

Stereoisomerization of the Bornyl Radical during Aliphatic Nucleophilic Substitutions

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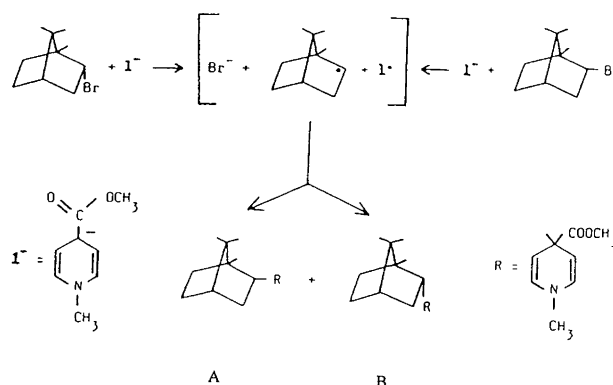
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The mechanism of the reaction between the anion of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine (1^-) and *endo*-2-bromo-1,7,7-trimethylbicyclo[2.2.1]heptane (bornyl bromide) and between 1^- and *exo*-2-bromo-1,7,7-trimethylbicyclo[2.2.1]heptane (isobornyl bromide) has been investigated. In both cases the *endo* and *exo* substitution products were produced with a small dominance of the inversion product. While the product distribution was independent of temperature for the reaction with bornyl bromide, the yield of the *endo*-product increased at lower temperatures in the reaction with isobornyl bromide. Clear-cut evidence of a mechanism change in the latter case was not observable in an Arrhenius plot. Different mechanistic interpretations as regards to S_N2 and electron transfer reactions are discussed.

The nucleophilic substitution reactions between the anion of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine (1^-) and *endo*-2-bromo-1,7,7-trimethylbicyclo[2.2.1]heptane (bornyl bromide) and between 1^- and *exo*-2-bromo-1,7,7-trimethylbicyclo[2.2.1]heptane (isobornyl bromide) have previously been shown to proceed mainly by an electron transfer (ET) mechanism (Scheme 1).¹ The formation of the two substitution products A and B suggested the intermediacy of the 2-bornyl radical in both cases. With bornyl bromide and isobornyl bromide the proportion of A to B at room temperature was 1.4:1 and 1:1.3, respectively. These conclusions were also in accordance with kinetic investigations in which the rate constant of the substitution reaction (k_{SUB}) was compared with the rate constant of a known ET reaction (k_{ET}).² The k_{SUB}/k_{ET} ratio found for bornyl and isobornyl bromide was 0.20 and 0.40, respectively. A k_{SUB}/k_{ET} ratio near one is interpreted to indicate that the substitution reaction is an outer-sphere ET with a negligible bonding stabilization of the transition state (TS), whereas a higher ratio can be interpreted in terms of an additional electronic stabilization of TS compared to the outer-sphere ET-TS.

During the previous investigation¹ it was not possible to establish which of the two compounds, A or B, was the *exo* and which was the *endo*. However, a separation of the two products has now been achieved by use of flash chromatography, and an X-ray crystallographic determination of the structure of the hydrogenated and quaternized product of B has revealed that B is the *endo*-com-



Scheme 1.

pound.³ A slight excess of inversion at the central carbon atom is thus occurring in the substitution reactions, and it seems likely that there is a preference for a spatial distribution of the two reactants in the transition state in which 1^- is attacking the alkyl halide from behind. This steric congestion of the TS may be interpreted in terms of a competition between an outer-sphere ET characterized by a negligible stabilization of TS and resulting in stereochemical equilibration at the central carbon atom and an S_N2 mechanism in which inversion will occur. Alternatively the results may be explained by a single mechanism; an inner-sphere ET having a small but not negligible stabilization of the TS, i.e. a certain overlap between the HOMO of the nucleophile and the LUMO of the alkyl halide. The degree of freedom in the transition

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state of such an inner-sphere ET mechanism would be diminished compared to the corresponding outer-sphere ET, and the distribution of the *endo* and *exo* coupling products would reflect the arrangement of the two reactants in the transition state. This situation is reminiscent of one studied recently for the reaction between a radical anion and an alkyl halide.⁴ A third possible interpretation is that both substitution reactions proceed by an outer-sphere ET and that the dominance of the inversion product in the coupling process between 1^- and the 2-bornyl radical may simply be attributed to the shielding effect of the leaving group, the bromide ion.

