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# Anionic reduced forms of electron-deficient arenes in reactions with C – C bond formation

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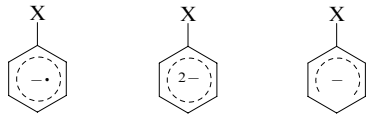
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**Abstract. The state-of-the-art research related to the use of stable anionic reduced forms (radical anions, dianions, cyclohexadienyl anions) of electron-deficient arenes as synthons for the design of short synthetic pathways from basic reagents to compounds difficult to prepare is analysed. The role of these anionic forms as models for the study of competition of polar and single-electron reaction mechanisms, especially for elucidation of relevant structural features, is considered. The bibliography includes 195 references.**

## I. Introduction

One- or two-electron reduction of an aromatic compound resulting in the formation of an anionic form (AF), *viz*., a radical anion (RA), a dianion (DA) or (after subsequent protonation) a cyclohexadienyl anion (CHDA), is an efficient method of its activation for the reaction with electrophilic reagents.[1–6]




RA DA CHDA

X = $NO_2$, $SO_2R$, C(O)R, CN.

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This approach is especially important in the case of electron-deficient arenes, which practically do not react with carbon-centred electrophiles and therefore cannot be readily used as simple 'building blocks' in the assembly of complex organic molecules. The transformation of an electron deficient arene into AF converts it into an electron-excessive reagent with high nucleophilic or reductive reactivity, keeping intact all elements of the initial structure. The transformation into RA also drastically increases the reactivity with respect to free radicals. The AF of functionalised arenes differ from their precursors in the direction of reactions with electrophiles and the ionic character of AF provides additional methods of the direction control. The electron-deficient character of arenes favours generation of relatively stable AF in preparatively significant concentrations and hence, their use as active anionic and radical synthons.

In the reactions with electrophiles, AF may act as nucleophiles (the $S_N$ mechanism), reducing agents (the ET mechanism), radical traps and as bases. Elucidation of the regularities determining the outcome of competition between different AF reaction pathways is extremely important for the development of theoretical background of application of reductive activation in synthesis and in case of competition of the $S_N$ and ET mechanisms, for further development of fundamentals of the reactivity of organic compounds.

Most of the studies of reaction mechanisms of arene AF are based on the use of electrochemical and spectroscopic kinetic methods. The suggestions about the reaction mechanisms in these cases are usually inferred from the comparison of the observed reaction rates with those of model reactions or with the reaction rates according to the ET mechanism calculated by the Marcus equation and its modifications.[7–23] However, in the cases where the structure of products is unknown, information obtained from kinetic tests about the reaction mechanism is inconclusive. In contrast, the 'structural' approach, which includes the application of mechanism-testing reagents, provides information about the type of AF reaction mechanism from the analysis of the structure of reaction products. This method was applied for studying the alkylation mechanism of AF of polynuclear arenes.[1–4,24–27]

The present review summarises the data on the reactions of AF of electron-deficient arenes (nitro compounds, ketones, alkyl aryl sulfones, nitriles, azaheterocycles) with electrophilic reagents resulting in a carbon–carbon bond formation. We discuss the studies where possible applications of arene reductive activation in synthesis have been disclosed on the basis of structure of the reaction products as well as the reaction mechanisms have been established with the help of special reagents.

