Solvent Microstructure Effect on Reaction Stereochemistry; Ring Opening of Chalcone Oxides

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The stereochemistry and kinetics of acid-catalysed ring-opening reactions of epoxides are reported. Predominant inversion is found in the usual hydroxylic solvents. As the nucleophilicity of the solvent diminishes and acidity increases, the stereochemistry changes to predominant retention. Electron-donating substituents also tend to favour retention. In mixed solvents, the solvent microstructure is altered, leading to net retention for nucleophiles such as methanol. The exception is dioxane–methanol, which gives enhanced inversion. Molecular mechanics calculations indicate an electrostatic preference for the retention route, but a steric preference for inversion. The activation parameters indicate a negative entropy for both inversion and retention paths. Possible reasons are discussed for the entropy of the retention route being in the range normally found for $A2$ reactions.

Proton transfers are frequently invoked in reaction mechanisms, but have seldom been studied *per se*.[1] Usually, proton transfers are not interpreted in detail, owing to the custom of providing only the simplest mechanism consistent with available data. In enzymic processes, a much more detailed description of proton transfers is given, sometimes on the basis of no more detailed data.[2] The present work explores the possible influence of proton transfers on the stereochemistry of epoxide openings. As in many carbocation reactions, stereochemistry is determined in competing fast reactions following a kinetically dominant step. The effect of proton transfer *vis-à-vis* reversion of the oxonium ion to the carbocation is intimately associated with solvent microstructure, *i.e.* the surroundings of the carbocation.[3]

An early review by Parker noted the variability of the stereochemistry of epoxide openings.[4] Jordlander and his co-workers showed that opening of chalcone oxide occurred with retention.[5] Later, House corrected the regiochemistry reported by Jordlander, and showed that chlorohydrins of opposite stereochemistry were formed in ethanol *vs.* ether as solvent.[6] Brewster showed that stilbene oxide opens with retention.[7] The pesticide dieldrin opens in sulphuric acid solutions with retention.[8] In dypnone oxide (2), Wasserman and his co-workers attributed the overall retention to a double inversion; the first inversion closed a four-membered ring using carbonyl oxygen as nucleophile.[9] Back and his co-workers, House, and the early German workers showed that rearrangement of the system occurs in which the acyl group migrates.[5,6,10] Thus, either the carbonyl oxygen or carbon may be involved, *cf.* (3) *vs.* (4) in Scheme 1.

In other work, arguments have raged over whether the acid-catalysed opening of simple epoxides is $A1$ or $A2$ in character. Entropy of activation and volume of activation data (supporting an $A2$ process) were in conflict with acidity function data.[4,11–13] The Bunnett improvement on the original Hammett–Zucker treatment still favours an $A1$ process for ethylene oxide.[14] The general problem of epoxide openings has a sinister aspect, *i.e.* the opening of the 'ultimate carcinogen,' benzpyrenediol epoxide.[15]

Epoxide opening has been studied in detail by Macchia and his co-workers.[16] This work demonstrated the sensitivity of the stereochemistry to reaction conditions, *e.g.* temperature. In general, retention of configuration was found in cases in which a relatively high degree of positive charge character is present at the benzylic carbon, whereas inversion is associated with S_N2-like reaction modes. In reactions showing net retention, hydrogen bonding of the attacking nucleophile to oxygen centres and also ion pairing were considered to be important.

At the outset of the present study, chalcone oxides (1) seemed to offer a solution to the problem of $A1$ *vs.* $A2$ openings. Earlier work has shown that carbonyl groups markedly accelerate S_N2 attack at α-carbon atoms.[17,18] Although the reason for this effect remains controversial, the practical effect in (1) is that a reaction essentially S_N2 nature should give substitution x to carbonyl, whereas an S_N1 reaction should provide products derived from a benzylic carbocation. Thus, benzenethiolate reacts with (1) to give (6) and benzaldehyde. These products arise from a retro-Aldol reaction of the initially formed product (5).† No reaction was observed with hydroxide.‡[21] The possibility of an electron-transfer process instead of S_N2 was tested using benzeneselenolate as nucleophile on (1c). However, no CIDNP was observed during monitoring of [77]Se.[22,23]

In a diastereoisomeric system such as (1), the question arises whether a bias toward a certain stereochemistry might be imposed by the diastereoisomerism of the sytem.[24] To test this possibility, 4,4'-dimethoxychalcone oxide (1a) was investigated. As Table 1 shows, this substrate gave similar degrees of retention and inversion in most solvents. Similarly, *cis*- and *trans*-(1c) give similar retention : inversion ratios in methanol as solvent.

The possibility of nucleophilic involvement of the benzoyl oxygen was investigated through variation of the substituent on the benzoyl group. A methoxy group should markedly enhance the ability of carbonyl oxygen to participate in epoxide cleavage. However, both (1c) and (1g) and also (1e) and (1f) gave very similar stereochemical results. The small variation is not in agreement with a direct nucleophilic involvement of carbonyl in the ionization process.

Solvent Effects.—Chalcone oxide (1c) and its *p*-chloro analogue (1d) give predominant inversion in the common alcohols as solvent. Sterically hindered alcohols such as isopropyl alcohol give particularly high degrees of inversion (Table 1). More acidic media, which involve weaker nucleophiles, give a slight dominance of retention, as was also evident in Macchia's work.[16]

Ethylene glycol was investigated as solvent to see whether a hydrogen bond between carbonyl and one glycol hydroxy group would induce the other to attack a particular face of the

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† The retro-Aldol reaction is common in Darzens condensations.[19]
‡ This is an important point, as an alternative path described by Russian workers is possible, involving prior attack at carbonyl by alkoxides eventually giving epoxides derived from the ketone carbonyl group.[20]