In order to gain further insight into the mechanism of the two substitution reactions the temperature dependence of the ratio of A to B was measured. Preparative reductions of $1^+ ClO_4^-$ in the presence of bornyl bromide or isobornyl bromide were performed at five different temperatures in the interval from -40 to $50^\circ C$. The results are shown in Table 1 and, as can be seen, a situation is never obtained in which the ratio of A and B is the same for both the bornyl and isobornyl systems, regardless of temperature. The transition states of the two systems can therefore not be totally alike.

For bornyl bromide the ratio of A to B is independent of the temperature in the interval investigated, indicating that no changes are occurring in the mechanism. The existence of a competing S_N2 process can be excluded in this case. If an S_N2 mechanism did exist an enhanced dominance of the inversion product would be expected at lower temperatures. This is due to the fact that the S_N2 mechanism in general is expected to be less favourable compared to the ET mechanism from an entropic point of view, and that the entropy term is less important at lower temperatures.

For isobornyl bromide the ratio A:B is constant and equal to 1:1.3 at temperatures from 25 to $50^\circ C$, but at lower temperatures the ratio decreases to attain a value of 1:4.5 at $T = -40^\circ C$. The amount of inversion product thus increases as the temperature is lowered, and a possible interpretation is that a competition between ET and S_N2 exists. If this is the case, and if the substitution reaction is assumed to proceed by an ET mechanism at higher temperatures, then the ratio of the rate constant for the S_N2 mechanism (k_{S_N2}) and the ET mechanism (k_{ET}) may be calculated from the distribution of products

Table 1. The *exo:endo* (A:B) product distribution for the reaction between 1^- and bornyl bromide or isobornyl bromide.

$T/^\circ C$	A:B (bornyl bromide)	A:B (isobornyl bromide)
50	1.3:1	1:1.3
25	1.4:1	1:1.3
0	1.4:1	1:2.5
-20	1.4:1	1:3.5
-40	^a	1:4.5

^a The reaction between 1^- and bornyl bromide was too slow for obtaining reliable results at $T = -40^\circ C$.

Table 2. Rate constants k_{SUB} for the reaction between 1^- and isobornyl bromide measured by a potentiostatic method¹⁰ at different temperatures.

T/K	$k_{SUB}/M^{-1} s^{-1}$
333.2	6.4
326.2	3.5
319.2	1.8
308.7	0.79
298.2	0.28
289.6	0.12
281.6	5.7×10^{-2}
273.2	2.7×10^{-2}
267.1	1.1×10^{-2}
259.2	4.2×10^{-3}
254.7	2.4×10^{-3}

to be 0.52, 0.96 and 1.39 at $T = 0, -20$ and $-40^\circ C$, respectively. The shift in mechanism from S_N2 to ET as a function of temperature should in principle be observable in an Arrhenius plot.[†] The temperature dependence of the rate constants for the reaction between 1^- and isobornyl bromide was therefore measured in the temperature interval from -18 to $60^\circ C$. An extension of this interval to $-50^\circ C$ would have been desirable, but the reactions were too slow at temperatures below $-20^\circ C$ for reliable results to be obtained. In Table 2 the results obtained are recorded and the corresponding Arrhenius plot ($\ln k_{SUB}$ vs. $1/T$) is shown in Fig. 1. As can be seen, the points seem best represented by one straight line, and no clear-cut evidence of a mechanism change can be confirmed. However, it should be emphasized that the temperature interval investigated is too small to allow exclusion of competition between two reaction mechanisms.

The activation energy E_a as calculated from the slope is $16.75 \text{ kcal mol}^{-1}$, and the activation entropy ΔS_{298}^\ddagger is found to be $-6.7 \text{ cal mol}^{-1} \text{ K}^{-1}$.^{*} Previously E_a and ΔS_{298}^\ddagger have been measured for the reaction between 1^- and bornyl bromide to $17.78 \text{ kcal mol}^{-1}$ and $-8.9 \text{ cal mol}^{-1} \text{ K}^{-1}$, respectively.⁵ The rate constant for the reaction between 1^- and isobornyl bromide ($k_{SUB} = 0.30 \text{ M}^{-1} \text{ s}^{-1}$ at $T = 25^\circ C$) is about 15 times higher compared with that for 1^- and bornyl bromide ($k_{SUB} = 0.018 \text{ M}^{-1} \text{ s}^{-1}$ at $T = 25^\circ C$).⁵ For dissociative electron transfer the most important parameters influencing the activation Gibbs energy (and thus the rate constant) are expected to be the standard potential $E_{1/1}^\circ$ of the nucleophile, the standard potential $E_{RBr/RBr}^\circ$ of the alkyl bromide RBr, and the reorganization energy for the reaction, given mainly by the dissociation energy ΔH_{BDE}° of the C-Br bond in RBr.⁶ The potentials $E_{RBr/RBr}^\circ$ can

[†] Assuming the same form of the Eyring equation for the S_N2 and ET mechanism the difference in activation enthalpy and entropy may be estimated to be about -3 kcal mol^{-1} and $-13 \text{ cal mol}^{-1} \text{ K}^{-1}$ for the two mechanisms.

