

Complete Inversion of Configuration in Aliphatic Nucleophilic Substitution Reactions with Small Inner-Sphere Stabilization

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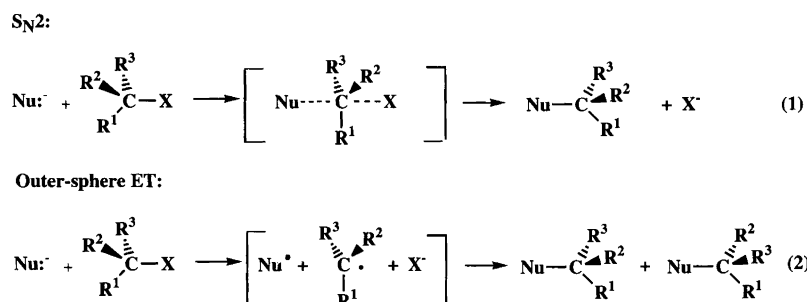
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The stereochemistry of the nucleophilic reaction of the enolate anion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine (1^-) with (*R*)-(-)- and (*S*)-(+)-2-bromobutane has been investigated and correlated with the inner-sphere stabilization of the reactions calculated from the ratio $k_{\text{SUB}}/k_{\text{ET}}$, where k_{SUB} is the rate of substitution and k_{ET} the expected rate of electron transfer. It was shown that 1^- reacts with 2-bromobutane with nearly complete inversion of configuration (99.7%). A complete shift in stereochemistry of the nucleophilic reactions of 1^- with alkyl halides from racemization to complete inversion is induced by a small increase in the inner-sphere stabilization of the transition state from 0 to 3 kcal mol⁻¹. The results in this work suggest that the S_N2 inversion process in general is extremely sensitive towards inner-sphere stabilization.

The relationship between the S_N2 mechanism and electron transfer (ET) in aliphatic nucleophilic substitution has been debated intensively from both an experimental and a theoretical point of view over the last 20 years.¹⁻²⁰ A typical S_N2 reaction [eqn. (1)] is characterized by a backside attack on the central carbon atom by the nucleophile, requiring a geometrically well defined transition state and a relatively strong bonding between the central carbon atom and both the attacking nucleophile and the leaving group. The reaction proceeds through inversion of the configuration of the electrophilic center. A typical reaction of this type is the Finkelstein reaction, e.g., ethyl chloride reacting with chloride ion. We have, however, been able to show that, for some substitution

reactions between easily oxidizable nucleophiles and sterically hindered alkyl halides, the rate determining step is the transfer of a single electron [eqn. (2)].⁴⁻⁷

In the outer-sphere (non-bonded) electron transfer (ET) reaction the interaction between Nu⁻ and R¹R²R³C-X is negligible, suggested to be less than 1 kcal mol⁻¹,¹⁹ and the mechanism indicates a certain lifetime of the radicals in the transition state (TS). For the enolate anion 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine (1^-) it was shown by means of radical probes that the radicals 1^\cdot and R¹R²R³C[·] did not diffuse out of the solvent cage, indicating that the radicals have a lifetime shorter than the lifetime of the encounter complex.⁸ The lifetime of the encounter complex is in



Scheme 1.

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the order of 10⁻¹⁰ s, which should be sufficient time for the R¹R²R³C[•] radical to perform a 180° rotation leading to racemization of the stereochemistry of the reaction.

Outer-sphere ET substitutions are, however, rare and restricted to sterically hindered substrates. In general, there is partial bond formation between Nu[•], R¹R²R³C[•] and :X⁻ in the TS which lowers the activation barrier relative to the TS of the outer-sphere ET process. This reduction in the free energy of activation, ΔΔG[‡], usually named the inner-sphere stabilization, may be estimated by comparing the rate of substitution *k*_{SUB} with the expected outer-sphere rate *k*_{ET} for the reaction. ΔΔG[‡] may be calculated using eqn. (3),

$$\Delta\Delta G^{\ddagger} = -2.3RT \log k_{\text{SUB}}/k_{\text{ET}} \quad (3)$$