	X	Y	R
(1) a	MeO	MeO	H
b	Me	H	H
c	H	H	H
d	Cl	H	H
e	NO₂	H	H
f	3-NO₂	MeO	H
g	H	MeO	H
(2)	H	H	Me
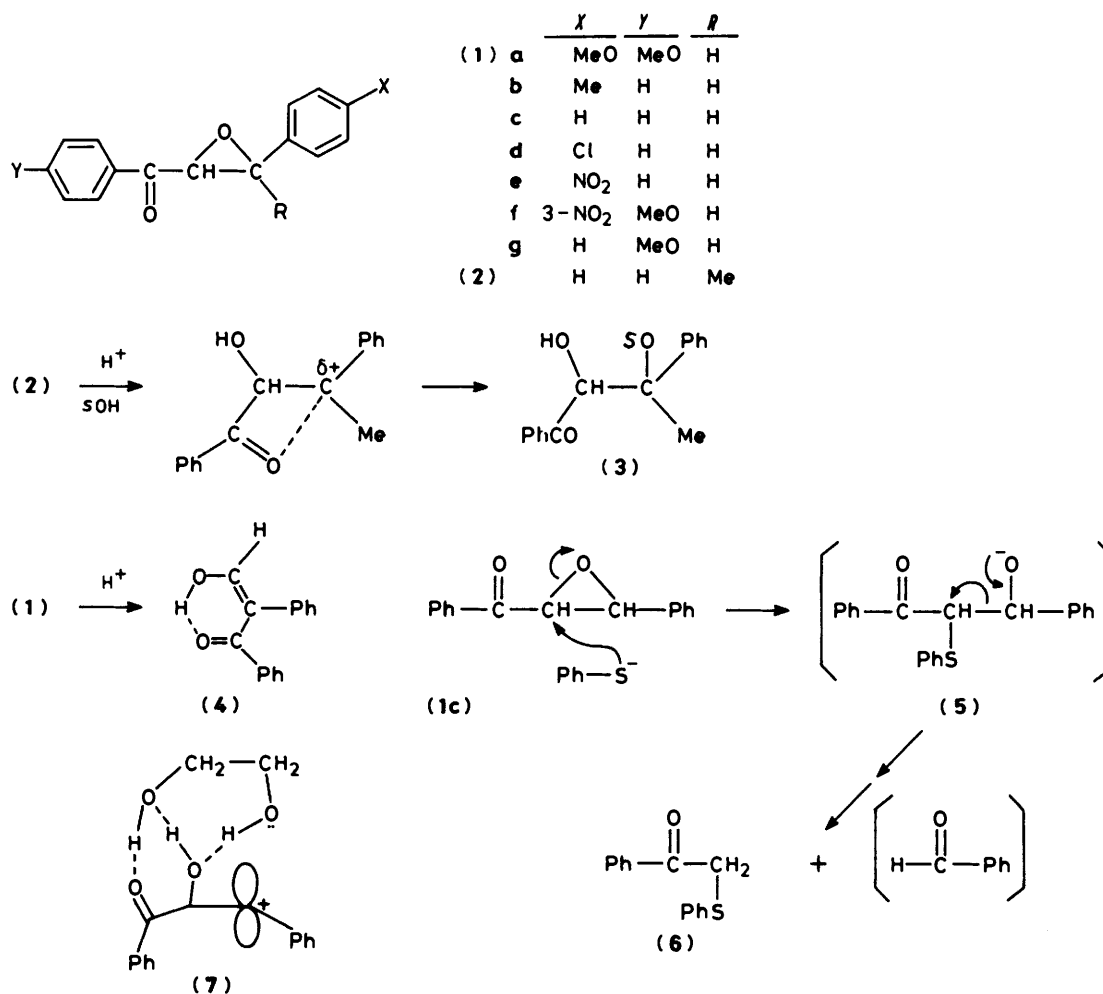
Scheme 1.

Table 1. Percentages of retention product from reactions of chalcone oxides (1) in pure solvents[a,b]

	X	Pr^iOH	EtOH	MeOH	HOCH₂CH₂OH	CF₃CH₂OH	HOAc
(1a)	p-MeO[f]	48[c]		49 ± 1		51	58 ± 2
(1b)	p-Me	40 ± 2	45 ± 3	54 ± 2	47 ± 3	55 ± 3[e]	63 ± 3[e]
(1c)	H	16 ± 1	16 ± 1	25 ± 1	20 ± 4	58 ± 3[e]	52 ± 2[e]
(1d)	p-Cl	d	16 ± 1	21 ± 1	28 ± 3	64 ± 2[e]	57 ± 5[e]
(1e)	p-NO₂	d		ca. 0		d	d

[a] No co-solvent present; however, trifluoroethanol may have retained a slight admixture of water. [b] Reactions run at ambient temperature except as noted. [c] The remainder from 100% represents inversion product, i.e. 52% in this case. [d] Unreactive. [e] Reaction temperature 60 °C. In most cases tested, the product ratio was not highly temperature sensitive. [f] p,p'-(MeO)₂.

cation.[24,25] As a result of hydrogen-bond saturation effects, ethylene glycol, as a pure solvent, is similar to methanol. However, when the reaction is run with a small amount of ethylene glycol in an inert co-solvent, considerably more retention is observed [78% for (1b) or (1c) in 25:1 nitromethane–ethylene glycol; cf. 63% and 69% in 25:1 nitromethane–methanol]. Structure (7) illustrates one possible hydrogen-bonding scheme leading to retention.

In general, product ratios were similar when toluene-p-sulphonic acid or trifluoroacetic acid (TFA) was used as catalyst. Pure TFA gave rearrangement and decomposition products. However, in solvent mixtures having a large inert solvent component, trifluoroacetate products were occasionally found in very low yields after short reaction times. These products showed a very high degreee of retention (ca. 85% is a common figure). It is possible to follow the course of reaction in CDCl₃ with TFA by n.m.r. Retention (ca. 90%) is strongly dominant.[26–28*]

In general, the product range shades from retention for p-methyl (1b) to almost complete inversion for the p-nitro compound (1e) in alcoholic solvents (cf. Table 1). In less

* However, a number of ordinary S_N1 reactions proceed with retention of configuration without any possibilities for hydrogen bonding to groups on the carbocation (although hydrogen bonding to the leaving group is postulated.[27]

Table 2. Reactions in mixed solvents; percentage of retention product[b]

Solvent	Ratio	Product type	Substrate (1b) (p-Me)	(1c) (H)	(1d) (p-Cl)[d]
MeCN–MeOH	5:1	–OMe[f]	60	44 ± 1	62
	50:1	–OMe	59 ± 1	62 ± 1	74 ± 2
MeNO2–MeOH	50:1	–OMe	63	69 ± 6	72 ± 1
[CH2]4SO2[c]–MeOH	50:1	–OMe	67 ± 3	64	68
CF3CH2OH–MeOH	5:1	–OMe	68	64 ± 4	69
		–OCH2CF3	62	57 ± 3	e
CF3CH2OH–HOAc	5:1	–OAc	62	62 ± 1	a
		–OCH2CF3	ca. 66	ca. 67 ± 3	~76
HOAc–MeOH	5:1	–OMe	61 ± 1	45[d]	48 ± 3
		–OAc	59 ± 4	56[d]	51
	50:1	–OMe	62	51 ± 1[d]	
		–OAc	63	50 ± 3[d]	64
[CH2CH2O]2[g]–MeOH	5:1	–OMe	40 ± 1	15 ± 1[d]	16
	50:1	–OMe	37 ± 3	15[d]	12 ± 1
[CH2CH2O]2[g]–HOAc	5:1	–OAc	46 ± 4	45 ± 2[d]	ca. 50

[a] High degree of retention; exact percentage not obtained. [b] If x is the percentage of retention product, $100 - x$ is the percentage of inversion. [c] Tetramethylene sulphone. [d] Temp. 60 °C rather than ambient temperature. [e] An accurate determination was not possible. [f] Methyl ether product [cf. Scheme 2, products (12) and (13), where $OS = OMe$]. [g] Dioxane.

nucleophilic solvents, all reactive substrates give net retention.[16]

The p-methyl substrate (1b) gives results quite close to those for the p-methoxy case (1a), although generally more retention is found. The data in Table 1 were taken for very short reaction times, in an effort to reduce equilibration (if any).

