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# ON THE STEREOISOMERIZATION OF RADICALS DURING ALIPHATIC NUCLEOPHILIC SUBSTITUTIONS

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**Abstract:** Bornyl and isobornyl bromide react with an enolate ion $\mathbf{1}^-$ to the same products which indicates a stereoisomerization during the aliphatic nucleophilic substitution. Substitution of $\mathbf{1}^-$ with a "radical clock" suggests a radical coupling within the solvent cage. Reaction between a radical clock and anion radicals suggests in this case a coupling outside the solvent cage.

Electron-transfer reactions in organic chemistry have been the subject of much research during the latest two decades,[1] and their possible importance in a number of "classical" reactions has been discussed.

Besides the classical reaction schemes for the aliphatic nucleophilic substitution, $S_N1$ and $S_N2$, another scheme involving the transfer of a single electron has recently been proposed. It has been found,[2] that in certain cases the rate of the substitution reaction ($k_{SUB}$) between an easily oxidized anion, such as the enolate ion of 4-methoxycarbonyl-1-methyl-1,4- dihydropyridine ($\mathbf{1}^-$), and a sterically hindered alkyl halide was the same as that which would be expected for the transfer of an electron to the alkyl halide from an anion radical (a one-electron reductant) with the same oxidation potential as the anion ($k_{SET}$). These results were suggested to be examples of an aliphatic nucleophilic substitution in which the rate-determining step was the transfer of a single electron; such a reaction may be regarded as an "outer-sphere" electron transfer (ET), i.e., the stabilization of the transition state for the ET is less than about 1 kcal mole$^{-1}$.

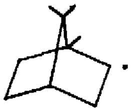
The substitution of less hindered alkyl halides with the same easily oxidized anions proceeded usually somewhat faster than expected for a pure outer-sphere ET, equivalent to a decrease of the energy of the TS (1-5 kcal mole$^{-1}$) compared with that of an outer-sphere TS. This decrease might be due to some kind of bonding between the reactants in the TS, possibly the formation of a charge-transfer complex. It was hypothesized that there might exist transition states with different degrees of stabilization ranging from no stabilization in the pure outer-sphere ET-TS to that in the classical $S_N2$-TS, an inner-sphere ET-TS.

The aliphatic nucleophilic substitution reaction between an anion An$^-$ and an alkyl halide RX with an ET-TS may be depicted as (Eq. (1)):

$$An^- + RX \rightleftharpoons [An^\cdot + R^\cdot + X^-] \rightleftharpoons AnR + X^- \qquad (1)$$

The scheme thus implies that $An^\bullet$ and $R^\bullet$ exist as radicals in a certain time-interval. But how "free" are such radicals? Do they have time to stereoisomerize at the central carbon atom? Do they even have time to leave the solvent cage?

The first question was addressed using the reaction between $\mathbf{1}^-$ and bornyl bromide and between $\mathbf{1}^-$ and isobornyl bromide. Electrochemical reduction of 4-methoxycarbonyl-1-methylpyridinium iodide ($\mathbf{1}^+$) in N,N-dimethylformamide (DMF) at the potential of the second reduction wave (-1,3V *vs* AgI/Ag, 0,1 M $I^-$ in DMF) in the presence of a slight excess of *endo*-2-bromo-1,7,7-trimethyl-bicyclo [2.2.1] heptane (*endo*-**2**, bornyl bromide) yielded two substitution products (A and B) with the ratio A : B = 1,4 : 1. Similarly, when $\mathbf{1}^+$ was reduced in the presence of *exo*-**2** (isobornyl bromide) the same compounds were optained, but in the ratio A : B = 1 : 1,3.