in which *k*_{ET} is obtained by measuring the rate of electron transfer between the alkyl halide and an aromatic radical anion A^{-•} with the same oxidation potential as the nucleophile. In the reaction of 1⁻ with *t*-BuBr, *s*-BuBr and *n*-BuBr *k*_{SUB}/*k*_{ET} = 2.5, 170 and 3000, respectively, corresponding to an increase in the inner-sphere stabilization from negligible to 5 kcal mol⁻¹ on going from sterically hindered to less sterically hindered alkyl halides.⁴ These results suggest that there exists a continuous spectrum of transition states in which the bond formation between Nu[•] and the alkyl radical increases from the outer-sphere ET limit of <1 kcal mol⁻¹ to 25–30 kcal mol⁻¹ (X = Br) in the Finkelstein reactions. In the outer-sphere limit the reaction may proceed with complete racemization of the stereochemistry whereas complete inversion is observed when the bond formation in TS is strong. The question is how strong the bond formation or inner-sphere stabilization need to be in order to obtain predominately inversion of stereochemistry. In other words how sensitive is the degree of inversion, *I*, defined as the mol% *I* = [inversion/(inversion + retention)] × 100% in relation to the inner-sphere stabilization ΔΔG[‡]?

In a series of papers the stereochemistry of the substitution reactions of 1⁻ with bornyl bromide, isobornyl bromide, norbornyl bromide and *trans*-2-bromomethoxycyclohexane was investigated.^{10–12} For these sterically hindered alkyl bromides *k*_{SUB}/*k*_{ET} ≈ 1 was obtained. This ratio indicates a pure outer-sphere ET correlating well with the stereochemical results of nearly 100% racemization. In substitution reactions with some inner-sphere interaction in the TS (*k*_{SUB}/*k*_{ET} > 1), much less is known about the stereochemical correlation. In the reaction of 1⁻ with *cis*-2-bromomethoxycyclohexane *k*_{SUB}/*k*_{ET} = 103 (ΔΔG[‡] = 3 kcal mol⁻¹) and nearly complete inversion (> 99.5%) was found.¹² This result suggests that the inversion process of the nucleophilic substitution is very sensitive towards even small inner-sphere stabilizations in the TS. In order to add more experimental evidence to this preliminary conclusion we initiated a stereochemical investigation of the reaction between 1⁻ and the (*R*)-(-)- and (*S*)-(+)-2-bromobutanes. Stereochemical investigations of the test nucleophile

1⁻ with optically active alkyl halides have not previously been performed mainly due to the difficulties in accurate determination of the enantiomeric excess of both starting alkyl halide and substitution product. However, with the development of commercially available chiral GC and HPLC columns such an investigation is now quite straightforward.

Experimental

Materials (*S*)-(+)- and (*R*)-(-)-2-butanol, bromine and 1,2-bis(diphenylphosphino)ethane, were obtained from Aldrich. HPLC grade dichloromethane and *N,N*-dimethylformamide (DMF) were obtained from Merck and Fluka, respectively. The 4-methoxycarbonyl-1-methylpyridinium perchlorate was prepared according to the method of Daasbjerg and Lund.¹¹ The optically active 2-bromobutanes were synthesized according to the method of Schmidt and Brooks with some modifications.²¹

(*S*)-(+)-2-Bromobutane In a three-necked bottle equipped with thermometer, magnetic stirrer and an argon inlet, 1,2-bis(diphenylphosphino)ethane (5.98 g, 15.0 mM) was dissolved in 25 ml of dichloromethane (dried over 4 Å molecular sieves) and cooled to 0 °C. With argon bobbling, bromine (4.82 g, 30.5 mM) dissolved in 5 ml of CH₂Cl₂ was slowly added with a 1 ml syringe. The rate of addition was adjusted so that the reaction temperature was kept below 10 °C. After the addition of bromine, the cooling bath was removed and (*R*)-(-)-2-butanol (1.84 g, 24.9 mM) was added under argon. After 15 min at ambient temperature, 70 ml of diethyl ether and then 140 ml of pentane were added. The white crystalline precipitate was removed carefully by vacuum filtration and the precipitate washed twice with 25 ml of a 1:2 diethyl ether–pentane solution. The organic phases were combined and the diethyl ether–pentane removed by distillation at atmospheric pressure on a 50 cm distillation column filled with glass rings. The remaining 2-bromobutane was transferred to a small still and distilled at atmospheric pressure at 88–92 °C. Yield 1.53 g (45%). The optical purity was determined by chiral GC analysis.