^{*} The activation entropy ΔS_{298}^\ddagger at the temperature T may be calculated from: $\Delta S_{298}^\ddagger = 4.576(\log k_{SUB} - 10.753 - \log T) + E_a T^{-1}$, where k_{SUB} is the rate constant at the temperature T and E_a is the activation energy given in cal mol^{-1} .

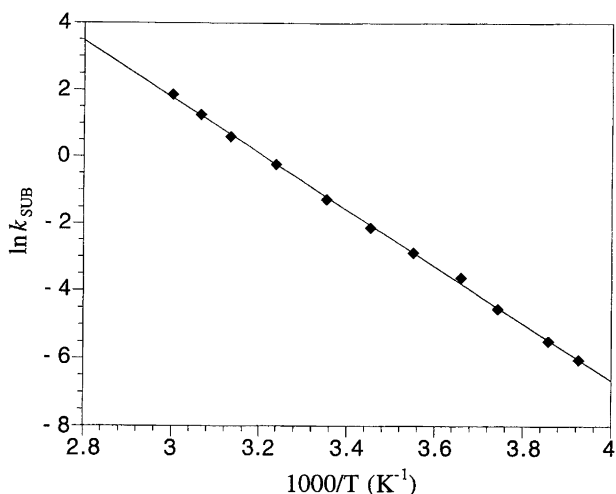


Fig. 1. Temperature dependence of the rate constant of the reaction between 1^- and isobornyl bromide in DMF/TBABF₄ obtained by homogeneous kinetic measurements using a rotating disk electrode.

be calculated from the bond dissociation Gibbs energy $\Delta G^\circ_{\text{BDE}}$ of the C–Br bond in RBr and the standard potential of the Br/Br⁻ couple, $E^\circ_{\text{Br/Br}^-}$, as deduced from a simple thermochemical cycle. Neither $\Delta H^\circ_{\text{BDE}}$ nor $\Delta G^\circ_{\text{BDE}}$ is expected to differ much when RBr is bornyl bromide or isobornyl bromide. The difference in the experimental rate constants for the two substitution reactions can therefore probably be attributed to different degrees of stabilization of the corresponding transition states. Furthermore, this is supported by the fact that the $k_{\text{SUB}}/k_{\text{ET}}$ ratio found for bornyl bromide ($k_{\text{SUB}}/k_{\text{ET}} = 0.20$) is smaller than that of isobornyl bromide ($k_{\text{SUB}}/k_{\text{ET}} = 0.40$). However, it should be mentioned that the corresponding activation entropies are of similar size, indicating that any differences present in the steric requirements of the two transition states are not reflected in the values of ΔS^\ddagger_{298} .

In summary, it may be concluded that a likely interpretation of the experimental results is as follows. In the two substitution reactions the preferential arrangement of the two reactants is one in which the nucleophile can perform its attack on the alkyl halide from behind. The distance to the nucleophile 1^- in the TS is greater for bornyl bromide, and the stabilization energy is thus smaller than in the corresponding case with isobornyl bromide, even though this circumstance is not detectable in the magnitude of the activation entropies. In both cases the mechanism is probably an electron transfer, in which the alkyl radical and 1^- are produced in close vicinity. The two radicals are in principle free to form a bond either in the *endo* or *exo* position of the bridge system, but owing to the restriction in the spatial distribution of the two reactants in the TS of especially the isobornyl system, an excess of inversion product is to be expected. In this connection the possible influence of the shielding effect of the leaving group, the bromide ion, on the coupling process

between 1^- and the 2-bornyl radical favouring the inversion product should also be kept in mind. The temperature dependence of the product distribution for isobornyl bromide may be an indication of an interplay between the influence of the temperature on the arrangement of the reactants in the TS, the viscosity of the solvent, the motion of the two radicals before coupling and the coupling rate. On the other hand, the results for isobornyl bromide may also be explained purely as a result of a competition between an outer-sphere ET and S_N2 mechanism, the latter being dominant at lower temperatures. Even though the Arrhenius plot does not show a clear indication of a mechanism change, this explanation can not rigorously be excluded.