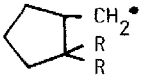


**2**•

$R_2\dot{C}(CH_2)_3CH = CH_2$

3• R = $CH_3$

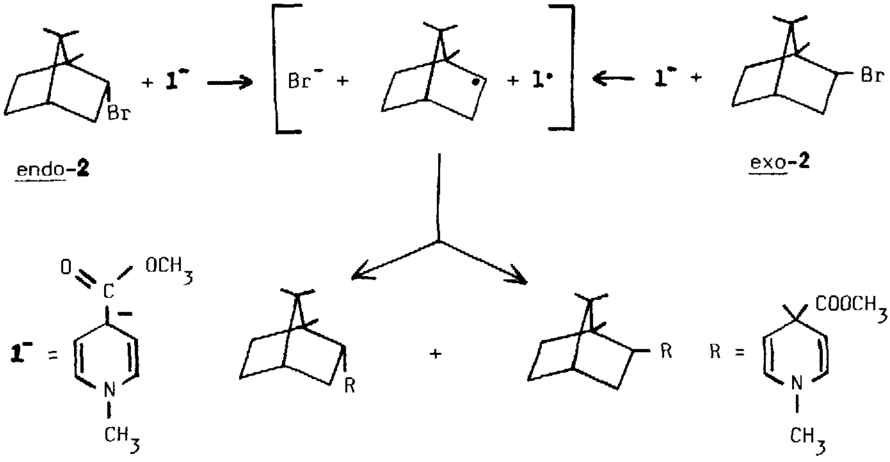
5• R = H



3c• R = $CH_3$

5c• R = H

Bornyl bromide and isobornyl bromide do not isomerize detectably in DMF at 25 °C during 24 h which excludes an $S_N1$-reaction of *endo*-**2** or *exo*-**2** being responsible for the observed stereoisomerization. Furthermore, it has been shown for 2-substituted norbornyl derivatives that a very high *exo*:*endo* ratio of the substitution products is observed in $S_N1$-reactions[3] and that a significant difference is found in the rates of the *exo* and *endo* derivatives.[4] The rate constants for the reaction between $\mathbf{1}^-$ and *exo*-2-bromonorbornane and between $\mathbf{1}^-$ and *endo*-2-bromonorbornane were approximately equal. Addition of an equivalent concentration of iodide to *endo*-**2** in DMF (25 °C) did not yield any bornyl or isobornyl iodide during 24 h. An isomerization caused by an $S_N2$-reaction of the iodide in $\mathbf{1}^+$ is thus not responsible for the stereoisomerization in the reaction between $\mathbf{1}^-$ and *endo*-**2** and *exo*-**2**. The reaction can be formulated (Eq. (2)):



(2)

In the $^1$H NMR-spectra of *endo*-**2** and *exo*-**2** (and some other *endo*-*exo* pairs) the proton at the substituted carbon in the *endo*-form has two vicinal couplings and a relatively large third coupling, whereas the third coupling is quite small in the *exo*-form. The $^1$H NMR-spectra of A[5] and B[6] both exhibited a slightly different, but relatively large third coupling. Differences in chemical shifts for the methyl groups were suggestive, but not sufficiently large to clearly indicate the *exo/endo* relationship of A and B. It has thus not yet been established which of the two compounds, A or B, is the *exo* and which is the *endo* product; it is thus not known whether there is a slight excess of retention or inversion at the central carbon atom in the reaction, although a slight excess of inversion seems most likely.

The ratio $k_{SUB} : k_{SET}$ has been measured by cyclic voltammetry in a way similar to that previously employed.[2] For *endo*-**2** and *exo*-**2** $k_{SUB} : k_{SET}$ indicated a TS close to a pure ET-TS.

These results show that the **2**-radical has a life-time during the substitution reaction at least comparable with the rate of inversion of the radical. But is the life-time of $\mathbf{2}^{\cdot}$ long enough to permit it to escape from the radical-pair solvent-cage? In order to investigate that the reaction between $\mathbf{1}^-$ and an anion radical and between $\mathbf{1}^-$ and a "radical clock"[7] was investigated.

For the reaction with $\mathbf{1}^-$, 6-bromo-6-methyl-1-heptene (**3-Br**) was chosen; by using a bromide rather than an iodide the complications[8] which may be encountered by using an iodide would be avoided. The cyclization of $\mathbf{3}^{\cdot}$ to $\mathbf{3c}^{\cdot}$ is relatively slow ($k \sim 10^5$-$10^6$)[7,9,10] and the formation of a cyclized coupling product would indicate a radical combination outside the solvent cage.

Electrochemical generation of $\mathbf{1}^-$ from $\mathbf{1}^+$ in the presence of **3-Br** gave no detectable cyclized coupling product. However, as $\mathbf{1}^-$ is formed by reduction of $\mathbf{1}^{\cdot}$ the radical $\mathbf{3}^{\cdot}$, formed by reaction with $\mathbf{1}^-$, would, if it escaped the solvent cage, encounter a high concentration of $\mathbf{1}^{\cdot}$ and thus have a rather short life-time. The situation is similar to that in the electrochemical reduction of anthracene (**4**) to its anion radical ($\mathbf{4}^{\cdot-}$) in the presence of 6-bromo-1-hexene (**5-Br**). When a relatively high current density (10 mA cm$^{-2}$) was used (giving a relatively high steady-state concentration of $\mathbf{4}^{\cdot-}$) a high ratio ( 10 : 1) of uncyclized coupling product (**4-5**) to the cyclized coupling product (**4-5c**) was found, whereas at low current density (0.2 mA cm$^{-2}$) a ratio of approximately 1 : 1 for **4-5** : **4-5c** was observed. The reactions are (Eqs. (3)-(7)).