The white precipitate was isolated and recrystallized from ethanol m.p. 263–265 °C (lit. 264–266 °C),²² ³¹P NMR (CDCl₃): δ 34.6, relative to an external reference of 85% H₃PO₄ and 15% D₂O (lit. δ 32.8).²³ The product was identified as the diphosphine dioxide (Ph)₂P(O)CH₂CH₂P(O)(Ph)₂.

Comment: before distillation the diphosphine dioxide by-product was eliminated by precipitation with a large volume of diethyl ether–pentane. Complete elimination of the diphosphine dioxide is crucial in order to obtain a product of high optical purity. Remaining diphosphine dioxide may cause loss of optical activity of the bromides during the distillation. A similar phenomenon is observed

in the reaction of optically active alcohols with triphenylphosphine.²⁴

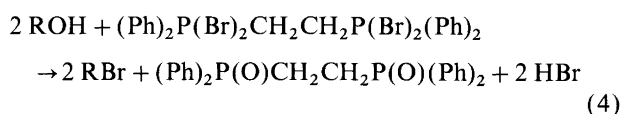
Apparatus The enantiomeric excess of the optically active 2-butanols and 2-bromobutanes were obtained by GC-FID. A Hewlett-Packard 5890 GC-FID with an FS Lipodex C 25 m 0.25 mm internal diameter chiral GC-column from Macherey Nagel was used, injection temperature 250 °C, column head pressure 25 kPa, helium flow 0.5 ml min⁻¹ and column temperature constant at 30 °C. The substitution products were analyzed by HPLC on a Lipodex A, 25 cm 4 mm internal diameter chiral column from Baker. The eluent mixture was 99% hexane and 1% 2-propanol, flow = 0.60 ml min⁻¹. The HPLC instrument used was a Waters system with a 5527 pump and 5557 diode array detector. The ¹H NMR and MS spectra were recorded with a Bruker 250 MHz spectrometer and a Hewlett Packard 5890 A gas chromatograph equipped with a 5971 A MSD, respectively.

Procedure Reaction of 1⁻ with optically active 2-bromobutane. 1⁺ ClO₄⁻ (100 mg, 0.5 mM) was first reduced to the stable 1[•] radicals in an H-cell at a Pt net electrode in an argon-deaerated 30 ml solution of DMF-0.1 M tetrabutylammonium tetrafluoroborate (TBABF₄). The potential was fixed at -0.5 V vs. Ag/AgI, 0.1 M I⁻ in DMF and the temperature of the cell kept at ambient temperature (22 °C) by means of a water bath. After 32 C (*n*=1) the current stopped and a nicely green-colored cathodic solution was obtained. The potential was then lowered to -1.3 V and further reduction of 1[•] to the yellow-brown solution mixture of 1[•]/1⁻ was accomplished by passing 30–35 °C rapidly (<10 min) through the cell. The enolate 1⁻ was not completely stable and in order to obtain the maximum concentration of the ion it was essential to perform the reduction step relatively quickly. Immediately after the electrolysis was stopped optically active 2-bromobutane (80 μl, 1 mM) was added. The yellow-brown color disappeared in seconds. The catholyte was poured into water and extracted with diethyl ether. The organic phase was separated and the diethyl ether removed under reduced pressure. The product was dissolved in 10 ml of hexane and analyzed on a chiral HPLC column. Spectral data are given below of the optical active product (*S*)-1,4-dihydro-4-methoxycarbonyl-1-methyl-4-(2-methylpropyl)pyridine (*S*)-2 (see Scheme 2) obtained by the reaction of 1⁻ with (*R*)-(-)-2-bromobutane. ¹H NMR (CDCl₃): δ 0.78 (d, 3 H, ³J=6.9 Hz), 0.85 (m, 3 H), 1.3–1.7 (m, 3 H), 2.86 (s, 3 H), 3.68 (s, 3 H), 4.39 (1 H, d, ³J=7.54 Hz), 4.41 (1 H, d, ³J=6.5 Hz), 5.91 (1 H, d, ³J=7.54 Hz), 5.93 (1 H, d, ³J=6.5 Hz). MS [*m/z* (%): 209 (0.3), 153 (15), 152 (100), 151 (7.5), 150 (40), 124 (7), 121 (22), 120 (41), 93 (25), 92 (9).

