

On the Coupling of Anion Radicals with Sterically Hindered Alkyl Halides

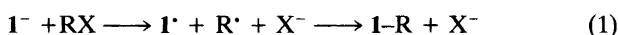
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Daasbjerg, K., Hansen, J. N. and Lund, H., 1990. On the Coupling of Anion Radicals with Sterically Hindered Alkyl Halides. – Acta Chem. Scand. 44: 711–714.

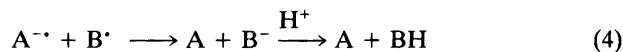
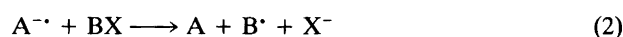
Electrochemically generated anion radicals of anthracene have been coupled in DMF with bornyl and isobornyl bromides and *exo*- and *endo*-norbornyl bromides; anion radicals of quinoxaline have been coupled with bornyl and isobornyl bromides. The *exo*- and *endo*-bromides gave in all cases nearly the same product distribution. The reaction between quinoxaline anion radical and optically active 2-bromobutane gave racemization. These results are taken as an indication that the coupling reaction between aromatic anion radicals and these sterically hindered alkyl halides involves a dissociative electron transfer (ET) from the anion radical to the alkyl halide followed by coupling between the thus formed alkyl radical and another anion radical.

In our current investigation¹⁻³ on electron transfer (ET) in aliphatic nucleophilic substitution it has previously been shown³ that the reaction between the enolate anion of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine (1^-) and bornyl and isobornyl bromides gave a mixture of *exo*- and *endo*-substitution products in nearly the same proportions. *exo*- and *endo*-norbornyl bromides, on reaction with 1^- , also gave a mixture of *exo*- and *endo*-substitution products, but the *exo/endo* ratio depended somewhat on the starting halide. This has been interpreted by assuming a nearly 'pure' ET transition state (TS) with negligible bonding stabilization in the reaction between 1^- and bornyl and isobornyl bromides [eqn. (1)], whereas the TS for the norbornyl bromides are assumed to have a small bonding stabilization between 1^- and the central carbon atom.



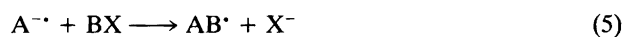
The bonding stabilization in TS between the attacking nucleophile and the central carbon atom of the electrophile has also been estimated on the basis of $k_{\text{SUB}}/k_{\text{SET}}$, where k_{SUB} is the rate of the substitution reaction and k_{SET} the rate of the ET to the alkyl halide from an aromatic anion radical with the same redox potential as the anion.

This argument assumes that the reaction between an anion radical of an aromatic hydrocarbon and the alkyl halides under investigation involves an ET rather than a classical $\text{S}_{\text{N}}2$ reaction. Evidence for that was published more than twenty years ago⁴ [eqns. (2)–(4)], but some stereochemical results⁵ have been taken as evidence for competition between ET and $\text{S}_{\text{N}}2$ reactions.



Whereas the reaction between the anion 1^- and BX [eqn. (1)] is assumed to take place within a solvent cage, the coupling reaction between anion radicals and alkyl halides [eqns. (2) and (3)] requires that the alkyl radical has to leave the solvent cage in order to encounter another anion radical. The time interval between the ET [eqn. (2)] and the coupling [eqn. (3)] should thus be long enough for a nearly complete stereochemical equilibration.

If, on the other hand, an $\text{S}_{\text{N}}2$ -like reaction takes place, bonding between the anion radical and the central carbon atom occurs, which will lead to inversion at the central carbon. The role of the second anion radical is then to reduce the coupled radical [eqns. (5) and (6)].