## II. Reactions of anionic reduced forms of nitroarenes with alkylating and acylating reagents

The reactions of RA and DA of nitrobenzene (**1**) generated electrochemically or by treatment with alkali metals in THF, HMPT, DMF or liquid ammonia with primary and secondary alkyl halides,[28–31] dihaloalkanes,[32] as well as with carboxanhydrides and acyl halides [32,33] involve the nitro group and yield *N*,*O*-dialkyl- and *N*,*O*-diacyl-derivatives of phenylhydroxylamine, respectively (Scheme 1).[29,31] (Small amount of *N*,*N*-dialkylanilines are also produced in the former case). The yields of *N*,*O*-dialkylhydroxylamines increase with the increase in the mobility of the leaving group in the series $Bu^nCl < Bu^nBr < Bu^nI$ (69%, 90% and 99%, respectively [28]), polarity of the solvent (THF < THF–HMPT, THF–DMF, $NH_3$ < DMF) and the degree of reduction of substrate.[29–31] The reaction of the halide $Bu^tI$ significantly changes the alkylation products of RA $(\mathbf{1})^{-\bullet}$: alongside with the functional group transformation products, *viz*., [*N*-(*tert*-butyl)aniline and *N*-(*tert*-butyl)-*N*-phenylhydroxylamine], approximately the same amount of the benzene ring alkylation product, *viz*., *p*-(*tert*-butyl)nitrobenzene, is formed (see Scheme 1).[30,31,34] The same products are formed in the reactions of the nitrobenzene DA.[31]

The formation of hydroxylamine alkyl- and acyl-derivatives in the reactions with primary and secondary alkyl halides and acylating agents is attributed to the nucleophilic character of anionic forms of nitrobenzene.[28–33] The nitro group is the reaction centre of these molecules due to predominant localisation of the negative charge on this group.[35,36] The suggested $S_N$ mechanism of these reactions is supported by the observed increase in the yields of dialkylhydroxylamines in the series $Bu^i < Bu^s < Bu^n$, with the replacement of $Bu^nCl$ by $Bu^nI$ and with the increase in polarity of the solvent.[28–30] However, a different direction in the reaction with $Bu^tI$ and the very fact of alkylation in *para*-position of AF $(\mathbf{1})^{-\bullet}$ and $(\mathbf{1})^{2-}$ are reasonable to attribute to the ET mechanism, which includes the dissociative electron transfer from RA or DA to the alkyl halide followed by recombination of alkyl radical and RA $(\mathbf{1})^{-\bullet}$ (Ref. 30). Obviously, the replacement of $S_N$ mechanism by ET on going from primary and secondary alkyl halides to tertiary ones is caused, alongside with the steric hindrance for the nucleophilic attack, by increased affinity of alkyl halide to dissociative electron capture. As a result, the rate of electron transfer from RA $(\mathbf{1})^{-\bullet}$ is increased (Refs 8–10, 31). Thus the study of the dependence of logarithms of electron transfer rate constants ($\log k_{ET}$) on the standard potentials of reducing agents [8,10,37] for the reaction of RA $(\mathbf{1})^{-\bullet}$ with $Bu^tI$ makes it possible to estimate the value of $k_{ET}$, which was found to be $\sim 10^2$ litre $mol^{-1}$ $s^{-1}$ (Ref. 31). This value is 2–3 orders of magnitude larger than those for its isomers.

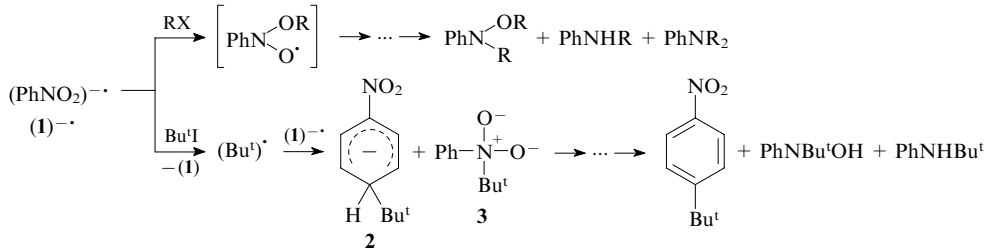
**Table 1**. The effects of a counter-ion, salt concentration and additives on the product ratio of *N*- and *C*-*tert*-butylation of radical anion $(\mathbf{1})^{-\bullet}$ in liquid ammonia.[34]