Results and discussion

The optically active 2-bromobutanes were synthesized from commercially available optically active 2-butanols

by treatment with the bromination reagent 1,2-bis(diphenylphosphino)ethane tetrabromide in dichloromethane according to the procedure by Schmidt and Brooks [eqn. (4)].²¹



The one-step synthesis is easy to perform in reasonable isolated yields (45–51%). The *R* and *S* forms of the 2-butanols and the 2-bromobutanes were base-line separated on the chiral GC column. From Table 1 it is seen that the enantiomeric excess of the 2-butanols and the synthesized 2-bromobutanes are almost identical. The synthesis is therefore nearly 100% stereospecific with inversion of configuration.

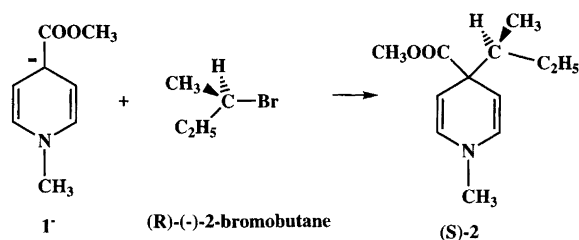
The nucleophile 1⁻ was generated electrochemically by reduction of 4-methoxycarbonyl-1-methylpyridinium perchlorate (1⁺) in DMF in two steps. Immediately after the electrolysis was stopped optically active 2-bromobutane was added to the solution of 1⁻. The reaction between 1⁻ and (*R*)-(-)-2-bromobutane is illustrated in Scheme 2 and representative HPLC chromatograms of this reaction and with (*S*)-(+)-2-bromobutane are shown in Fig. 1A and 1B, respectively. It can be seen that the two enantiomeric forms of the product 2 are nicely base-line separated.

Three reactions were performed with (*S*)-(+)-2-bromobutane and two with (*R*)-(-)-2-bromobutane and each product was injected three times onto the HPLC column and the ratios between the two enantiomers were obtained using the UV absorption at 289 nm. The results are shown in Table 2; the enantiomeric excesses of the substitution products are nearly the same as the enantiomeric

Table 1. Enantiomeric excess, ee, of the synthesized 2-bromobutanes and of the 2-butanols used as the starting materials in the synthesis of the 2-bromobutanes.

Compound	Yield (%)	ee (GC) (%) ^a
(<i>R</i>)-(-)-2-Butanol	—	84.2
(<i>S</i>)-(+)-2-Butanol	—	86.9
(<i>R</i>)-(-)-2-Bromobutane	45	85.90 ± 0.10 ^b
(<i>S</i>)-(+)-2-Bromobutane	51	85.10 ± 0.11 ^b

^a ee obtained by GC on a chiral column. ee = 100Num [(*A_R* - *A_S*)/(*A_R* + *A_S*)]. *A_R* and *A_S* are the areas for the *R* and *S* enantiomers, respectively. ^b Standard deviation on the ee values obtained from seven GC injections of the sample.



Scheme 2.

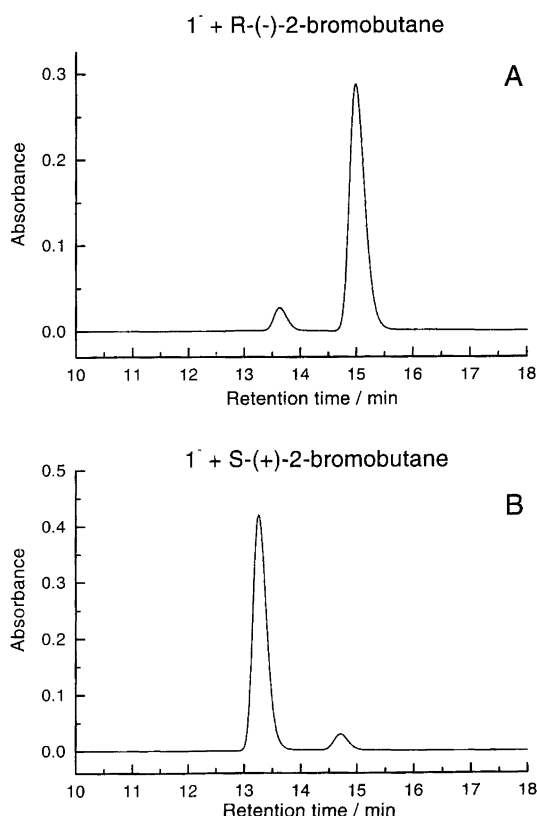
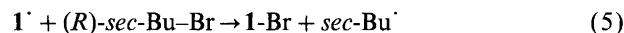