Experimental

Materials. Bornyl bromide⁷ and isobornyl bromide⁸ were prepared according to the references given. 4-Methoxycarbonyl-1-methylpyridinium perchlorate was obtained from an aqueous solution containing 4-methoxycarbonyl-1-methylpyridinium iodide and sodium perchlorate. The 4-methoxycarbonyl-1-methylpyridinium iodide was prepared from the reaction between the methyl ester of isonicotinic acid and methyl iodide in acetonitrile kept in a closed vessel at 50°C overnight. 4-Methoxycarbonyl-1-methylpyridinium perchlorate was recrystallized from ethanol before use.

Apparatus. In all the electrochemical experiments the cell used was an H-cell, the counter-electrode was a carbon electrode and the reference electrode a silver wire in DMF/0.1 M TBABF₄. In the preparative experiments the working electrode was a platinum net, and in the electroanalytical experiments a rotating-disk electrode (a gold electrode of diameter 3 mm). The recording system and potentiostat have been described previously.⁹ The temperature in the cathodic compartment of the cell was measured with a NiCr–NiAl temperature probe connected with a Lutron TM-905 digital thermometer. The probe was put inside a glass tube with methanol. For the high temperature experiments ($T > 0^\circ\text{C}$) a thermostatted water bath was used, and for the low-temperature experiments ($T < 0^\circ\text{C}$) a thermostatted methanol bath was used. The NMR spectra were recorded with a Varian Gemini 200 MHz spectrometer.

Procedure. The rate constants in the electroanalytical experiments were measured by means of a potentiostatic method using a rotating-disk electrode following the procedure described in Ref. 10. The concentration of 1^- was 2–5 mM and the alkyl halide was always added in an excess of at least ten. At each temperature value chosen the experiments were repeated at least twice. In the preparative experiments about 100 mg of 1^+ClO_4^- and an excess of alkyl halide were added to a 50 mL DMF/TBABF₄ solution. The highest excess factor (10) of the

alkyl halide was used at the lowest temperature. The solution was deaerated for 15 min with argon before the electrolysis was commenced at a controlled potential (-1.6 V vs. SCE). When the reduction had finished (ca. 2 F mol^{-1}) water was added, and the products were extracted with diethyl ether. After being dried, the solvent was removed *in vacuo*. The ratio of A and B was determined by the use of ^1H NMR, and the experiments were performed twice at each temperature. Compound B could be isolated by flash chromatography using silica gel 60 (Merck, korngroße 0.040–0.063 mm) and a 7% ether/petroleum ether solution as eluent. The petroleum ether was distilled before use. The flow rate was kept constant at 5 cm min^{-1} .¹¹ The first product isolated from the column was the *endo*-compound followed by a mixture of the *endo*- and *exo*-compounds. The *exo*-compound could only be isolated in detectable amounts. Five grams of the mixture (A:B = 1:4.5) prepared from a preparative reduction of $\mathbf{1}^+$ and isobornyl bromide at -40°C in order to increase the yield of the isolable compound were put on the column, and about 400 mg *endo*-dihydropyridine coupling product could be isolated as a liquid. Attempts to quaternize the dihydropyridine coupling product to get a crystalline derivative were unsuccessful, so the compound (250 mg) was hydrogenated to the hexahydropyridine derivative at ambient pressure and temperature in 40 ml of ethanol using PtO_2 (80 mg) as catalyst. The hydrogen uptake was slow (several hours), so the hydrogenation was allowed to run to completion during the night. The catalyst was filtered off, and the ethanol removed *in vacuo*. The residue was dissolved in acetonitrile (10 ml) and quaternized with an excess of methyl iodide at 35°C for 18 h; on addition of diethyl ether and cooling the quaternized hexahydropyridinium derivative crystallized in thin needles. Several attempts to get sufficiently large crystals for an X-ray structure determination by recrystallization with slow cooling from several solvents and

solvent mixtures or slow evaporation of solutions in different solvents were unsuccessful; the compound crystallized nicely, but in very thin needles. The compound was therefore dissolved in water and precipitated as the perchlorate salt by addition of a saturated solution of sodium perchlorate. The perchlorate salt with a melting point of 248°C was filtered off, dried and dissolved in acetone. Slow evaporation of the solvent produced several crystals suitable for an X-ray structure determination, which showed the compound to be an *endo* derivative.³ ^1H NMR (DMSO): δ 0.78 (s, 3H), 0.84 (s, 3H), 0.89 (s, 3H), 3.08 (s, 3H), 3.13 (s, 3H), 3.74 (s, 3H), 1.0–3.5 (m, 16H). ^{13}C NMR (DMSO): δ 174.5, 59.1, 58.9, 55.5, 52.4, 52.3, 50.4, 48.9, 46.6, 45.4, 43.6, 30.3, 29.0, 28.4, 28.0, 27.2, 19.4, 18.9, 16.1.

The ^1H NMR spectra of A and B are given in Ref. 1.

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