| Metal | Salt concentration /mol litre$^{-1}$ | Additive | N/C |
|---|---|---|---|
| Li | 0.1 | – | 0.65 |
| Na | 0.1 | – | 0.97 |
| K | 0.1 | – | 1.40 |
| Rb | 0.1 | – | 1.70 |
| Cs | 0.1 | – | 1.94 |
| Na | 0.1 | 15-crown-5 | 0.87 |
| Na | 0.1 | DCH-18-crown-6 [a] | 0.98 |
| K | 0.1 | DCH-18-crown-6 [a] | 0.71 |
| Na | 0.05 | – | 1.00 |
| Na | 0.5 | – | 1.00 |
| Na | 0.1 | NaI | 1.10 |
| Na | 0.1 | NaBr | 1.00 |

**Note**. The molar ratio of the salt of RA $(\mathbf{1})^{-\bullet}$ and $Bu^tI$ is 1 : 2.
[a] DCH is dicyclohexano.

The ratio of the *N*- and *C*-*tert*-butylation products (N/C) of RA $(\mathbf{1})^{-\bullet}$ remains the same [31] when the reaction with $Bu^tI$ takes place in the presence of cyclohexa-1,4-diene as the radical trap.[38,39] This implies that no selective inhibition of any competitive reaction pathways occurs and suggests the similarity of mechanisms of formation of intermediates **2** and **3** (see Scheme 1). However, their ratio is sensitive to factors affecting ionic association (Table 1), obviously due to a different extent of delocalisation of negative charge in the transition states (TS). The transition state of N-alkylation is similar to localised anion **3** (see Scheme 1) and exhibits higher electron affinity than TS of C-alkylation, which is similar to delocalised anion **2**.[34] The increase in the N/C ratio with the increase in the radius of alkali metal cation in the series $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$ was explained [34] by the increase in ionic association in this series due to the decrease in solvation of metal cation by liquid ammonia.[40] This, in turn, results in higher stabilisation of localised transition state of *N*-*tert*-butylation (similar to anion **3**). Lithium cation is the most solvated in liquid ammonia among the alkali metal cations,[40] and the ratio N/C ≈ 0.6, observed for the reactions of lithium salt of RA $(\mathbf{1})^{-\bullet}$ in this medium and of sodium salt in a

Scheme 1



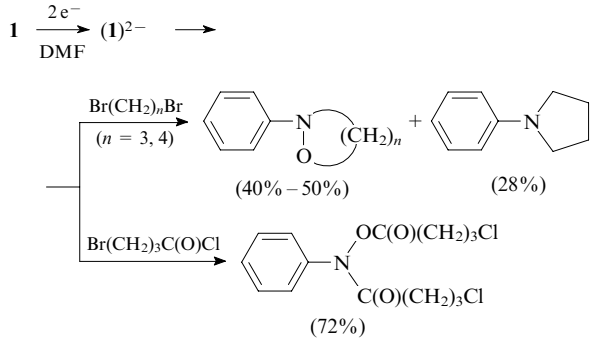

R = Me, $Pr^i$, $Bu^n$, $Bu^i$, $Bu^s$, Ac; X = Cl, Br, I, OAc.

$NH_3$–HMPT mixture with $Bu^tI$, probably reflects the regioselectivity of recombination of *tert*-butyl radical with free RA $(\mathbf{1})^{-\bullet}$. For the sodium salt of RA $(\mathbf{1})^{-\bullet}$ the N/C ratio decreases with the increase in polarity of the media in the series $NH_3$–THF (N/C = 5.7) > $NH_3$ (1.0) > $NH_3$–HMPT (0.6).[41]

Variation of sodium salt of RA $(\mathbf{1})^{-\bullet}$ concentration from 0.05 to 0.5 mol litre$^{-1}$ does not affect the composition of the *tert*-butylation products in liquid ammonia. This indicates that the type of ionic association of RA salt (predominantly, solvent-separated ion pairs[42]) is similar throughout this concentration range.