Fig. 1. Chiral HPLC of the products from the reactions between 1^- and (*R*)-(-)- and (*S*)-(+)-2-bromobutane. The chromatograms were obtained at 289 nm.

excess of the starting 2-bromobutanes. The absolute configurations of the two peaks in Figs. 1A and 1B were not determined. However it has recently been shown that a slight excess of the inverted substitution product was obtained in the reaction of 1^- with bornyl bromide.¹¹ Based on this result it is reasonable to assume that (*R*)-(-)-2-bromobutane and (*S*)-(+)-2-bromobutane is transformed into the inverted product configurations (*S*)-2 and (*R*)-2, respectively. The reaction of 1^- with 2-bromobutane therefore proceeds with nearly complete inversion of configuration.

It is important to reduce 1^- before the optically active 2-bromobutane is added to the solution. This is a slight change compared with our usual procedure in which the

electrolysis of 1^+ is performed in presence of the alkyl bromide.⁴ Experiments performed in the usual way gave variations in the enantiomeric excess of the products which may be explained by a bromine atom abstraction racemisation process [eqns. (5) and (6)].



In order to test this hypothesis 1^+ was reduced at the first reduction wave of $1^+/1^-$ in presence of (*S*)-(+)-2-bromobutane. After two hours the green solution of 1^+ was further reduced to 1^- and the enantiomeric excess of the product obtained by HPLC. As seen from Table 2 some racemization has taken place.

Table 3 contains an analysis of the stereochemical results of the reactions between 1^- and various stereochemical probes obtained from a previous investigation¹² and the present work. The observed degree of inversion of the nucleophilic reaction, $I = [\text{NuR}' / (\text{NuR}' + \text{NuR}) \times 100\%$, where NuR' and NuR are the mole inversion and retention products, respectively, is compared with the degree of inversion I_{ET} expected for a substitution reaction following an outer-sphere dissociative ET mechanism. The expected ET inversion, $I_{\text{ET}} = [\text{ARH}' / (\text{ARH}' + \text{ARH})] \times 100$, may be estimated from the ratio between the inversion and retention substi-

Table 3. The corrected inversions I' or % S_N2 character of the reactions between the nucleophile 1^- with various alkyl bromides, RX, in DMF.

RX	Ref.	I_{ET} (%) ^a	I (%) ^b	$I' = \% S_{\text{N}}2$ ^c
<i>trans</i> -2-Bromomethoxy-cyclohexane	12	17	25	10
<i>cis</i> -2-Bromomethoxy-cyclohexane	12	83	99.5	97
2-Bromobutane	This work	50	99.7	99.4

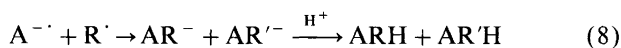
^a $I_{\text{ET}} = \text{ARH}' / (\text{ARH}' + \text{ARH})$ where ARH' and ARH are the mole equivalent inverted and retention products, respectively, of the reaction between A^- and RX. ^b $I = \text{NuR}' / (\text{NuR}' + \text{NuR})$ where NuR' and NuR are the mole equivalent inverted and retention products, respectively, of the reaction between 1^- and RX. ^cCorrected inversion $I' = \% S_{\text{N}}2 = 100(I - I_{\text{ET}}) / (100 - I_{\text{ET}})$.

Table 2. Enantiomeric excess of the reactions between electrogenerated 1^- and optically active 2-bromobutanes.

RX	ee (%) of RX	ee (%) of 2	<ee> (%) of 2	Degree of inversion (%)
(<i>R</i>)-(-)-2-Bromobutane ^a	85.90 ± 0.10	85.29 ± 0.18 85.27 ± 0.45	85.26	99.3
(<i>S</i>)-(+)-2-Bromobutane ^a	85.10 ± 0.11	85.59 ± 0.07 85.75 ± 0.27 84.25 ± 0.10	85.20	100.1
(<i>S</i>)-(+)-2-Bromobutane ^b	85.10 ± 0.11	78.15 ± 0.16	78.15	91.8

^a 1^- was generated before the addition of RX (see the text). ^b 1^- was generated in the presence of RX. ^cAll samples were injected three times onto a chiral HPLC column and the average ee and standard deviations were calculated based on the peak ratios obtained at 289 nm.