$$\mathbf{4} + e^- \rightleftharpoons \mathbf{4}^{\cdot-} \tag{3}$$

$$\mathbf{4}^{\cdot-} + \mathbf{5\text{-}Br} \longrightarrow \mathbf{4} + \mathbf{5}^{\cdot} + Br^- \tag{4}$$

$$\mathbf{4}^{\cdot-} + \mathbf{5}^{\cdot} \longrightarrow \mathbf{4\text{-}5}^- \xrightarrow{H^+} \mathbf{4\text{-}5\text{-}H} \tag{5}$$

$$\mathbf{5}^{\cdot} \longrightarrow \mathbf{5c}^{\cdot} \tag{6}$$

$$\mathbf{4}^{\cdot-} + \mathbf{5c}^{\cdot} \longrightarrow \mathbf{4\text{-}5c}^- \xrightarrow{H^+} \mathbf{4\text{-}5c\text{-}H} \tag{7}$$

At low current density (low $\mathbf{4}^{\cdot-}$ ) the rate of (5) is relatively low and (6) competes successfully with (5); (5) and (7) are then equally preferred coupling reactions. The results are thus incompatible with an $S_N2$-type reaction between $A^{\cdot-}$ and RX being the main reaction.

An attempt was made to simulate the "low-current density" experiment by generating the somewhat unstable enolate ion $\mathbf{1}^-$ with a low background concentration of $1^\bullet$ by adding two equivalents of $\mathbf{4}^{\bullet-}$ to $\mathbf{1}^+$ (eq. 8), immediately followed by addition of **3-Br**.

$$2\,\mathbf{4}^{\bullet-} + \mathbf{1}^+ \xrightarrow{K} 2\,\mathbf{4} + \mathbf{1}^- \qquad (K > 100) \qquad (8)$$

The coupling product **1-3** was not accompanied by any of the cyclized coupling product, **1-3c,** as judged by NMR. This is in accordance with expectations[8] for relatively slow "radical clocks". However, it is noteworthy that during the reaction of (1,1-dimethyl-5-hexenyl)magnesium chloride with benzophenone a substantial part (73%) of the 1,6-addition product was cyclized.[11] It is not clear[11,12] whether the coupling to this product takes place within the solvent cage or between freely diffusing radicals and ketyls. Also substantial cyclization occurs in the reaction between 6-bromo-1-heptene and $Me_3SnLi$[13] or $Me_3SnNa$[14] in THF; interestingly enough, in the reaction between $Me_3SnNa$ and (+)-2-bromooctane[15] a high degree of inversion was observed.

The conclusion is that in the transition-state of the aliphatic nucleophilic substitution, in the cases where the transfer of a single electron is the rate-determining step, the radicals formed are free to stereoisomerize at the central carbon atom, but the two radicals in the solvent cage (e.g., $\mathbf{1}^{\bullet}$ and $\mathbf{2}^{\bullet}$) combine so fast that they probably do not live long enough to leave the solvent cage.

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5. $^1$H NMR-spectrum of A ($CDCl_3$): 0.70 (s,3H); 0.75 (s,3H); 0,87 (s,3H); 0.9-1.75 (m,5H); 1.30 (q,J = 11,8Hz, 9,5Hz, 1H); 1.60 (octet, J = 11.8Hz, 8.0Hz, 3-4Hz, 1H; 2,15 (octet,J = 9,5Hz, 8.0Hz, 1.5Hz, 1H); 2.80 (s,3H); 3.67 (s,3H); 4.21 (q,1H,J = 8Hz, 3Hz); 4.41 (q,1H,J = 8Hz, 3Hz); 5.77 (q,1H,J = 8Hz,2Hz); 5.94 (q,1H,J = 8Hz, 2Hz).
6. $^1$H NMR-spectrum of B ($CDCl_3$): 0.74 (s,3H); 0.76 (s,3H); 0.82 (s,3H); 0.9-1.75 (m,4H); 1.24(q,J = 12.2Hz, 6.0Hz, 1H); 1.69 (m,J = 12.2Hz, 11.5Hz, 4.5Hz, 2.8Hz, 1H ; 1.96 (octet,1H,J 11.5Hz, 6.0Hz, 2.6Hz); 2.05-2.12 (m, 1H); 2.84 (s,3H); 3.63 (s,3H); 4.54 (q,1H,J = 8.4Hz, 3Hz); 4.68 (q,1H,J = 8.4Hz, 3Hz); 5.80 (q,1H,J = 8.0Hz, 2Hz) 5.89 (q,1H,J = 8Hz, 2Hz).
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