The addition of crown ethers does not virtually affect the yield and the N/C ratio of *tert*-butylation products of sodium salt of RA $(\mathbf{1})^{-\bullet}$. At the same time, the yield of the reaction products of potassium salt of RA $(\mathbf{1})^{-\bullet}$ is tenfold higher and the N/C ratio decreases twofold in the presence of crown ethers. Probably, this means that the ionic association of sodium salt remains unchanged while that of potassium salt becomes significantly weaker. Accordingly, the addition of a tenfold excess of NaBr and NaI decreases the yield of alkylation products of sodium salt of RA $(\mathbf{1})^{-\bullet}$ two- to fourfold, but does not change the N/C ratio. The increase in the yield due to complexation of sodium ion by crown ether is consistent with the increase in the concentration of more reactive weakly associated salts of RA $(\mathbf{1})^{-\bullet}$,[5] and the decrease in the N/C ratio, with similarity of the direction of recombination of RA $(\mathbf{1})^{-\bullet}$ with *tert*-butyl radical with the direction of free RA .

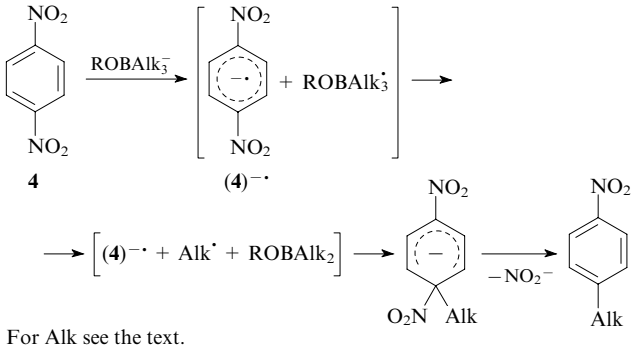
The reaction of electrochemically generated DA $(\mathbf{1})^{2-}$ with 1,3-dibromopropane or 1,4-dibromobutane in DMF results in hydroxylamine cyclic *N*,*O*-dialkyl derivatives due to alkylation of the nitro group oxygen atom and ring closure involving the nitrogen atom.[32]




*N*-Phenylpyrrolidine is also formed in the reaction of dianion with $Br(CH_2)_4Br$. Electrolysis of a mixture of nitrobenzene and 4-bromobutyryl chloride yields *N*,*O*-diacylhydroxylamine, which is a product of double acylation and substitution of the chlorine atom for bromine due to the chloride anion accumulation.

It was shown[29,30,32] that DA $(\mathbf{1})^{2-}$ reacts with primary and secondary alkyl halides according to the $S_N$ mechanism and with *tert*-butyl iodide, according to the ET mechanism, *i.e.* the alkylation mechanism depends on the structure of alkyl in the same way for both RA $(\mathbf{1})^{-\bullet}$ and DA $(\mathbf{1})^{2-}$. However, the DA is more reactive and produces higher yields of di(alkyl)phenylhydroxylamines.[30]

The reactions of *p*-dinitrobenzene (**4**) with trialkylboranes ($Et_3B$; $Bu^n_3B$; 9-R-9-borabicyclo[3.3.1]nonane, where R = cyclo-$C_nH_{2n+1}$ ($n$ = 5–7); 2-norbornyl; 2,6,6-trimethylbicyclo[3.1.1]hept-3-yl) in the presence of bases (PhOK, $Bu^tOK$, $Bu^tONa$, $Bu^tOLi$, $Pr^iONa$, NaH, $Bu^nLi$), occur *via* RA $(\mathbf{4})^{-\bullet}$ and afford the corresponding *p*-alkylnitrobenzenes in ~55%–85% yield with preformed alkylboranes and 20%–30% with alkylboranes generated *in situ*.[43,44]




For Alk see the text.

A suggested[44] reaction mechanism includes electron transfer from a complex anion formed by trialkylborane and a base to nitroarene. It is followed by intra-cage recombination of the RA of the substrate with alkyl radical, which is formed upon decomposition of alkoxyboranyl radical.