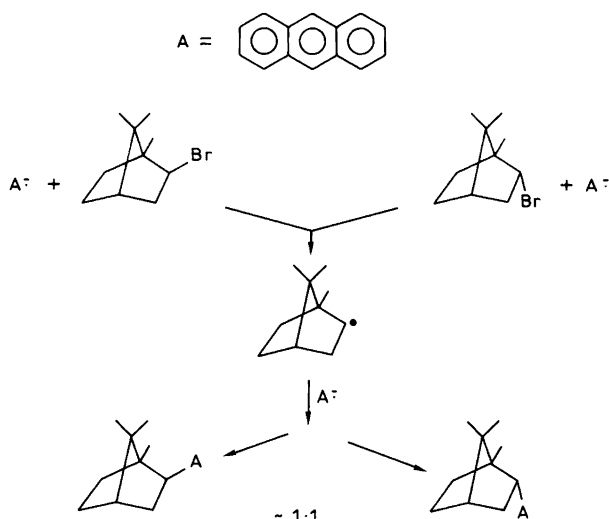
The reaction between 1^- and bornyl/isobornyl bromides has been used as a model reaction to indicate the possibility of a nucleophilic substitution with a 'pure' ET as the rate-determining step, and it was thus essential to investigate the stereochemical outcome of a reaction between a number of aromatic anion radicals and these halides. Anion radicals of anthracene and quinoxaline were chosen as examples of aromatic and heteroaromatic compounds, and

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bornyl bromide, (*endo-2*, *endo-2*-bromo-1,7,7-trimethylbicyclo[2.2.1]heptane) and isobornyl bromide, (*exo-2*), were used as alkyl halides together with *endo-2*-bromonorbornane (*endo-3*, *endo-2*-bromobicyclo[2.2.1]heptane) and *exo-2*-bromonorbornane (*exo-3*). A 'classical' chiral reagent, (*R*)-(-)-2-bromobutane (**4**) was used in a reaction with quinoxaline anion radical.

Results and discussion

Reduction of anthracene in DMF in the presence of *exo-2* or *endo-2* gave the same 1:1 mixture of 9-(*exo-2*-bornyl)-9,10-dihydroanthracene and 9-(*endo-2*-bornyl)-9,10-dihydroanthracene (Scheme 1). No substitution products in the 1 and 2 positions of the anthracene were isolated, but the presence of minor amounts of such products were detected by ¹H NMR and GLC-MS.



Scheme 1.

The steric results from the reaction between anthracene anion radical and *exo-2* and *endo-2* clearly indicates that the stereochemical information is lost during the reaction. The transition state thus cannot be S_N2-like and it indicates that the reaction sequence is eqns. (2) and (3) rather than eqns. (5) and (6).

In the reduction of anthracene in the presence of *exo-3* or *endo-3* substitution was observed in the 1,2 and 9 positions and the *exo/endo* ratios were independent of whether *exo-3* or *endo-3* was the substrate. It has not been possible to establish which is *exo* and which is *endo* in the product pairs.

The formation of some 2-norbornyl-3,4-dihydroanthracene is unexpected; possibly 2-norbornyl-2,3-dihydroanthracene is formed primarily; it may then rearrange to the isolated product. The ¹H NMR spectrum is in accordance with the proposed formula (see the Experimental) and the mass spectrum with a molecular peak of 100% also suggests the norbornyl substituent at an sp²-hybridized carbon.

From the reduction of quinoxaline in the presence of

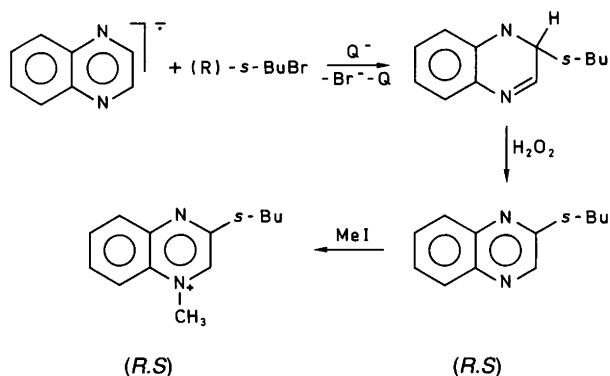
exo-2 or *endo-2* the same isomer (**4a**) of 2-bornylquinoxaline was isolated from both reactions as the major product; it was accompanied by minor amounts of the other isomer (**4b**). The dihydro derivative is presumably formed initially and probably oxidized during work-up to the aromatic compound; a disproportionation to a mixture of the aromatic compound and the tetrahydro derivative, as found in the reaction between quinoxaline anion radical and *t*-butyl bromide,¹ followed by oxidation of the tetrahydro derivative, may also be possible.

