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THE KINETICS AND MECHANISM(S) OF NUCLEOPHILIC ATTACK BY CATECHOLATE ANION ON EPIBROMOHYDRIN-d_2

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The reaction which forms hydroxymethylbenzodioxane from epibromohydrin and catecholate anion was examined by ultraviolet spectroscopy for the kinetics and by proton nuclear magnetic resonance spectroscopy to follow the fate of CD_2 from reactant to product. Over the practical temperature range it was found that both CH_2 positions in the epihalohydrin are attacked by catecholate anion to give product. Therefore, the difference in energy for the two pathways was small. The individual rate constants were obtained from the total rate constants. Further, the individual $\Delta H\ddagger$ and $\Delta S\ddagger$ values were calculated. It was found that the pathway of higher $\Delta H\ddagger$ had the less negative $\Delta S\ddagger$, which explains the subtlety of two mechanisms being operative over the available temperature range. Interestingly, it proved impossible to prepare epibromohydrin with two deuteriums at only one position in what appeared to be a relatively straightforward synthesis.

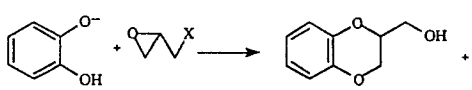
INTRODUCTION

In 1966, it was reported,[1] based solely on kinetic studies, that nucleophilic attack on epihalohydrins takes place exclusively at the ring CH_2 position. At that time we had some very preliminary data,[2] suggesting that nucleophilic attack took place at both the ring CH_2 and the chloro CH_2 position in epichlorohydrin, with attack at the ring CH_2 position predominating.

In the period 1979–84, it was quantitatively established[3,4] that nucleophilic attack on such systems took place at both positions. One study[3] also demonstrated that relatively more attack took place at the X—CH_2 position as better leaving groups, X, were introduced. These were non-kinetic isotopic labeling studies; each labeling experiment was conducted at a single temperature.

We then decided to concentrate our efforts on a single substrate, epibromohydrin, making a complete kinetic and isotopic labeling study.[5] In this way we hoped to discover the subtle differences between the two competing reactions.

Our standard reaction, [equation (1)] has become the formation of hydroxymethylbenzodioxane[6] because of the following reasons: the system lends itself well to UV spectroscopy for kinetics; it lends itself (in principle) to easy CD_2 introduction at the ring CH_2 position of epibromohydrin; since the product is a well defined crystalline solid, and since it has two unique methylene environments, it lends itself well to NMR spectroscopy for following the fate of the CD_2 from reactant to product.



(1)

This work combined a kinetic and a deuterium labeling study at several temperatures to find the relative proportions of each operative mechanism at these temperatures. Using UV spectroscopy for the kinetics (see Experimental), the observed rate constant for the appearance of product hydroxymethylbenzodioxane was obtained at three temperatures. Using deuterium labelling experiments, individual rate constants for the two pathways were obtained at the same three temperatures. From these it was possible to derive the reaction parameters $\Delta H\ddagger$ and $\Delta S\ddagger$ for the competing reactions, leading to a more detailed understanding of the mechanism of each of those competing reactions.

EXPERIMENTAL

Kinetics. The kinetics were followed by UV spectroscopy using a Varian Cary Model 219 spectrophotometer. The solvent system was ethanol–water (1 : 1). To obtain activation parameters the kinetics were run at constant temperatures (±0·1 °C) of 25, 40

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and 60 °C. This narrow range of temperatures was dictated by the practicalities of setting the temperatures to obtain reliable rates in a reasonable time span but not so high (>60 °C) that extensive decomposition resulted. The reactions were followed for up to 65% of the reaction. Duplicate kinetic runs yielded rate constants reproducible to within ±3%. The initial ratio of epibromohydrin to catecholate anion was set at 2·23 : 1. Using the appropriate 3 × 3 determinants containing molar absorptivities and absorbances, the concentration of the product 2-hydroxymethyl-1,4-benzodioxane was calculated according to Cramer's rule,[7] using the equation

$$C_p = \frac{\begin{vmatrix} 5874 & 6800 & A^{237} \\ 2300 & 2700 & A^{276} \\ 3400 & 3500 & A^{292} \end{vmatrix}}{4.738 \times 10^9} \quad (2)$$

It was necessary to resort to such an approach since catechol, catecholate anion and hydroxymethylbenzodioxane all absorb at or near the maximum absorbances of the reacting system. In order to obtain the absorbance values for that equation, the absorbance at the three wavelengths at different reaction times were measured. The appropriate molar absorptivities were measured for catechol and hydroxymethylbenzodioxane. Literature values[8] of the molar absorptivities of the catecholate anion at the three wavelengths were used since they had been determined in the same aqueous alcohol solvent system. All these molar absorptivities are summarized in Table 1.

Initially the concentration of product, C_p, was calculated from the absorbance data. Then the concentration of epibromohydrin, C_{EBH}, and the concentration of catecholate anion, $C_{\bar{A}}$, were calculated. The usual plot of $\ln(C_{EBH}/C_{\bar{A}})$ versus time gave the total second-order rate constant, k_T.