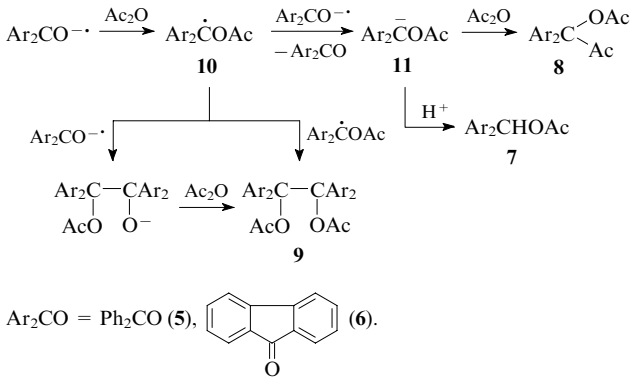
The replacement of one of the nitro groups by a less electron-withdrawing group (CN, Bz, $SO_2Ph$, CHO) significantly decreases the yields of *p*-alkylnitrobenzenes. In all cases, it was other than $NO_2$ group in the *para*-position that was substituted. According to the ET mechanism, an alkyl radical displaces the substituent at the carbon atom possessing the highest spin density (as indicated by quantum chemical calculations). These results suggest a high selectivity of intra-cage recombination in contrast to the diffuse recombination in the reactions of AF of nitrobenzene with $Bu^tI$ (see above) and in the reactions of AF of dicyanobenzenes with alkyl halides (see Section V).

## III. Reactions of anionic reduced forms of aromatic ketones and their derivatives with C-electrophiles

### 1. Acylation

The acylation of RA and DA of benzophenone (**5**) and fluorenone (**6**) generated by both electrochemical reduction in DMF and MeCN[32,45,46] and interaction with alkali metals (Li, Na) in THF and dimethoxyethane (DME),[47,48] by carboxanhydrides and acyl chlorides (mainly by acetic anhydride and acetyl chloride) (Scheme 2) involves the carbonyl group. Acetates **7** and **8** and in some cases diacetoxypinacone (**9**) are the main reaction products.[47] Ester **8** is the main reaction product of RA $(\mathbf{5})^{-\bullet}$ with acetic anhydride, but ester **7** is the predominant product in the presence of crown ethers or in dilute solutions.[45,48] It was shown by the CIDNP method[48] that initially the O-acylation of the radical anion (ketyl) takes place followed by the reduction of the thus obtained acetoxy-

Scheme 2




$Ar_2CO$ = $Ph_2CO$ (**5**),  (**6**).

diphenylmethyl radical **10** by another RA molecule, resulting in the formation of carbanion **11** and then of esters **7** and **8**.

The acylation products of DA $(\mathbf{5})^{2-}$ and $(\mathbf{6})^{2-}$ are similar to those of the respective RA described above. The mechanism of their formation may include electron transfer from DA to the acylating agent.[48]

## 2. Alkylation

The study of the mechanism of alkylation of AF of ketone **5** was started by a series of papers.[49–53] Several possible mechanisms were considered for the reaction of sodium salt of RA $(\mathbf{5})^{-\bullet}$ with EtBr in liquid ammonia yielding an alcohol **12a**: reduction of EtBr to an organometallic compound and the reaction of the latter one with ketone **5**; disproportionation of RA followed by DA alkylation; reduction of the alkyl halide resulting in the formation of the alkyl radical which later undergoes recombination with RA; nucleophilic attack of the alkyl halide by an oxygen atom of RA followed by reduction of the formed radical **13** to anion **14** which, in turn, undergoes the Wittig rearrangement (only the latter mechanism is shown).