To test the lability of products under the experimental conditions, (1b) was converted into the hydroxy acetate (12). This product was treated with methanol (with TFA catalyst) for 20 h (normal reaction conditions) to see if the acetate would be converted into a methyl ether. The conversion was very low (< 3%).

Mixed Solvents.—The point of interest is the ability of solvent to serve as a proton-transfer agent in the inversion pathway. In the retention pathway, internal proton transfer and/or proton transfer to the proton carrier (say trifluoroacetate) are important phenomena. Thus, it is of interest to consider the effect of mixed solvents on reaction stereochemistry (cf. Table 2). The changes are most pronounced at high dilution (e.g. the 50:1 ratios of co-solvent to nucleophilic solvent).

The dominance of inversion observed for (1b) and (1c) in pure methanol changes to a slight net retention in most mixed solvents. In nitromethane–methanol, the degree of retention for (1c) and (1d) surpasses that of the p-methyl substrate (1b), which gave retention even in pure methanol. In many of the solvent systems listed in Table 2, the stereochemistry is rather insensitive to the type of co-solvent used or to the substrate. In these cases, about 60% retention is a common figure. The exception is the co-solvent dioxane, which gives enhanced inversion for methanol and for acetic acid as nucleophiles.
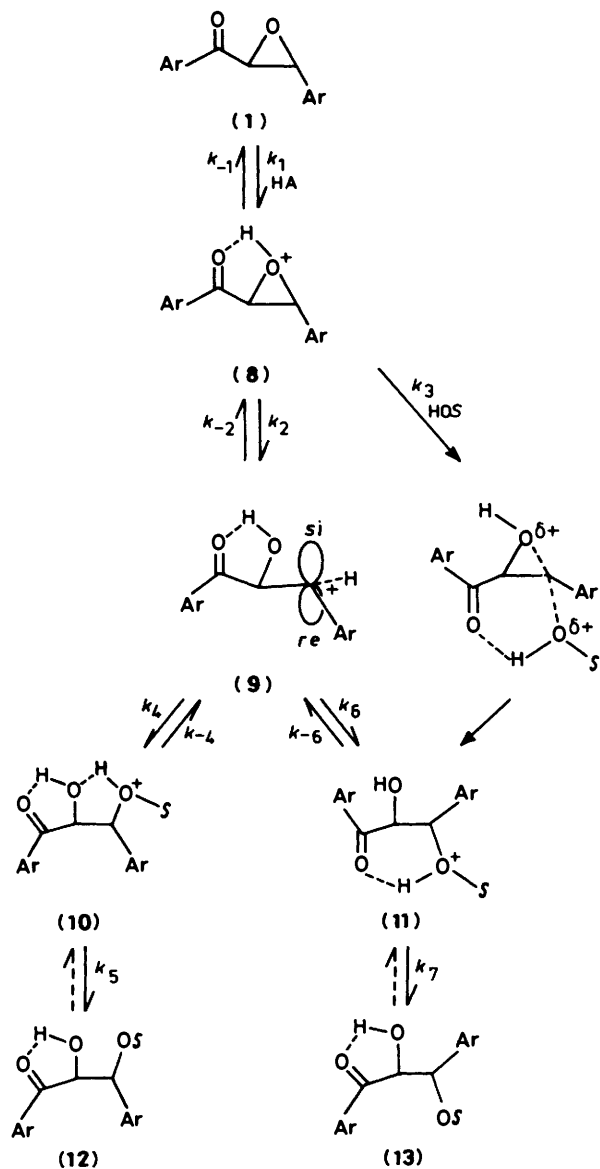
Mechanism.—Effect of solvent microstructure. Scheme 2 illustrates present ideas of the reaction paths giving retention vs. inversion. This mechanism is similar in many respects to that postulated by Macchia and his co-workers.[16] In the present case, it is clear that carbonyl has a subtle effect that is not due to participation. Substrates lacking carbonyl give much higher degrees of inversion (e.g. 1,2-epoxy-1,3-diphenylpropane, ca. 85%). A hydrogen-transfer involvement of carbonyl seems likely. One possibility for this influence is indicated in Scheme 2. Hydrogen bonding through a set of donor and acceptor centres involving carbonyl could enhance the selective solvation of the

si face of the molecule, leading to enhanced retention. The hydrogen-bonding postulate has been supported by theoretical calculations.[25b,c] However, it is important not merely to form a hydrogen bond, but also to provide a path involving elimination of the hydrogen from the oxonium ion (11). The oxonium ion possesses an excellent leaving group in the protonated solvent molecule. The degree of retention is affected not only by the magnitude of k_4 with respect to k_6, but also by the reversion to product formation ratios k_{-4}/k_5 vs. k_{-6}/k_7. The additional possibilities of proton transfer from the oxonium ion (10) resulting from si attack favour retention by inhibiting the step corresponding to k_{-4}. Superimposed on this mechanism is an S_N2-like inversion process involving re attack. This process, nonetheless, is fundamentally different from a true S_N2, which should give different regiospecificity; cf. (6).[29]

It seems clear that an organized proton-transfer system involving hydrogen-bonded donors and acceptors is responsible for much of the efficiency of enzymic systems.[2,30] The same type of relay is believed to stabilize the oxonium ion on the si face more than on the re face, thus favouring retention. The counterion, trifluoroacetate, near the epoxide oxygen, probably serves as the ultimate proton acceptor. This additional factor favours retention over inversion, especially in solvents of lesser ability to accept protons, i.e. some of the mixed solvent systems.

Bulky nucleophiles such as isopropyl alcohol probably do not permit the system of hydrogen bonds to be as firmly established on the si face. The lesser steric problems in re face attack favour inversion with these nucleophiles. Solvents such as trifluoroethanol (TFE) give lesser amounts of inversion, owing to low nucleophilicity (i.e. k_3 is unimportant). In addition, the oxonium ions resulting from attack of TFE, (10) and (11), are more subject to reversion to the cation. The loss of the excess of hydrogen is enhanced by the acidity of the oxonium ion.[31] Substrates that give carbocations of greater stability, e.g. X = p-Me (1b), are also less subject to nucleophilic involvement by the solvent leading to inversion. Also the reversion to the carbocation is more probable in the case of (1b). The reversion is eliminated to a certain extent by the proton relay on the si face of the molecule.