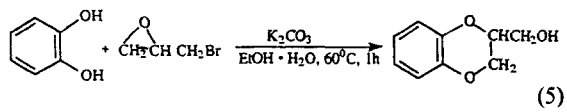
Synthesis. The syntheses[9,10] were relatively straightforward. The sequence is given in equations (3)–(5). We practiced on unlabeled material to maximize yields and then used $LiAlD_4$ in place of $LiAlH_4$ carrying out the whole sequence under identical conditions.

$$BrCH_2CHBrCO_2Et \xrightarrow[Et_2O,\ -70\ ^\circ C,\ 2\ h]{LAH\cdot AlCl_3} BrCH_2CHBrCH_2OH \quad (3)$$

Table 1. Molar absorptivities (l mol^{-1} cm^{-1})

	ε^{237}	ε^{276}	ε^{292}
Catechol	5874	2300	3340
Catecholate anion	6800	2700	3500
2-Hydroxymethyl-1,4-benzodioxane	455	2390	147

$$Br\,CH_2CHBrCH_2OH \xrightarrow[H_2O,\ 25^\circ C,\ 6h.]{Ca(OH)_2} \underset{O}{CH_2CH\,CH_2Br} \quad (4)$$



(5)

Deuterium–hydrogen analysis. Proton spectra of the appropriate reactant and product were obtained using a Varian XL–200 NMR spectrometer. In the case of 2,3-dibromo-1, 1-d_2-propan-1-ol [equation (3)], it was easy to see that the material was 99% dideuterated at the hydroxymethyl position.

In the case of the dideuterated epibromohydrin [equation (4)], the methine hydrogen was used as the internal standard and the integrals of the two distinct methylene hydrogen environments were obtained. From these integrals the relative amounts of the two distinct dideuteromethylene environments were calculated.

Similarly, in the case of dideuterated 2-hydroxymethyl-1,4-benzodioxane [equation (5)], the methine hydrogen was used as the internal standard and the integrals of the two distinct methylene hydrogen environments were obtained. Then the relative amounts of the two distinct dideuteromethylene environments were calculated.

RESULTS AND DISCUSSION

The kinetics were studied on undeuterated material; the studies to obtain the relative rate constants for attack at individual positions were run on dideuterated material. No corrections were made for the possibility of secondary isotope effects. Both theory[11] and experiment[12] suggest that the isotope effect, k_H/k_D will be inverse but close to 1·0 in the available temperature range.

The dideuterated epibromohydrin was found to be 79% dideuterated at the ring CH_2 position and 21% at the bromo-CH_2 position. This result has analogy in the Payne rearrangement[13] of epoxycarbinols in the presence of base. One referee suggested the intermediacy of the anion of 1,3 dibromopropan-2-ol in the preparation of the epibromohydrin, to account for the partial scrambling. Using the equation

$$\alpha = k_a(0\cdot79) + k_s(0.21 \qquad \text{where} \qquad k_a + k_s = 1 \qquad \text{and} \qquad 0 \leqslant \alpha \leqslant 1 \quad (6)$$

where k_a is the relative rate constant for addition of catecholate anion at the ring CH_2 position, k_s is the relative rate constant for substitution by catecholate anion at the bromo-CH_2 position and α is the relative integral related to the hydroxy-CH_2 in the product, the values for k_a and k_s were obtained at three different temperatures. These experimental and some calculated values (±1%) are given in Table 2.

Table 2. Relative rate constants at different temperatures

T (°C)	k_a	k_s	k_a/k_s
0 (calc.)	0·99	0·012	82
25	0·97	0·034	29
40	0·94	0·058	16
60	0·90	0·10	9·0
146 (calc. isokinetic)	0·5	0·5	1·0
∞ (calc.)	$4·2 \times 10^{-4}$	1·0	$4·2 \times 10^{-4}$

From the kinetics, the total second-order rate constants, k_T, at the three temperatures were obtained. From these data the apparent activation energy $E_a(T)$ was calculated. The value, 13 kcal mol^{-1} (1 kcal = 4·184 kJ), is not unreasonable because, it reflects predominant attack in base to open a three-membered epoxide ring for which[13] the activation energy, E_a, is 16·6 kcal mol^{-1}. The attack on epichlorohydrin[1] by oxygen anions has an activation energy, E_a, of 16·7 kcal mol^{-1}, which suggests that ring opening predominates. If the studies could have been carried out above the isokinetic temperature, where halide displacement predominates, the value for the activation energy E_a would be expected to be closer to 21·9 kcal mol^{-1}, which is typical for an S_N2 process.[14] When we carried out a calculation using total rate constants, over the range 146–∞ °C, we obtained an apparent activation energy, $E_a'(T)$, of 19 kcal mol^{-1}.