$$(\mathbf{5})^{-\bullet}\,Na^+ \xrightarrow[-NaBr]{S_N\ EtBr} \underset{\mathbf{13}}{Ph_2\dot{C}OEt} \xrightarrow[-(\mathbf{5})]{(\mathbf{5})^{-\bullet}} \longrightarrow (Ph_2\bar{C}OEt)Na^+ \xrightarrow{\text{the Wittig rearrangement}} (Ph_2EtCO^-)Na^+ \longrightarrow \underset{\mathbf{12a}}{Ph_2EtCOH}$$

**14**

All these mechanisms were rejected as simulation of the pathways mentioned revealed disagreement between the observed and the calculated kinetic parameters and the quantitative composition of the alkylation products of RA $(\mathbf{5})^{-\bullet}$. For the interaction of sodium salt $(\mathbf{5})^{-\bullet}$ with EtBr in liquid ammonia, the most probable reaction mechanism includes nucleophilic attack of the alkyl halide by the carbon atom of the carbonyl group of RA yielding intermediate radical **15** followed by its reduction to anion **16** which, in turn, is transformed into the reaction product **12a**.[49–53]

$$(\mathbf{5})^{-\bullet}\,Na^+ \xrightarrow[-NaBr]{S_N\ EtBr} \underset{\mathbf{15}}{Ph_2EtCO^{\bullet}} \xrightarrow[-(\mathbf{5})]{(\mathbf{5})^{-\bullet}} \underset{\mathbf{16}}{(Ph_2EtCO^-)Na^+} \longrightarrow \mathbf{12a}$$

The dependence of the composition of the alkylation products on the structure of alkyl halides was examined in order to investigate the reactivity of RA $(\mathbf{5})^{-\bullet}$.[49–61] This RA generated by the interaction of ketone **5** with alkali and alkaline-earth metals in THF and liquid ammonia is C-alkylated in α-, *para*- and *ortho*-positions yielding alcohol **12**, 4- and 2-alkylbenzophenones (**17** and **18**, respectively), and also O-alkylated to form ethers **19** and **20**.

$$(\mathbf{5})^{-\bullet}M^+ \xrightarrow{RX} \underset{\mathbf{12a-h}}{Ph_2RCOH} + Bz\text{–}C_6H_4\text{–}R + \underset{\mathbf{17a-h}}{} + Bz\text{–}C_6H_3(R)\text{–} + \underset{\mathbf{18a-h}}{} + \underset{\mathbf{19a-h}}{Ph_2HCOR} + \underset{\mathbf{20a-h}}{Ph_2RCOR}$$

M = Li, Na, K, Cs, $^1/_2$ Ba, $^1/_2$ Mg; R = Et (**a**), Me (**b**), $Pr^n$ (**c**), $Pr^i$ (**d**), $CH_2{=}CH(CH_2)_4$ (**e**), $Bu^t$ (**f**), *tert*-$C_5H_{11}$ (**g**),  (**h**); X = Br, I.

The content of α-alkylation products (alcohols **12**) decreases and the content of O-alkylation products (ethers **19** and **20**) increases with the increase in the atomic radius of the counter-ion and enhancement of its solvation.[54–57] In the reactions with tertiary alkyl halides, the RA $(\mathbf{5})^{-\bullet}$ undergoes only C-alkylation yielding compounds **12f** and **17f** (Refs 54 and 55) in the case of $Bu^tI$ and compounds **12g**, **17g**, **18g** in the case of *tert*-$C_5H_{11}I$.[57] The increase in the effective charge of cation of the salt of radical anion $(\mathbf{5})^{-\bullet}$ decreases the extent of *para-tert*-butylation in THF while in liquid ammonia the ratio **12f**:**17f** does not depend on the nature of the cation.[56] The latter fact as well as EPR data suggest that in liquid ammonia the salts of RA $(\mathbf{5})^{-\bullet}$ exist either as solvent-separated ionic pairs or as free ions.[58]

Analysing the effects of various factors on the mechanism of reactions of RA $(\mathbf{5})^{-\bullet}$ with alkyl halides, one may undoubtedly conclude that the reactions with tertiary alkyl halides follow the ET mechanism yielding only C-alkylation products. The probability of the $S_N$ mechanism contribution increases for secondary and primary alkyl halides, the nucleophilic attack in these cases is carried out by both oxygen atom and α-,[49–53] *para*- and *ortho*-carbon atoms[54–57] of the radical anion.