The major isomer **4a** was quaternized with methyl iodide to 1-methyl-3-(2-bornyl)quinoxalinium iodide; an X-ray crystallographic determination⁶ of the structure indicated that the quinoxaline nucleus was bound in the *endo*-position of the bicycloheptane system. The attack leading to *endo* substitution thus seems to be more favored than an *exo* attack, possibly due to steric shielding by the 7-methyl groups. *exo-2* gives slightly less (2–4%) of **4b**, whereas *endo-2* gives 10–15%. An explanation for this slight difference in the *exo/endo* ratio is not obvious; a similar difference in the ratio is not observed in the reactions with anthracene anion radical. The higher charge density at nitrogen in the quinoxaline anion radical compared with the charge density at carbon in the anthracene anion radical may play a role for the observed effect.

It is noticeable that the reduction of quinoxaline in the presence of acetic anhydride gives *N*-acylation to 1,4-diacetyl-1,4-dihydroquinoxaline,⁷ whereas the reaction with sterically hindered alkyl halides give *C*-alkylation to 2-alkyl-1,2-dihydroquinoxaline. The difference in reaction site in the reductive acylation and alkylation reaction could be interpreted in terms of a bonding in the acylation reaction between the anion radical and acetic anhydride followed by an ET from a second anion radical, eqns. (5) and (6), whereas the reaction with the alkyl halides follow eqns. (2) and (3).

Reduction of quinoxaline in DMF in the presence of (*R*)-(-)-2-bromobutane gave a product without detectable optical rotation. However, as the optical rotation of fully resolved 2-(2-butyl)-1,2-dihydroquinoxaline is unknown, this compound (or the quinoxaline and tetrahydro derivative which is formed from the dihydro derivative by disproportionation) was oxidized to the quinoxaline, which was quaternized with methyl iodide. The ¹H NMR spectrum in CDCl₃ of the major (90–95%) quaternized product in the presence of 30 mol % of tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)₃] showed two separate peaks of equal height for the *N*-methyl groups, indicating equal concentrations of the two enantiomers (Scheme 2). As neither the optical rotation nor the ¹H NMR spectrum revealed any excess of one of the enantiomers, the stereochemical outcome of the reaction is considered to be at least 95% racemization.

The reaction between the anthracene anion radical and optically active 2-haloctanes⁵ has been reported to involve a competition between an S_N2 and an ET reaction with the latter being the more important (S_N2/ET for RI = 5:95 and



Scheme 2.

for RBr = 8:92). The experiments were performed a little differently from those reported here, in that the anthracene was first reduced to the anion radical and then an equivalent amount of RX was added, whereas in this investigation the aromatic compound was reduced in the presence of an excess of alkyl halide. This might explain the slight difference in the stereochemical results.

The results of the reactions of aromatic anion radicals with the bornyl derivatives and optically active 2-bromobutane indicate that in these systems the role of an S_N2 -like reaction path is negligible. It thus follows that the use of the rate of the reaction between such aromatic anion radicals and the sterically hindered alkyl halides as a measure of the rate (k_{SET}) of an electron transfer reaction is a valid approximation.

Experimental

Apparatus. Optical rotations were measured with a Perkin-Elmer 241 polarimeter, the ^1H NMR spectra with a Varian Gemini 200 MHz spectrometer.

Materials. Bornyl⁸ and isobornyl bromides,⁹ and *exo*-¹⁰ and *endo*-norbornyl bromides¹¹ were prepared according to the references given. (*R*)-(-)-2-bromobutane was made from (*S*)-(+)-2-butanol (Aldrich) using PBr_3 as the brominating agent.¹² HBr was prepared according to Ref. 13.

Reductive couplings. The aromatic compound (1 mmol) was reduced in 30 ml DMF containing 0.1 M tetrabutylammonium fluoroborate at the potential of the first reduction wave in the presence of an alkyl bromide. When the reduction was finished, water was added and the coupling product was extracted with diethyl ether, which was washed free of DMF with water. After drying, the solvent was removed *in vacuo* and the ^1H NMR spectrum recorded and the product distribution determined by GC.