In mixed solvents, nucleophilic attack of the minor component on the re face is still possible, but if the major solvent constituent, say tetramethylene sulphone, is not a good proton acceptor, the oxonium ion (11) is not readily stabilized by

O O

Ar Ar

(1)

k_{-1} k_1
HA

H

O O$^+$

Ar

Ar

(8)

k_3
HOS

k_{-2} k_2

H si

O O

Ar $-$H

$+$

re Ar

H O$^{\delta+}$

Ar

Ar

Ar

O O$^{\delta+}$

H S

(9)

k_4 k_{-4} k_6 k_{-6}

H O H

O O$^+$ S

Ar Ar

(10)

Ar HO Ar

O O$^+$

H S

(11)

k_5

H O OS

O

Ar Ar

(12)

k_7

H O Ar

O

Ar OS

(13)

Scheme 2.

proton loss. The enhanced inversion observed in dioxane solutions is believed to be due to the fact that this solvent is a good proton acceptor, but not a proton donor. Thus, dioxane enhances k_7 relative to k_{-6}.[32]

Other solvents, such as trifluorethanol, are not good proton acceptors but are good proton donors. Mixed solvents involving TFE give stereochemical results similar to those with tetramethylene sulphone or nitromethane because of the adverse balance between proton acceptance by neutral TFE and back-donation of protonated TFE.[31,33,*]

Molecular mechanics calculations. MM2 Calculations were used to approximate the energy of the carbocation (9) at a range of approach distances of the nucleophile in question.[35] The segment of MM2 of chief interest is 'dipolar interactions.'[36] At short approach distances, the overall 'steric energy' is unrealistically high, owing to steric effects between the nucleophile and

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* Correlation of stereochemistry with various types of donor–acceptor LFERs was not successful, cf. ref. 34.

cation, as the counteracting effect of development of covalency is not included. The starting point of the calculations stems from a previously minimized geometry of the carbocation. Most calculations involved a direct approach of the nucleophile to the top of the p orbital, but some off-centre approaches were also investigated.[37,38]

The first set of calculations used the original parameters of the MM2 program, e.g. a dielectric constant of 1.0. For water as nucleophile, the calculations predict an electrostatic preference for si approach (retention). The dipolar term is roughly constant at -13.8 ± 1.3 kJ mol^{-1} at approach distances of 2.6—1.6 Å. For re approach, the energies are also roughly constant at -5.9 kJ mol^{-1} (same distances). As MM2 does not permit covalency in hydrogen bonding, the interaction of water with the oxygens of the substrate is purely electrostatic. The minimization of energy appears to lessen lone-pair–lone-pair interactions by directing a hydroxy hydrogen atom towards the lone pair of another oxygen, thus imparting a resemblance to a classical hydrogen bond (cf. Scheme 2).

For methanol as nucleophile, the dipolar energies vary from -2.1 to -5.4 to -2.9 kJ mol^{-1} (si approach), cf. -1.7 to -3.8 to -4.6 kJ (re approach), at distances of 3.0, 2.0, and 1.5 Å. The effect of an off-centre approach to the p orbital is sizeable, giving a better overall energy, although the dipolar term becomes repulsive. Thus, the small differences in dipolar interactions just quoted should not be regarded as significant.
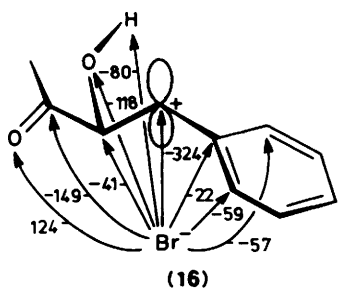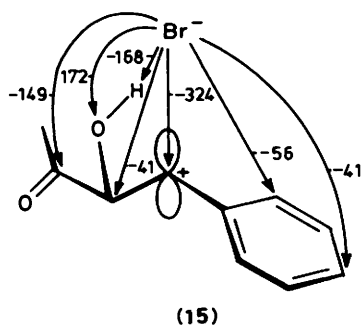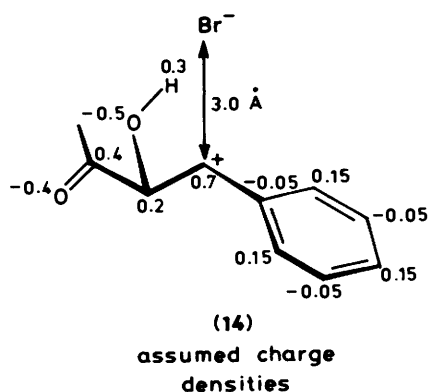
In Table 2, an unusual solvent effect was noted for dioxane, i.e. enhanced inversion. The characteristics of a possible nucleophilic involvement of dioxane were simulated in MM2 calculations using dimethyl ether as nucleophile. At 2.0 Å, the dipolar energy, -2.5 kJ mol^{-1}, is the same for either direction of approach. Despite the greater size of the nucleophile, the difference in overall steric energy between the si and re directions of approach ($+24$ kJ) is smaller for dioxane than for water ($+36$ kJ) at 2.0 Å.

An alternative set of calculations utilized corrections suggested by Kroon-Batenburg et al., which permit a more realistic treatment of hydrogen bonding.[35] A smaller 'size' of the lone pairs at oxygen is used, and in our calculations the dielectric constant was set at 4. For water as nucleophile, si approach is again preferred according to the dipolar terms (-2.1 vs. -0.4 kJ at 3 Å, and -3.1 vs. -1.3 kJ at 2 Å). An additional correction for hydrogen bonding provides a 4 kJ preference for si approach at 3 Å, although at 2 Å this difference disappears owing to the very close proximity of the substrate OH to water. In actuality, it seems likely that internal rotation of the substrate would occur in order to maximize hydrogen-bonding stabilization, and minimize steric effects. Between 4 and 2 Å, the van der Waals' terms of MM2 change from attraction to repulsion, with regard to the nucleophile, climbing to 88 kJ (si approach) vs. 67 kJ (re approach). Approximately 46 kJ of this van der Waals' energy is due to the 'repulsive' interaction of the nucleophile with the cation.

In methanol, the Kroon-Batenburg approach predicts a 4 kJ preference for si attack at 3 Å (combined H bonding and dipolar terms) that is opposed by a 1.3 kJ steric preference for re attack. Similar results are apparent for dimethyl ether as nucleophile. In fact, all calculations consistently predict the same trends, i.e. an electrostatic preference for si attack vs. a steric preference for re attack.

Other data. A few runs were done in the presence of Et$_4$NBr. In the case of bromide as nucleophile, a proton transfer to stabilize an intermediate, such as the oxonium ion (10) or (11), is not necessary.[39] Under a variety of conditions, the ratio of retention to inversion is near unity. In acetic acid as solvent, a 52:48 ratio of the bromohydrins (12) and (13) (OS = Br) is the type of result frequently found. However, in methanol, no bromohydrin is observed, in part owing to the higher nucleo-

(14)

assumed charge
densities

(15)

(16)

Scheme 3.

Table 3. Rate constants and activation parameters for reaction of (1c) in methanol[a]

Temp. (°C)	$k/l\ mol^{-1}\ s^{-1}$		$\Delta H^{\ddagger}/kJ\ mol^{-1}$		$\Delta S^{\ddagger}/J\ mol^{-1}\ K^{-1}$	
	ret.[a]	inv.[b]	ret.	inv.	ret.	inv.
45.0	0.0414	0.103				
35.0		0.0630[c]				
25.0	0.0068	0.0196	68.6	64.0	−54	−63

[a] Overall: $\Delta H^{\ddagger} = 64.4$ kJ mol^{-1}; $\Delta S^{\ddagger} = -59$ J mol^{-1} K^{-1}. [b] Rate constants for retention and inversion, as indicated. [c] Overall rate constant.

