Stereospecific Radical–Radical-anion Combination in the Reductive Aminoalkylation of Anthracene

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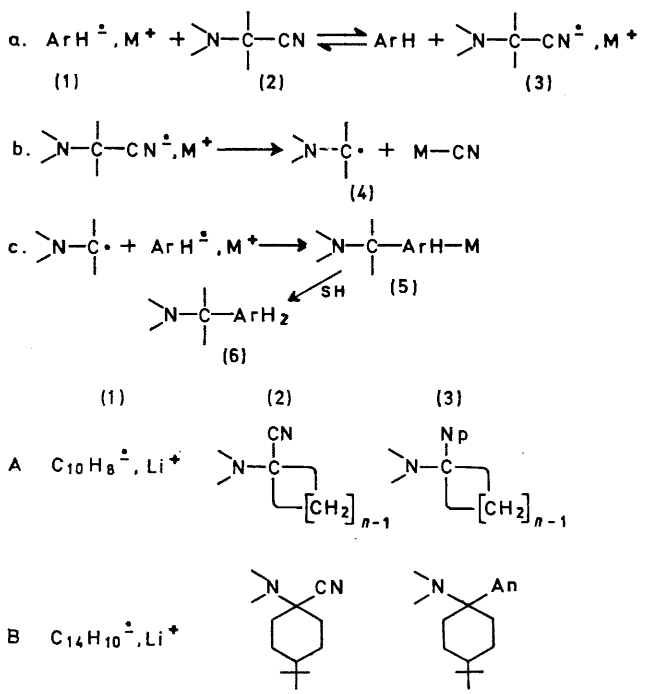
Summary The aminoalkylation of lithium dihydroanthracenylide occurs with complete retention of the configuration and the C$_\alpha$CN bond-breaking involves sp^3–sp^2 hybridisation change; the most consistent explanation of these results is the directing effect of LiCN on the radical–radical-anion combination.

α-AMINO-NITRILES are well known "pseudosalts"[1] particularly useful in the aminoalkylation of Grignard reagents.[2] An extension of these reactions was reported using alkali-metal derivatives of aromatic compounds instead of organomagnesium halides.[3] Because of the radical-anion character of these nucleophiles the following scheme was suggested for this reaction:



SH = Proton donor; Np = 1,2- and 1,4-dihydronaphthalene; An = 9,10-dihydroanthracene; $\rangle$N = piperidino.

We report here two types of experiment supporting the main line of this scheme and giving more detailed information on the stereochemistry of the reaction.

(i) The rate of the reaction of lithium dihydronaphthylide (1A) with cyclic amino-nitriles (2A) in tetrahydrofuran is ring-size-dependent. The reaction is instantaneous at room temperature on the laboratory time scale for $n = 5$, 7, and 8 but very slow for $n = 6$ and 12. From these two compounds at room temperature a relatively stable amino-nitrile–lithium complex (3) is formed and the reaction is complete only after several hours or after heating. The compounds (6A) formed in these reactions have satisfactory spectral and analytical data.

The formation of complexes (3A; $n = 6$ and 12),† from which the starting amino-nitrile (2A) can be obtained on hydrolysis, is in agreement with the reversible *a* step. Concerning the significance of the ring-size–rate correlation, its use as a mechanistic criterion is well known[5] and it is established that a significantly lower rate for $n = 6$ and $n = 12$ than for $n = 5$, 7, and 8 cannot fit either carbanion[6] or sp^3 radical formation.[7] It is, however, in good agreement with reactions involving sp^3–sp^2 hybridisation change,[5] and was also observed for the formation of planar free radicals.[8] So we have to assume the formation of a planar aminoalkyl radical (4) in step *b*.

(ii) If we assume the formation of a planar aminoalkyl radical intermediate even in ethereal solution, we may expect the formation of the same product in the reaction of lithium dihydroanthracenylide (1B) with each of the two stereoisomeric amino-nitriles (2B). The following results show, however, that this is not the case.

From the reaction of lithium dihydroanthracenylide with the *seq. trans*-isomer of the α-amino-nitrile (2B)[9] in ether, only one isomer of compound (6B) is formed: *seq. trans*-9-(4-t-butyl-1-piperidinocyclohexyl)dihydroanthracene, m.p. 126°, τ (CMe$_3$) 9·05,‡ hydrochloride m.p. 238°, τ (CMe$_3$): 9·05.‡ From the reaction of lithium dihydroanthracenylide with a mixture of 20% *seq. trans*- and 80% *seq. cis*-isomers of amino-nitrile (2B) obtained by the method of Mousseron *et al.*,[10] we obtain a mixture of 20% *seq. trans*- and 80% *seq. cis*-isomers of compound (6B) [*seq. cis*-isomer m.p. 144°, τ (CMe$_3$): 9·23;‡ hydrochloride m.p. 210°, τ (CMe$_3$): 9·11].‡ The configuration of these isomers is established from the chemical-shift differences of the t-butyl signals of the free amines and their hydrochlorides,[11] and this attribution of the configuration is in good agreement with other featurs of the n.m.r. spectra. These results show that the aminoalkylation of lithium dihydroanthracenylide occurs, within the limits of experimental error, with complete retention of the configuration.

Stereoselective radical reactions are well known and retention of the configuration has been observed in cage reactions[12] and in the reduction of cyclopropyl halides involving radical intermediates[13] or by the formation of strained radicals in the presence of high concentration of a scavenger[14] as well as in alkali-metal reductions,[15] but high stereospecificity with unstrained radicals is observed only in the frozen state.[16] The complete retention of configuration observed in the present reaction indicates that the aminoalkyl radical is generated in a similarly well ordered environment, in which the radical anion (1) is on the CN side of the complex (3). We consider this ordering as a consequence of the known ion-pair agglomeration of alkali-metal adducts of aromatic hydrocarbons and various salts.[17]

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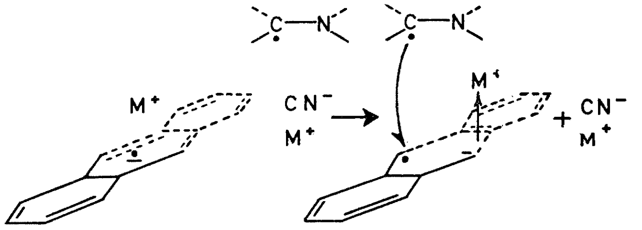
† An e.s.r. study confirms the radical character of this complex.[4]
‡ Chemical shift for CDCl$_3$ solution with Me$_4$Si as internal standard.

Such an agglomeration between compounds (3) and (1) may be represented as in the Figure.



FIGURE

So, if step *c* is very fast, as is known for radical combination processes,[18] product formation occurs before the $>$N–C· radical rotates or diffuses from the solvent cage. So the presence of CN–M on the one side of the radical $>$N–C· directs the approach of the radical anion (1B) to the same side. The C–C bond formation occurs after the lateral displacement of the metal dihydroanthracenylide and metal cyanide agglomeration.

Alkylation of alkali-metal adducts of aromatic hydrocarbons is also well known[19] so stereoselectivity can be expected for these reactions also.

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