Anthracene and bornyl or isobornyl bromide. The reaction mixtures from anthracene anion radical and *endo*-2 or *exo*-2 gave identical ^1H NMR spectra interpreted as a 1:1 mixture of 9-(*exo*-2-bornyl)-9,10-dihydroanthracene and 9-(*endo*-2-bornyl)-9,10-dihydroanthracene. Which of these

stereoisomers is isomer A and which is isomer B is not known. ^1H NMR (CDCl_3), isomer A: δ 4.17 (d, H-10 α , J = 17.4 Hz), 3.78 (d, H-10 β , J = 17.4 Hz), 3.94 (d, H-9, J = 10.6 Hz); isomer B: δ 4.15 (d, H-10 α , J = 17.4 Hz), 3.76 (d, H-10 β , J = 17.4 Hz), 4.06 (d, H-9, J = 9.5 Hz). The following signals could not be assigned to a given isomer: δ 0.18, 0.72, 0.80, 0.85, 0.96, 1.16 (6 methyl signals), 0.5–2.3 (2×8 aliphatic H), 7.1–7.5 (2×8 aromatic H). Mass spectrum of the isomeric mixture [m/z (%)]: 179 (66), 178 (100), 137 (46), 95 (17), 81 (59), 67 (18), 55 (16), 41 (33).

Quinoxaline and bornyl or isobornyl bromides. The reaction mixtures from quinoxaline anion radical and either bromide had nearly the same ratio (9:1) of isomers of 2-(2-bornyl)quinoxaline as judged from the ^1H NMR spectrum. Major isomer, **4a**: ^1H NMR (CDCl_3): δ 0.89 (s, 3 H), 0.94 (s, 3 H), 1.07 (s, 3 H), 0.8–3.2 (7 aliphatic H), 3.43 (ddd, 1 H, J = 10.0, 6.0, 2.3 Hz), 7.60–7.75 (m, 2 H), 8.00–8.10 (m, 2 H), 8.66, (s, 1 H). Mass spectrum [m/z (%)]: 266 (16), 195 (8), 181 (11), 168 (8), 158 (17), 157 (100), 145 (10), 144 (21), 129 (13), 103 (9), 102 (15), 95 (20), 79 (8), 77 (17), 76 (16), 67 (13), 55 (18), 53 (11), 43 (13), 41 (41). Minor isomer, **4b**: From the ^1H NMR (CDCl_3) of the isomer mixture the following signals could be attributed the minor isomer: δ 0.55 (s, 3 H), 1.00 (s, 3H), 1.20 (s, 3 H), 8.58 (s, 1 H). Mass spectrum [m/z (%)]: 266 (30), 251 (17), 195 (16), 186 (16), 185 (100), 183 (39), 181 (23), 170 (9), 169 (27), 168 (19), 145 (16), 144 (44), 129 (15), 102 (25), 81 (21), 79 (20), 77 (45), 76 (26), 67 (39), 65 (15), 55 (27), 53 (27), 51 (20), 50 (16), 43 (20), 41 (93). **4a** was quaternized with methyl iodide in acetonitrile to 1-methyl-3-(2-bornyl)quinoxalinium iodide, m.p. 232 °C, ^1H NMR (CDCl_3): δ 0.94 (s, 3 H), 1.00 (s, 3 H), 1.10 (s, 3 H), 0.8–2.2 (7 aliphatic H), 3.92 (dd, 1 H, J = 10.9, 6.3 Hz), 4.92 (s, 3 H), 8.07–8.18 (m, 2 H), 8.33–8.46 (m, 2 H), 10.06 (s, 1 H). An X-ray crystallographic structure determination showed the compound to be an *endo* derivative.⁶

Anthracene and *exo* or *endo* norbornyl bromides. The crude reaction mixture was separated on a column of silica using 2% diethyl ether/petroleum ether as the eluent.

9-(2-Norbornyl)-9,10-dihydroanthracene, major isomer (yield: 38–45%), ^1H NMR spectrum (CDCl_3): δ 3.44 (d, H-9, J = 10.4 Hz), 3.79 (d, H-10 α , J = 17.8 Hz), 4.14 (d, H-10 β , J = 17.8 Hz). Minor isomer (yield: 9–11%), ^1H NMR (CDCl_3): δ 3.44 (d, H-9, J = 10.4 Hz), 3.77 (d, H-10 α , J = 17.8 Hz), 4.12 (d, H-10 β , J = 17.8 Hz). The signals from 2×11 aliphatic H (δ = 0.8–2.4) and 2×8 aromatic H (7.1–7.3) could not be assigned to the individual isomers. Mass spectrum [m/z (%)]: 274 (18), 179 (100), 178 (45), 95 (12), 67 (7), 57 (10), 55 (10), 44 (25), 43 (15), 41 (11), 40 (80).