Lithium salt of RA $(\mathbf{5})^{-\bullet}$ reacts with tertiary alkyl iodides faster than with the primary ones. Thus the rate constants are equal to 0.15 (for *tert*-$C_5H_{11}I$), 0.033 (MeI) and 0.086 litre $mol^{-1}\ s^{-1}$ [$CH_2{=}CH(CH_2)_4$ I]. In the latter case,[57] C-alkylation products **12e**, **17e**, **18e** are also formed according to the ET mechanism. The reagent of the 'radical clock' type *viz*., hex-5-enyl iodide, was used for the determination of recombination rate of RA with an alkyl radical ($k_{rec}$). Accepting an electron, this reagent affords hex-5-enyl radical, which readily isomerises into cyclopentylmethyl radical ($k_i \approx 10^5\ s^{-1}$ at 20 °C).[62] As a result, the products, containing hex-5-enyl fragment (**12e**, **17e**, **18e** ), as well as those containing cyclopentylmethyl fragment (**12e$^i$**, **17e$^i$**, **18e$^i$**) were obtained.

$$(\mathbf{5})^{-\bullet} + \text{hex-5-enyl-I} \xrightarrow[-(\mathbf{5}),\ -I^-]{ET} \text{hex-5-enyl}^{\bullet} \longrightarrow$$

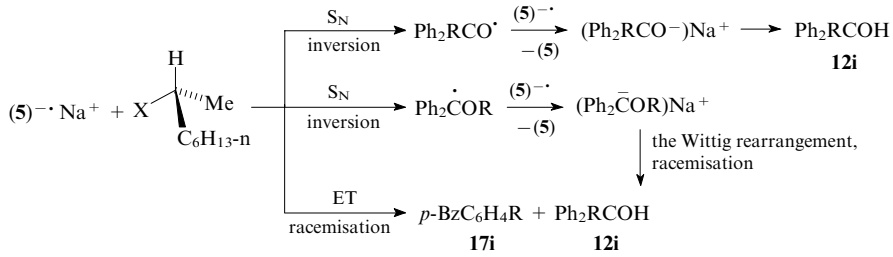
$$\xrightarrow[k_{rec}]{(\mathbf{5})^{-\bullet}} \mathbf{12e} + \mathbf{17e} + \mathbf{18e}$$

$$\xrightarrow{k_i} \text{cyclopentylmethyl}^{\bullet} \xrightarrow[k_{rec}]{(\mathbf{5})^{-\bullet}} \mathbf{12e^i} + \mathbf{17e^i} + \mathbf{18e^i}$$

The ratio of the yields (**12e** + **17e** + **18e**):(**12e$^i$** + **17e$^i$** + **18e$^i$** ), which is equal to $(k_{rec}\cdot[(\mathbf{5})^{-\bullet}]_0)/k_i$ and is the measure of the competition between the recombination of hex-5-enyl radical with RA and its isomerisation, decreases from 16 to 0.5 upon a decrease in the initial concentration of RA $[(\mathbf{5})^{-\bullet}]_0$ from 0.05 to 0.001 mol litre$^{-1}$. Using these data, the value of $k_{rec}$ was estimated ($\sim 1.5\times10^8$ litre $mol^{-1}\ s^{-1}$).