The calculation of individual second-order rate constants, k_α and k_σ, from the preceding data was undertaken, where k_α is the second-order rate constant for addition to the ring CH_2 position and k_σ is that for substitution at the bromo-CH_2 position. The values (±3%) are summarized in Table 3.

These data confirm that attack at the ring CH_2 position is dominant over the available temperature range. Further, they prove that although both rates increase with increasing temperature, attack at the bromo-CH_2 position increases more rapidly, indicating a larger activation energy $E_a(\sigma)$ for attack at the bromo-CH_2 position. The values (±2%) for E_as, enthalpy, entropy and free energy of activation are summarized in Table 4.

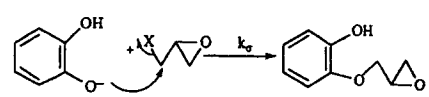
Table 4. Energies, enthalpies and entropies of activation

	E_a (kcal/mol)	$\Delta H‡$ (kcal/mol)	$\Delta S‡$ (e.u.)	$\Delta G‡$ (Kcal/mol)
from k_α	13	12	−34	22
from k_σ	20	19	−18	24

The apparent enthalpy, entropy and free energy of activation, based on the activation energy, $E_a(T)$, were not calculated because they are meaningless. Previously Chapman *et al.*[15] has stated that calculating activation parameters based on the kinetics of base-catalyzed ring opening of unsymmetrical epoxides is of no value unless one knows the product distribution. Then one can calculate individual rate constants and, from them, individual activation parameters, which are meaningful. In the same way, when one has a bifunctional electrophile where different nucleophilic attacks yield identical product, one must sort out the individual pathways, obtaining individual rate constants, and then the reaction parameters will be meaningful. Because Konecny[1] failed to do this in the epichlorohydrin system, he concluded that the sigma pathway was not operative when, in fact, it was the minor pathway and the alpha pathway was predominant but not exclusive.

In the present study, the activation parameters for the alpha pathway match well with those[16,17] for ring opening of epoxides in base; the activation parameters for the sigma pathway also match well with those[18] for bimolecular substitution, especially if the alkyl halide has a neighboring heteroatom.

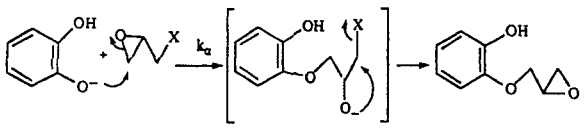
The competitive mechanisms based on the data now become clear. For the sigma pathway, the catecholate anion attacks the bromo-CH_2 of epibromohydrin in the rate-determining step [equation (7)], which leads directly to epoxide. For the alpha pathway, the catecholate anion attacks the ring CH_2 position in the rate-determining step, which leads by way of the inter-



(7)

Table 3. Total and individual rate constants

T (°C)	k_T (l mol^{-1} s^{-1})	k_α (l mol^{-1} s^{-1})	k_σ (l mol^{-1} s^{-1})
0 (calc.)	$1·3 \times 10^{-5}$	$1·3 \times 10^{-5}$	$1·6 \times 10^{-7}$
25	$9·2 \times 10^{-5}$	$8·9 \times 10^{-5}$	$3·1 \times 10^{-6}$
40	$3·1 \times 10^{-4}$	$2·9 \times 10^{-4}$	$1·8 \times 10^{-5}$
60	$1·0 \times 10^{-3}$	$9·2 \times 10^{-4}$	$1·0 \times 10^{-4}$
146 (calc.)	$8·0 \times 10^{-2}$	$4·0 \times 10^{-2}$	$4·0 \times 10^{-2}$
∞ (calc.)	$6·2 \times 10^{8}$	$2·6 \times 10^{5}$	$6·2 \times 10^{8}$



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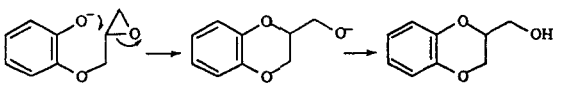

(9)

mediate shown in equation (8) to the same epoxide. Then the anion of the epoxide [equation (9)] intramolecularly attacks the ring CH position to give the alkoxy anion, which becomes product after protonation. This intramolecular attack on the ring CH position of the epoxide, leading preferentially to a six- rather than a seven-membered ring, is interesting because the attack is on the more substituted carbon. In intermolecular attacks on epoxides in basic solution[19] usually the site of attack is the less substituted carbon.

In summary, we have made a complete kinetic study of the reaction of epibromohydrin and catecholate anion; we have also carried out isotopic labeling experiments at several temperatures. We have found that attack at the ring CH_2 position, the alpha pathway, predominates at attainable temperatures, but that attack at the bromo-CH_2 position, the sigma pathway becomes more competitive at the higher temperatures. The enthalpies of activation are reasonable for the individual mechanism offered. The entropies of activation are also reasonable for the individual mechanism offered. Since the entropy of activation for the alpha pathway is approximately twice as negative as that for the sigma pathway, the sigma pathway becomes important very quickly at higher temperatures and is predicted to predominate above 146 °C, the calculated isokinetic temperature.

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