tution products (ARH' and ARH) obtained in the reaction between aromatic radical anions A^{-•} and RX [eqns. (7) and (8)]. This strategy assumes that the reaction between A^{-•} and RX follows an outer-sphere dissociative ET mechanism, an assumption which experimentally has been shown to be reasonably fulfilled for the alkyl bromides in Table 3.²⁵⁻²⁸



In the reactions of anthracene and quinoxaline radical anions with *trans*- and *cis*-2-bromomethoxycyclohexane (*trans*- and *cis*-3) the ratios between the *trans* and *cis* coupling products were 5:1 in all cases.¹² This result indicates an outer-sphere mechanism and a *trans*/*cis*-isomer substitution ratio that is independent of the size and type of radical which couples with the 2-methoxycyclohexyl radical. For *trans*-3 the predominant *trans* coupling isomer corresponds to the retention product while for *cis*-3 the *trans* coupling isomer corresponds to the inversion product. The ratio AR'H/ARH for *trans*-3 and *cis*-3 is therefore 1:5 and 5:1, respectively. In the case of 2-bromobutane AR'H/ARH = 1 is expected owing to the planar symmetry of the 2-butyl radical and the degree of inversion $I_{ET} = 50\%$ may be calculated according to the definition of I_{ET} . However the A^{-•} + RX reactions are assumed to follow an outer-sphere ET mechanism with 100% racemization and no S_N2 inversion component. Therefore in order to establish a corrected inversion scale in which the inversion of the A^{-•} + RX reference reactions are set to zero the following expression may be derived [eqn. (9)].

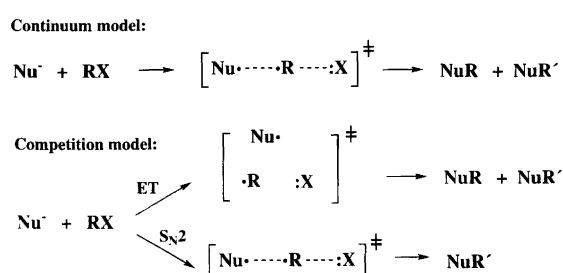
$$I' = 100(I - I_{ET}) / (100 - I_{ET}) \quad (9)$$

The corrected inversion I' may be interpreted as the % S_N2 character of the reaction. As seen from Table 3 values of I' or % S_N2 between 10 and 99.4% are observed.

In Table 4 the corrected inversions I' or % S_N2 values are correlated with the kinetic parameters k_{SUB}/k_{ET} , $\Delta\Delta G^\ddagger$ and $\Delta\Delta H^\ddagger$. $\Delta\Delta H^\ddagger$ represents the partial bond formation and bond breaking in the TS relative to the outer-sphere ET TS and is linked to $\Delta\Delta G^\ddagger$ by the expression $\Delta\Delta G^\ddagger = \Delta\Delta H^\ddagger - T\Delta\Delta S^\ddagger$ where $\Delta\Delta S^\ddagger$ is the entropy change relative to an outer-sphere TS.⁹ As seen from Table 4 the TS has only a slight %S_N2 character (10%) in the reaction between 1⁻ and the stereochemical

probe *trans*-2-bromomethoxycyclohexane. In this reaction the inner-sphere stabilization $\Delta\Delta G^\ddagger$ and the bond change in TS $\Delta\Delta H^\ddagger$ is less than 1 kcal mol⁻¹. The inner-sphere stabilizations are slightly higher (3 kcal mol⁻¹) in the reactions of 1⁻ with 2-bromobutane and *cis*-2-bromomethoxycyclohexane. The small increase of the inner sphere stabilization from 0 to 3 kcal mol⁻¹ ($\Delta\Delta H^\ddagger$ from 1 to 4 kcal mol⁻¹) induces a complete change in the stereochemistry, from racemization to nearly 100% inversion.

It has previously been suggested that the ET and S_N2 mechanisms are the extremes of a common mechanism and there is a continuous transition between these two extremes.^{4-6,16,17} The TS of this unified model is shown in Scheme 3.



Scheme 3.