Kinetics.—Table 3 lists the second-order rate constants for the acid-catalysed methanolysis of (1c). The rates were determined over a temperature range. By using the observed product ratios at the extrema of the temperature range, the observed rate constant was dissected into retention and inversion components. The activation parameters were calculated for both stereochemical routes.

The activation parameters indicate that the major factor responsible for the dominance of inversion is $\Delta H^{\ddagger}$. The entropy difference is surprisingly small. For the inversion path, $\Delta S^{\ddagger}$ is in the range for an $A2$ process, consistent with an approach of solvent as the carbocation forms.[13] The similarity of $\Delta S^{\ddagger}$ in the retention path is not as easily explained. It is possible, though not likely, that solvent attack is a kinetically significant event. Alternatively, spectator molecule(s) may exist (possibly the carrier of the proton used to protonate the epoxide).[32] This idea is attractive from the point of view that $\Delta S^{\ddagger}$ (ret.) *vs.* $\Delta S^{\ddagger}$ (inv.) is a reflection of the predilection for retention *vs.* inversion at the time of the rate-limiting step, which is almost certainly the rupture of the covalent C–O bond of the epoxide. However, as Italian workers have found sizeable effects of temperature on stereochemistry, changes in $\Delta S^{\ddagger}$ may be large in other cases.[16]

In conclusion, we agree with the Italian workers on the importance of hydrogen bonding (a static effect) in facilitating retention of configuration.[16] However, evidence exists that the dynamics of proton transfer affect the product ratio, in this particular set of molecules, through more effective proton removal, and less reversion of an oxonium intermediate to cation. The old controversy regarding $A1$ *vs.* $A2$ openings of epoxides should be re-evaluated in terms of the extensive stereochemical evidence indicating retention of configuration as well as the present case of a large negative $\Delta S^{\ddagger}$ for the retention route.

philicity of that solvent. For reactions involving 2.0M-bromide in acetic acid, the acetate products were reduced to a low level, *ca.* 20%, and their analysis is thus inaccurate. However, it is clear that the inversion product is now dominant, *e.g. ca.* 36:64 for retention to inversion in the case of (1c). Thus it appears that bromide pre-empts the *si* face of the cation and much of the *re* face as well.

The dominance of inversion in the acetate products when bromide is present could be due to attack of acetic acid on the ion pair involving bromide associated with the *si* face of the cation. The electrostatic segment of MM2 indeed suggests a stronger electrostatic interaction for the *si* ion pair [*cf.* models (14)—(16)]. The calculation program did not appear to respond to changes in dielectric constant, but the large energy differences would be attenuated in media of dielectric constant higher than the 1.0 value implicit in MM2. As in the previous sets of calculations, the electrostatic preference for *si* attack was opposed by a steric preference for *re* attack. Thus, the similarity of amounts of retention and inversion in the bromohydrin products may be due to an incursion of S_N2-like reaction modes. The enhanced inversion in the acetate products could indeed be due to *re* attack of solvent on the *si* bromide ion pair, which may be inhibited from directly forming the bromohydrin by steric effects.

Experimental

Methods of Epoxidation.—(a) m-*Chloroperbenzoic acid.* This oxidant was prepared by the method of McDonald.[40] To the appropriate alkene (0.1 g) in dichloromethane (*ca.* 50 ml) cooled to 0 °C, the peroxy acid (1.5 equiv.) was added with stirring at reduced temperature over 30 min. The solution was stirred at room temperature for an additional 12 h, then 10% sodium hydrogen sulphite solution was added until starch–iodine showed the absence of peroxides. The mixture was filtered to remove m-chlorobenzoic acid, and the two liquid layers were separated. The organic layer was extracted with saturated aqueous sodium hydrogen carbonate, and then with saturated aqueous sodium chloride, dried ($MgSO_4$), and filtered. The product was recrystallized to purity.

(b) *Hydrogen peroxide method.* To the alkene (0.1 g), sufficient methanol was added to afford a homogeneous solution at reduced temperature (10—15 °C) (usually *ca.* 25 ml). To this solution, NaOH (1.5 equiv.), dissolved in the minimum volume of aqueous 50% methanol, was added. For most chalcones, the

solution becomes orange-red at this stage. To this solution, 30% hydrogen peroxide (1.1 equiv.) was added dropwise with stirring over 10—15 min. The solution usually underwent a marked colour change. It was stirred for an additional 30 min at reduced temperature, then the peroxide was destroyed with aqueous 10% sodium hydrogen sulphite (monitored by starch–iodine).

The product was taken up with ether, dried ($MgSO_4$), and recrystallized to purity. Nitromethane was a good recrystallization solvent for epoxides too soluble in ethanol.

Substrates.—The substrates for reaction, *viz.* chalcone, m.p. 57—58 °C (lit.,[41] 56—57 °C); *p*-methylchalcone, m.p. 94—95 °C (lit.,[42] 96.5 °C); *p*-chlorochalcone, m.p. 101—102 °C (lit.,[43] 103—104 °C); *p*-nitrochalcone, m.p. 164—165 °C (lit.,[44] 164 °C); and 4'-methoxy-3-nitrochalcone, m.p. 137—138 °C (lit.,[44] 137 °C) were prepared by literature procedures.[41] 4,4'-Dimethoxychalcone and 4'-methoxychalcone were obtained from our research stores, and appeared pure by n.m.r.[45,46]

Substrate (1c) was prepared by method (b), with ethanol as solvent [m.p. 89—90 °C (lit.,[47] 90 °C); 77% yield]. Similarly, (1d) was made [m.p. 80—82 °C (lit.,[48] 80—81 °C)]. The preparation of (1b) by method (b) in ethanol was troublesome. It is important not to permit the reaction to go too long. The product, m.p. 83—84 °C (lit.,[48] 85 °C) (81% yield) was recrystallized in nitromethane. Also by method (b), (1e) was prepared; it was necessary to use 700 ml of 95% ethanol for 3 g of substrate (product m.p. 136—137 °C; lit.,[49] 138 °C; 67% yield); (1a) was similarly prepared (m.p. 111—112 °C), as was (1g) (m.p. 78.0—78.5 °C; lit.[50] 75 °C). The 70 eV mass spectrum of (1a) showed m/e 284.1054 (devn. 9 p.p.m.) (Calc. for $C_{17}H_{16}O_4$, m/e 284.1044).

cis-*Chalcone oxide.* This was prepared by a circuitous route.[51] The first step was the preparation of 1,3-diphenylprop-2-yn-1-ol, as follows. To lithium wire (0.27 g, 0.03 mol) sliced into small pieces and dropped directly into dry ether (100 ml), butyl bromide (2.6 g, 0.019 mol) was added dropwise at 0 °C under nitrogen until no further lithium remained. Phenylacetylene (2.0 g, 0.019 mol) in ether (2 ml) was then added with stirring over 0.5 h. Benzaldehyde (2.07 g, 0.019 mol) in ether (25 ml) was then added dropwise, and the mixture was stirred for an additional 1 h at 0 °C. The reaction was quenched with saturated aqueous $CaSO_4$, the layers were separated, and each layer was extracted with fresh portions of the other; the combined organic layers were washed with water (2 × 25 ml), then with cold aqueous N-NH$_4$Cl, then dried ($MgSO_4$), and evaporated, leaving crude product (3.1 g); the distillation cut of b.p. 160—164 °C at 1 mmHg (lit.,[51] b.p. 159 °C at 1.3 mmHg) was taken (76% yield).

