \Delta H^{\ddagger} - n\varphi L_2 \qquad (3)$$

The entropies of activation were calculated from $k$ and $\Delta H^{\ddagger}$ at 25 °C and listed in Table 3 (supplementary material). They decreased as the mole fraction of the cosolvent increased and were lower than that of TBC when compared in the same solvent systems. This may suggest that the formation of the three-membered ring structure of the sulfonium ion was less favored than the carbonium ion and that the decrease in $\Delta S^{\ddagger}$ in the presence of the cosolvent was caused by an increase in the water structure of the aqueous system. This made the ground-state solvation shells more difficult to break, resulting in a decrease in both entropy of activation and $k$ relative to that in pure water.

**Registry No.** CEES, 693-07-2; CEMS, 542-81-4; TBC, 507-20-0.

**Supplementary Material Available:** Tables 3–8 depicting rate coefficients for hydrolysis and results of analysis for heat capacities of activation (6 pages). Ordering information is given on any current masthead.

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# Ring-Opening Reactions of *cis*- and *trans*-2,3-Bis(4-methoxybenzyl)oxirane: Competition between Assistance by and Migration of an Aryl Group

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The study of the aryl participation in the oxirane ring-opening reactions in acidic conditions was extended to ($p$-methoxybenzyl)oxiranes *cis*-**2b** and *trans*-**3b** analogous to the ones unsubstituted on the phenyl ring, **2a** and **3a**, previously studied. The introduction of the $p$-methoxy group causes in the trans epoxide **3** the appearance of the syn adduct in the methanolysis reactions and a large increase in the same adduct in the hydrolysis, acetolysis, and trichloroacetolysis reactions. For the cis epoxide **2**, the presence of the para substituent causes the loss of complete anti stereoselectivity: in all the reactions but acetolysis, significant amounts of syn adduct are formed. Furthermore some reactions (see methanolysis) of the $p$-methoxy-substituted compounds **2b** and **3b** reveal the presence of significant amounts of rearranged 1,3-addition products of the type **31** and **29**, respectively, contrary to the corresponding reactions of the epoxides **2a** and **3a**. Except for the trichloroacetolysis in $CH_2Cl_2$, all the reactions of the trans epoxide **3b** show a higher syn stereoselectivity than do the corresponding reactions of the cis epoxide **2b**. The results obtained for the reactions of $p$-methoxy-substituted epoxides **2b** and **3b** further confirm the mechanism previously proposed in order to rationalize the reactions of the unsubstituted epoxides **2a** and **3a**, which involves the neighboring participation of the phenyl. However the presence of rearranged 1,3-addition compounds among the reaction products led us to insert into the mechanistic scheme the necessary modifications which imply competition between assistance by and migration of the aryl group.

The reactions under acidic conditions of oxiranes bearing neither aryl nor any other unsaturated system directly linked to the heterocyclic ring usually occur with complete or near complete anti stereoselectivity.[1-3] However, when either aryls, double bonds, or other unsaturated systems are directly linked to the oxirane ring, the steric course of the ring opening can range from complete retention to complete inversion of its configuration depending on the structure of the epoxide and on the reaction condition used.[1,2,4,5] In the case of 2-aryloxiranes the amounts of

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