The nucleophile attacks the substrate from behind as in a traditional S_N2 reaction with a certain bonding interaction in the TS which may vary from 0–1 kcal mol⁻¹ to larger values. If the bond interaction between Nu[•] and R[•] in the TS is small enough the planar R[•] radical will still have the possibility to rotate 180° in the solvent cage with the formation of both NuR and NuR'. This model has, however, been questioned and an alternative model proposed in which ET and S_N2 are two independently competing mechanisms (Scheme 3).^{13,14} If the nucleophile performs a back-side attack and the inner-sphere stabilization is higher than about 1 kcal mol⁻¹ the product will be exclusively the inversion product NuR'. In the low inner-sphere interaction limit the ET reaction may have a chance to compete with the S_N2 reaction due to fewer orientation requirements in the TS relative to the S_N2 TS, ($\Delta\Delta S^\ddagger > 0$).^{9,13,14}

The competition model suggests that relative the

Table 4. Correlation between k_{SUB}/k_{ET} , $\Delta\Delta G^\ddagger$ and $\Delta\Delta H^\ddagger$ with the % S_N2 character of the reactions between 1⁻ and various alkyl bromides, RX.

RX	Kinetic data from Ref.	k_{SUB}/k_{ET}	$\Delta\Delta G^\ddagger/\text{kcal mol}^{-1}$	$\Delta\Delta H^\ddagger/\text{kcal mol}^{-1}$	% S _N 2	Calculated % S _N 2 ^c
<i>trans</i> -2-Bromomethoxycyclohexane	12	0.87	< 1	1.0 ^b	10	≈ 0
<i>cis</i> -2-Bromomethoxycyclohexane	12	103	2.8 ^a	4.0 ^b	97	99.0
2-Bromobutane	4.8	170	3.1 ^a	4.2 ^b	99.4	99.4

^a Calculated from eqn. (3) (see the text). ^b Extrapolated from Fig. 3 in Ref. 8. ^c Calculated from eqn. (10).

weights of the two mechanisms S_N2 and ET may be directly linked to the ratio $k_{\text{SUB}}/k_{\text{ET}}$ [eqn. (10)].

$$\% S_{\text{N}2} = 100[(k_{\text{SUB}}/k_{\text{ET}}) - 1]/(k_{\text{SUB}}/k_{\text{ET}}) \quad (10)$$

As seen from Table 4 this simple relation predicts the corrected inversion or %S_N2 in the reactions of **1**⁻ with *cis*-2-bromomethoxycyclohexane and 2-bromobutane reasonably well. This may be an argument in favour of the competition model, however the experimental data are still too limited to determine which model is better.

The redox potential of the test nucleophile **1**⁻, $E^\circ(\mathbf{1}^{\cdot-}/\mathbf{1}^-) = -1.5$ V vs. SCE, is very negative for an anion and **1**⁻ is a more potent electron donor than most other nucleophiles. The inner-sphere stabilization will normally increase as the redox potential of the nucleophile becomes more positive.⁵ The majority of nucleophiles are therefore expected to react with 2-bromobutanes (and other alkyl halides) with higher inner-sphere stabilization than **1**⁻. These nucleophiles are thus expected to react with optically active *sec*-alkyl bromides with complete inversion. Partial racemization, $I = 70\%$ ²⁹ and 67% ,³⁰ has, however, been observed in the reactions of Me₃SnNa, $E^\circ(\text{Me}_3\text{Sn}^{\cdot-}/\text{Me}_3\text{Sn}^-) = -1.25$ V vs. SCE,¹⁹ with optically active 2-bromooctane in THF. The observed inversions correspond to 40% and 34% S_N2 character of the transition state, respectively. Therefore other nucleophile parameters than the $E^\circ(\text{Nu}^{\cdot-}/\text{Nu}^-)$ may be important in order to predict the stereochemistry of nucleophilic reactions.

Conclusions

It has been shown that the reaction of the enolate ion **1**⁻ reacts with 2-bromobutane with complete inversion of configuration. A complete shift in stereochemistry of the nucleophilic reactions of **1**⁻ with alkyl halides from racemization to complete inversion is induced by a small increase in the inner-sphere stabilization from 0 to 3 kcal mol⁻¹. The results in this work suggest that the S_N2 inversion process in general is extremely sensitive towards inner-sphere stabilization. Racemization may therefore only be expected in nucleophilic reactions with inner sphere stabilization of <1 kcal mol⁻¹. Such reactions may only be observed between nucleophiles with very negative redox potentials and sterically hindered alkyl halides.

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