The next intermediate, 1,3-diphenylprop-2-en-1-ol, was prepared from the foregoing oil (2.0 g, 9.6 mmol) placed in 95% ethanol (50 ml) and hydrogenated over Pd–C on CaCO$_3$–BaSO$_4$ (0.2 g) in a Parr shaker for 4.5 h. The catalyst was filtered off through Celite, and the solution was evaporated, providing the crude cis-alkene (1.95 g), b.p. 121—122 °C at 0.1 mmHg (lit.,[51] 147—150 °C at 113 mmHg; yield 96%).

The next intermediate, cis-2,3-epoxy-1,3-diphenylpropan-1-ol, was made by dissolving the cis-alkene (1.95 g, 9 mmol) in dichloromethane (50 ml) to which a solution of *m*-chloroperbenzoic acid (2.0 g, 9 mmol) in dichloromethane (100 ml) had been added dropwise [*cf.* method (a)], giving the epoxide (1.98 g), m.p. 82—83 °C; yield 97%.

The final step was oxidation to the cis-chalcone oxide. To the alcohol in pyridine (20 ml), chromic oxide (2.85 g) dissolved in pyridine (28 ml) was added; the mixture was stirred overnight. The solid was filtered off, and washed with ether (4 × 25 ml); this same solvent was used to extract the original filtrate. The combined organic layers were washed with aqueous N-NH$_4$Cl (50 ml) and with water, dried ($MgSO_4$), filtered, and evaporated, giving an oil (0.98 g) that slowly crystallized. Recrystallization

from light petroleum gave the product, m.p. 96—97 °C (lit.,[50] 96—97 °C).

trans-1,2-*Epoxy-1,3-diphenylpropane.* The parent alkene was prepared by the method of Kohler and Chadwell; m.p. 44—45 °C (lit.,[52] 44—46 °C). The alkene was oxidized by method (a), giving the epoxide, b.p. 163—164 °C at 10 mmHg (lit.,[53] b.p. 162—165 °C at 6 mmHg); yield 98%.

General Procedure for Epoxide Openings.—Chalcone oxide (1c) (1.0 g, 4.46 mmol) was dissolved in dried reagent grade methanol (75 ml) in a flask equipped with stirrer and nitrogen inlet; then the catalyst TsOH (0.1 g) was added as a solid, and the mixture was stirred for 6 h; solid NaHCO$_3$ (0.5 g) was added and the mixture stirred for 5 min. Then solvent (either ether or dichloromethane) was added and the mixture was stirred with aqueous NaHCO$_3$. The layers were separated, and the aqueous layer was extracted with ether or dichloromethane (2 × 30 ml). The combined organic layers were washed with saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and evaporated, providing the crude product, a yellow oil (1.09 g, *ca.* 95%). The content was analysed by n.m.r. integration.

In a later variation of this procedure, a solution of the epoxide (0.1—0.2 g) in the solvent in question (5 ml) was kept at room temperature for 20 h [except for (1b), for which the reaction time was 2—4 h]. In some cases, a higher reaction temperature was necessary (an oil immersion bath, usually at 60 °C, was used). The solvent was removed by a jet of air, which also eliminated TFA; CCl_4 was added and similarly evaporated off. The residual oil was taken up in $CDCl_3$ and analysed by ^{13}C or ^1H n.m.r. spectroscopy. In the former case, peak heights were used as a measure of product yield (a sufficiently long delay time between pulses was used in order to achieve similar relaxation for the two isomeric products). The yields of the various products were variable, although the stereochemistry was reproducible from run to run. Thus, yields are not emphasized in this paper, although the following are presented as roughly representative. The runs in methanol or other common alcohols as solvent were quite clean. In a typical reaction [(1b) in methanol], the methyl ether products were found to comprise 90% of the total material. In this determination, the n.m.r. integration of the phenyl region was taken as an internal standard, as it is unlikely that a phenyl group would be created or destroyed in the course of the reaction. However, the remainder of the product showed no visible alkyl absorptions. In another reaction [(1c) in methanol (5 ml) in the presence of 2.0 g of Et$_4$N$^+$Br$^-$], the products were: ethers (84%), benzaldehyde dimethyl acetal (13%), and methyl benzoate (*ca.* 2%). Surprisingly, no bromide was found (the n.m.r. absorptions of the bromide were known from other work). The reaction of (1c) in CH$_3$OD in nitromethane (1:50 v/v) at room temperature for 18 h gave 20% overall yield of ethers, 10% of an aldehyde believed to be the rearrangement product 3-oxo-2,3-diphenylpropanal, and a trace of a product, δ_H 7.5 (believed to be the enol form of the rearranged aldehyde). The n.m.r. absorption of the aldehydic hydrogen atom is δ 9.9, slightly less than that of benzaldehyde, which also was observed on occasion. In this particular run, trifluoroacetate products (14%) were observed. The runs in TFE were the most difficult to analyse, and the stereochemical data are the least accurate for runs in this medium. A typical run in TFE (TFE:MeOH ratio 5:1 v/v at 60 °C for 12 h) gave 37% trifluoroethyl ethers, plus 28% methyl ethers and only traces of other products having identifiable alkyl absorptions (thus the remainder of the products were aromatic). A run in HOAc with Et$_4$N$^+$Br$^-$ present (2.0 g in 5 ml of solvent) gave 82% bromides and *ca.* 10% acetates.

Kinetic Procedure.—All chalcone oxides were recrystallized three times before use. Dry methanol was obtained by distilling

reagent-grade methanol from $Mg(OMe)_2$; this solvent was stored over 3 Å molecular sieves. Dry toluene-p-sulphonic acid was obtained by dissolving TsOH hydrate in benzene, and removing the water via a Dean–Stark apparatus (m.p. 36— 38 °C after removal of benzene). The products of kinetic runs were analysed by n.m.r. (all sample points were run at the same time). For the points, the solvent was evaporated off, and the sample taken up in 0.5 ml of $CDCl_3$ [for (1d), more solvent was necessary]. Initial runs were performed in the presence of hexamethylbenzene as an internal integration standard. In later runs the combined phenyl absorptions were used as an internal standard.