1-(2-Norbornyl)-1,2-dihydroanthracene; both isomers, ^1H NMR (CDCl_3): δ 0.8–3.2 (14 H), 5.90–6.05 (m, H-3), 6.62 (d, H-4, J = 9.8 Hz), 7.3–7.5 (m, 4 H), 7.65–7.8 (m, 2 H). 2-(2-Norbornyl)-1,2-dihydroanthracene; isomer A, ^1H NMR (CDCl_3): δ 0.8–3.2 (14 H), 6.22 (dd, H-3, $J_{3,4}$ = 9.8

Hz, $J_{2,3} = 4.3$ Hz), 6.62 (d, H-4, $J = 9.8$ Hz) 7.3–7.5 (m, 4 H), 7.65–7.8 (m, 2 H); isomer B, $^1\text{H NMR}$ (CDCl_3): δ 0.8–3.2 (14 H), 5.90–6.05 (m, H-3) 6.62, d, H-4, $J = 9.8$ Hz) 7.3–7.5 (m, 4 H), 7.65–7.8 (m, 2 H). Yields of the 1- and 2-substituted products: 34–40%.

2-(2-Norbornyl)-3,4-dihydroanthracene, major isomer (yield: 9–12%), $^1\text{H NMR}$ (CDCl_3): δ 0.8–2.3 (11 H), 2.20–2.40 (m, 2 H), 2.85–3.00 (m, 2 H) 6.35 (br s, H-1), 7.3–7.5 (m, 4 H), 7.65–7.75 (m, 2 H). Minor isomer (yield: 1%): The only recognizable difference in the $^1\text{H NMR}$ spectrum of the isomers is that the signal at δ 6.35 for the major isomer appears instead at δ 6.46 for the minor. Mass spectrum [m/z (%): 274 (100), 206 (24), 194 (78), 193 (34), 192 (39), 179 (63), 178 (40), 165 (33), 44 (22).

Quinoxaline and (R)-(-)-2-bromobutane. The coupling products (yield 81%) were obtained as a 1:1 mixture of aromatic and tetrahydro derivatives when the reaction mixture was allowed to stand; 235 mg of the mixture were dissolved in 8 ml of ethanol and treated with 3 ml of 35% hydrogen peroxide and 1 ml of 2 M potassium hydroxide. It was kept at 40°C for 2 h; water was added and the product extracted with diethyl ether, which was washed with water and dried over molecular sieves 4A. Evaporation of the solvent gave 192 mg of the aromatic derivative; $^1\text{H NMR}$ (CDCl_3): δ 0.89 (t, 3 H, $J = 7.4$ Hz), 1.40 (d, 3 H, $J = 7.0$ Hz), 1.6–2.0 (m, 2 H), 2.95–3.15 (m, 1 H), 7.6–7.8 (m, 2 H), 8.0–8.2 (m, 2 H), 8.72 (s, 1 H). MS [m/z (%): 186 (21), 171 (52), 158 (100), 157 (56), 144 (40), 130 (26), 103 (21), 102 (22), 77 (30), 76 (59). 2-(2-Butyl)quinoxaline (100 mg) was dissolved in 2 ml of acetonitrile and 0.2 ml of methyl iodide added. The mixture was kept at 70°C in a closed vessel for 24 h. After cooling, 3 ml of diethyl ether were added and red crystals separated (40%); evaporation of the filtrate gave the material balance as unchanged start-

ing material. $^1\text{H NMR}$ of the quaternized product showed 90–95% of 3-(2-butyl)-1-methylquinoxalinium iodide and 5–10% of 2-(2-butyl)-1-methylquinoxalinium iodide. Major isomer, $^1\text{H NMR}$ (CDCl_3): δ 0.96 (t, 3 H, $J = 7.4$ Hz), 1.53 (d, 3 H, $J = 7.0$ Hz), 1.8–2.2 (m, 2 H), 3.43–3.55 (m, 1 H), 4.96 (s, 3 H), 8.1–8.2 (m, 2 H), 8.3–8.5 (m, 2 H), 10.35 (s, 1 H). On addition of tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [$\text{Eu}(\text{tfc})_3$] (30–40 mol %) the singlet at 4.96 was transformed into two singlets of equal intensity at δ 5.61 and 5.65. A solution of the 2-(2-butyl)quinoxaline mixture (10 mg in 1.0 ml ethanol) gave no detectable rotation.

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Received December 12, 1989.