References

1 R. P. Bell, 'The Proton in Chemistry,' Cornell University Press, Ithaca, New York, 1959, ch. 1.

2 (a) M. L. Bender, R. J. Bergeron, and M. Komiyama, 'The Bioorganic Chemistry of Enzymatic Catalysis,' Wiley, New York, 1984, ch. 1; (b) A. R. Fersht, and A. J. Kirby, Prog. Bioorg. Chem., 1966, 1, ch. 1; (c) W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, ch. 1; (d) F. M. Menger, J. Grossman, and D. C. Liotta, J. Org. Chem., 1983, 48, 905; (e) F. M. Menger, Stud. Org. Chem. (Amsterdam), 1982, 16; (f) T. C. Bruice, and S. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, pp. 16—21; (g) H. Dugas, and C. Penney, 'Bioorganic Chemistry,' Springer-Verlag, Heidelberg, 1981, ch. 5.

3 C. A. Kingsbury and D. C. Best, Bull. Chem. Soc. Jpn., 1972, 45, 3440.

4 (a) R. E. Parker and N. E. Isaacs, Chem. Rev., 1959, 59, 737; (b) other reviews include R. N. McDonald, in 'Mechanisms of Molecular Migrations,' vol. 3, ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1971, p. 67.

5 H. Jordlander, Chem. Ber., 1916, 49, 2282.

6 (a) H. O. House, J. Am. Chem. Soc., 1955, 77, 3070; (b) H. O. House and R. L. Watson, ibid., 1957, 79, 1488, 2490; (c) H. O. House and D. J. Reif, ibid., p. 6491; (d) H. O. House and D. J. Ryerson, ibid., 1961, 83, 979; (e) J. Kagan, D. Agadeppa, S. P. Singh, D. Meyers, X. Boyajran, C. Poocker, and B. E. Firth, ibid., 1976, 98, 4581; (f) R. A. Gorski, D. J. Dagli, and J. Wemple, ibid., 4587; (h) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, Tetrahedron, 1964, 20, 2531.

7 J. H. Brewster, J. Am. Chem. Soc., 1956, 78, 4061.

8 A. S. Y. Chu and W. P. Cochrange, Chem. Ind. (London), 1970, 1568.

9 H. H. Wasserman and N. Aubrey, J. Am. Chem. Soc., 1956, 78, 1726.

10 J. M. Domagala, and R. D. Back, J. Am. Chem. Soc., 1978, 100, 1605.

11 (a) F. A. Long, J. G. Pritchard, and F. E. Stafford, J. Am. Chem. Soc., 1957, 79, 2362; (b) J. Koskikallio, D. Pouli, and E. Whalley, Can. J. Chem., 1959, 37, 1360.

12 J. G. Pritchard and F. A. Long, J. Am. Chem. Soc., 1956, 78, 2667.

13 L. L. Schaleger and F. A. Long, Adv. Phys. Org. Chem., 1963, 1, ch. 1.

14 C. H. Rochester, 'Acidity Functions,' Academic Press, New York, 1970, p. 140.

15 (a) P. DiRaddo and T. H. Chagan, J. Org. Chem., 1982, 47, 1427; (b) N. E. Geacintov, A. G. Gagliano, U. Ibenez, and R. G. Harvey, Carcinogenesis (London), 1982, 247; (c) J. M. Janusz, A. R. Becker, and T. C. Bruice, J. Am. Chem. Soc., 1978, 100, 9269; (d) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, Tetrahedron Lett., 1974, 539.

16 (a) B. Berti, B. Macchia, and F. Macchia, Tetrahedron, 1968, 24, 755; (b) C. Battistini, P. Crotti, and F. Macchia, Tetrahedron Lett., 1975, 2091; (c) C. Battistini, P. Crotti, D. Damiani, and F. Macchia, J. Org. Chem., 1979, 44, 1643; (d) C. Battistini, A. Balsamo, G. Berti, P. Crotti, B. Maccia, and F. Macchia, J. Chem. Soc., Chem. Commun., 1974, 712; (e) A. Balsamo, P. Crotti, M. Feretti, and F. Macchia, Tetrahedron, 1977, 33, 1629; (f) G. Berti, B. Macchia, and F. Macchia, ibid., 1972, 28, 1299; (g) P. Crotti, A. Balsamo, B. Macchia, and F. Macchia, ibid., 1973, 29, 2183; (h) D. L. Barli, G. Belluci, G. Berti, B. Macchia, and F. Macchia, J. Chem. Soc., Perkin Trans. 1, 1974, 477.

17 (a) J. W. Thorpe and J. Warkentin, Can. J. Chem., 1973, 51, 927; (b) T. Masuiki, N. Furakawa, and S. Oae, Bull. Chem. Soc. Jpn., 1971, 44, 448; (c) D. N. Kevill, D. E. Weiler, and N. H. Cromwell, J. Am. Chem. Soc., 1966, 88, 4486.

18 R. Firestone, J. Org. Chem., 1969, 34, 3641.

19 F. W. Bachelor and R. K. Bansal, J. Org. Chem., 1969, 34, 3600; cf.

20 V. S. Karanovan, I. I. Kolesnikova, L. A. Timofeeva, and T. I. Temnikova, Zh. Org. Khim., 1972, 8, 248, and references cited therein.

21 (a) O. Widman, Ber., 1916, 49, 473; (b) See also A. A. Hamed, A. Essaway, and N. A. Salem, Indian J. Chem., Sect. B, 1978, 16, 693; (c) See, however, D. R. Burfield, S.-N Gan, and R. H. Smithers, J. Chem. Soc., Perkin Trans. 1, 1977, 666; (d) C. L. Kissel and B. Rickborn, J. Org. Chem., 1972, 37, 2060.

22 (a) E. C. Ashby, J. N. Argyropoulos, G. R. Meyer, and A. B. Goel, J. Am. Chem. Soc., 1982, 104, 6788; (b) A. Pross and S. S. Shaik, Acc. Chem. Res., 1983, 16, 363; (c) Cf. Linnett's work quoted extensively in ref. 18.

23 (a) A. R. Lepley and G. L. Closs, 'Chemically Induced Dynamic Nuclear Polarization,' Wiley-Interscience, New York, 1973; (b) see also G. H. Pasner and O. R. Rogers, J. Am. Chem. Soc., 1977, 99, 8208.

24 D. J. Cram, F. D. Greene, and C. H. DePuy, J. Am. Chem. Soc., 1956, 78, 790.

25 (a) J. Hine, S. M. Linden, and V. M. Kanagasaba, J. Am. Chem. Soc., 1985, 107, 1082; (b) J. Bauer and P. Politzer, Int. J. Quantum Chem., 1984, 25, 869; (c) H. Hopkinson, M. H. Lien, I. G. Czismadia, and K. Yates, Theor. Chim. Acta, 1978, 47, 97; (d) P. Politzer, K. C. Daiker, and V. M. Estes, and M. Baughman, Int. J. Quantum Chem., Quantum Biol. Symp., 1978, 5, 291; (e) R. P. Hanzlik and A. Hamburg, J. Am. Chem. Soc., 1978, 100, 1745; (f) J. E. Farrell, Jr., and G. H. Leow, ibid., 1979, 101, 1385; (g) V. J. Shiner, Jr., and J. G. Jewett, ibid., 1964, 86, 945; D. E. Sunko, I. Szele, and W. J. Hehre, ibid., 1977, 99, 5000; see, however, G. Bellucci, R. Bianchini, G. Ingrosso, and E. Mastrorilli, Gazz. Chim. Ital., 1978, 108, 11; (h) B. Gold and T. Leuschen, J. Org. Chem., 1981, 46, 1372.

26 (a) R. P. Hanzlik and R. B. Westkaemper, J. Am. Chem. Soc., 1980, 102, 2464; (b) J. Biggs, N. B. Chapman, A. F. Finch, and V. Wray, J. Chem. Soc. B, 1971, 55; J. Biggs, N. B. Chapman, and V. Wray, ibid., p. 71; (c) J. J. Dannenburg, J. K. Barton, B. Bunch, and B. J. Goldberg, J. Org. Chem., 1983, 48, 4524; (d) A. D. Allen, J. C. Ambidge, and T. T. Tidwell, ibid., p. 4527 (both papers report inversion in solvolysis of a secondary tosylate in TFA).

27 (a) K. Okamoto, T. Kinoshita, and J. Osada, J. Chem. Soc., Perkin Trans. 2, 1975, 253; (b) H. L. Goering and S. Change, Tetrahedron Lett., 1965, 3107; (c) P. A. Levene and P. Rotherm, Science, 1938, 38, 287, 510.

28 C. Battistini, P. Crotti, and F. Macchia, J. Org. Chem., 1981, 46, 434, report 65% retention in trichloroacetic acid capture in non-polar solvents.

29 S. Hoz and D. Speizman, J. Org. Chem., 1983, 48, 2914.

30 W. W. Bachovchin and J. D. Roberts, J. Am. Chem. Soc., 1978, 100, 8041.

31 (a) C. A. Bunton and C.-H. Paik, J. Org. Chem., 1976, 41, 40, give K_{dis} for TFE as 12.4. In general, this solvent is characterized by a low nucleophilicity, and a high ionizing power, somewhat similar to formic acid; (b) D. J. Raber, M. D. Dukes, and J. Gregory, Tetrahedron Lett., 1974, 667; (c) J. M. Harris, W. C. Neal, Jr., and M. D. Dukes, ibid., p. 2331, show that the Winstein–Grunwald relationship is inappropriate for this solvent; (d) P. von R. Schleyer, J. L. Fry, L. K. Lam, and C. J. Lancelot, J. Am. Chem. Soc., 1970, 92, 2452; (e) TFE is also not highly associated, unlike most alcohols, cf. R. Zana, J. Phys. Chem., 1974, 78, 529.

32 (a) A. Streitwieser, Jr., T. Walsh, and J. R. Wolfe, J. Am. Chem. Soc., 1965, 87, 3686; this work illustrates the usual effect of dioxane, i.e. acting as a nucleophile and thus promoting double inversion; (b) G. W. Calvin, A. D. Robertson, and S. Wakharkar, J. Chem. Soc., Chem. Commun., 1983, 312, for nucleophilic involvement of acetone; (c) solvents such as Me_2SO, unlike $[CH_2]_4SO$, are also prominent nucleophiles, cf. T. M. Santorusso and D. Swern, J. Org. Chem., 1975, 40, 2764; (d) In another context, a displacement of a nucleophile on a dioxane–cation complex is another possibility: cf. R. A. Sneen and J. Larsen, J. Am. Chem. Soc., 1969, 91, 362, and related papers; this work has received criticism, but the general concept is viable.

33 (a) E. M. Arnett, E. J. Mitchell, and T. S. S. R. Murtry, J. Am. Chem. Soc., 1974, 96, 3874; (b) see also H. B. Yang and R. W. Taft, ibid., 1971, 93, 1310; (c) R. Schowen, Prog. Phys. Org. Chem., 1972, 9, 275.

34 (a) V. Guttman, 'Co-ordination Chemistry in Non-Aqueous Solutions,' Springer-Verlag, Heidelberg, 1968, Ch. 2 covers most of the solvatochromic treatments; unfortunately, none of these worked for the present system; (b) E. M. Kosower, 'An Introduction to

H. E. Zimmerman and J. Ahramjian, J. Am. Chem. Soc., 1960, 82, 5459.

Physical-Organic Chemistry,' Wiley, New York, 1968, p. 293; (c) C. Reichardt, *Angew. Chem., Int. Ed. Engl.,* 1965, **4**, 29.

35. (a) N. L. Allinger, *Adv. Phys. Org. Chem.,* 1976, **13**, 1; (b) L. M. J. Kroon-Batenburg and J. A. Kanters, *Theochem.,* 1983, **14**, 417; (c) G. Wipff, A. Dearing, P. K. Weiner, J. M. Blaney, and P. Kollman, *J. Am. Chem. Soc.,* 1983, **105**, 997.

36. R. J. Abraham, L. Griffith, and P. Loftus, *J. Comput. Chem.,* 1982, **3**, 407; R. J. Abraham and Bretschneider, 'Internal Rotation in Molecules', ed. W. Orville-Thomas, Wiley-Interscience, New York, 1974, p. 481.

37. (a) I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.,* 1946, 173; (b) Rearrangements readily occur to sp^2 carbocation centres involving non-axial approach with regard to the *p* orbital.

38. F. M. Menger and L. G. Glass, *J. Am. Chem. Soc.,* 1980, **102**, 5409; this work illustrates that 'non-ideal' geometry with regard to orbital overlap is in fact permissible, and finally extinguishes the ideas about 'orbital steering' prevalent in biochemical circles.

39. B. Vorobyov and A. Smorodinski, *Org. React. (Tartu),* 1982, **19**, 3, 12.

40. R. N. McDonald, R. N. Steppel, and J. E. Dorsey, *Org. Synth.,* 1970, **50**, 15.

41. A. I. Vogel, 'Practical Organic Chemistry,' 3rd edn., Longman, London, 1956, p. 718.

42. H. Stobbe and K. Bremer, *J. Prakt. Chem.,* 1930, (2) **123**, 1.

43. C Walther and E. Raetze, *J. Prakt. Chem.,* 1902, (2) **65**, 258.

44. R. Sorge, *Ber.,* 1902, **35**, 1065.

45. F. Starkhauser and L. Gatterman, *Ber.,* 1892, **25**, 3535, 755.

46. P. Pfeiffer and E. Haack, *Justus Liebigs Ann. Chem.,* 1928, **460**, 156.

47. E. Weitz and A. Schaeffer, *Ber.,* 1921, **54**, 2327.

48. H. Jordlander, *Ber.,* 1917, **50**, 406.

49. S. Bodforss, *Ber.,* 1916, **49**, 2795.

50. E. Bergman and H. Wolfe, *J. Am. Chem. Soc.,* 1932, **54**, 1644.

51. H. H. Wasserman and N. Aubrey, *J. Am. Chem. Soc.,* 1955, **77**, 590.

52. E. P. Kohler and H. M. Chadwell, *Org. Synth.,* Coll. vol. I, 1932, 71.

53. J. Levy and M. Dvoleitzka-Gombinska, *Bull. Soc. Chim. Fr.,* 1931, **49**, 1771.