It was shown, using the reaction of RA $(\mathbf{5})^{-\bullet}$ with tetrahydrofurfuryl iodide as an example, that the alkyl radicals generated during the reaction recombine with RA rather than are reduced, because pent-4-ol, which is readily formed from the furfuryl anion, has not been observed among the reaction products.[57] The ET mechanism for C-alkylation of RA $(\mathbf{5})^{-\bullet}$ with methyl iodide was also confirmed by the value of the kinetic isotope effect (KIE) when a deuterated reagent was used ($k_{CH_3I}/k_{CD_3I} \approx 1.7$).[63] It is known that this mechanism is characterised by larger KIE values ($k_H/k_D = 1.1-1.7$) than the $S_N$ mechanism ($k_H/k_D = 1.056-0.980$).[64, 65] It should be noted that in similar reaction of sodium salt of naphthalene RA in THF, which proceeds by ET mechanism, and in the reduction

Scheme 3

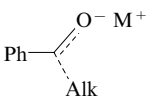



R is oct-2-yl (2-Oct); X = Br, I, OMs.

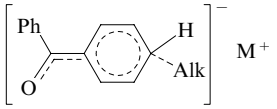
of MeI on platinum cathode the values of $k_{CH_3I}/k_{CD_3I}$ are close to those for the methylation of RA $(\mathbf{5})^{-\cdot}$ (Ref. 63).

The $S_N$ mechanism of the formation of C-alkylation products of sodium salt of RA $(\mathbf{5})^{-\cdot}$ was confirmed for the reactions with optically active 2-substituted octanes.[59,60] The enantiomer of alcohol **12i** with inverted configuration of the chiral centre is predominantly formed in this reaction. The extent of inversion increases in the series I < Br < OMs. The contribution of the $S_N$ mechanism is probably higher than it seems from the value of inversion of oct-2-yl fragment because a parallel formation of compound **12i** is possible through O-alkylation followed by the Wittig rearrangement, which increases the racemisation (Scheme 3).[60] The second reaction product, ketone **17i**, is racemic, which suggests the ET mechanism.[59]

The discussed approaches reveal possible alkylation mechanisms of RA $(\mathbf{5})^{-\cdot}$, but do not allow reliable determination of their contributions to the formation of a particular reaction product. Regioselectivity of the alkylation reaction may be directly connected with the mechanism only for the reactions with tertiary alkyl halides [56] and hex-5-enyl iodide,[57] because in both cases the ET mechanism is evident. The ratio of α- and *para*-alkylation products reflects the direction of diffuse recombination of the RA and alkyl radical. The extent of recombination on α-carbon atom decreases with the increase in steric hindrance on going from cyclopentylmethyl radical to *tert*-butyl and *tert*-pentyl radicals. The decrease in the extent of *para*- alkylation with the increase in the charge and solvation of cation [56] in the salt RA $(\mathbf{5})^{-\cdot}$ may be caused by the distribution of density of unpaired electron and of the charge. These factors respectively relate the transition states of α- (**21**) and *para*-alkylation (**22**) to both RA and the intermediate anions that are the precursors of final products. The effect of the cation agrees with both factors; however there is no explanation for the solvent effect.




**21**




**22**

The mechanism of O-alkylation has not been specially studied; however there are some indications of $S_N$ mechanism realisation, such as the increase in the yield of ethers **19** and **20** with the increase in the radius and solvation of the cation of the salt of RA $(\mathbf{5})^{-\cdot}$, as well as the absence of O-alkylation products in the reactions with tertiary alkyl halides and hex-5-enyl iodide.[57]

In contrast to RA $(\mathbf{5})^{-\cdot}$, it is the carbonyl group of DA $(\mathbf{5})^{2-}$ that is predominantly alkylated with $Pr^iBr$, $Bu^tBr$, MeX (X = Br, I, OTs) and dimethyl sulfate in THF and liquid ammonia.[55,66] Methylation of DA $(\mathbf{5})^{2-}$ furnishes ether **20b**. The products of α- (**12d**,**f**) and *para*-alkylation (**17d,f** ) are formed in the reactions with branched (R = $Pr^i$, $Bu^t$) alkyl halides while O-alkylation does not occur.[55] In this case, the dependence of direction on the character of the alkylating agent is similar to that observed in the reactions of RA; however, there is no information on the reaction mechanism.

Electrochemical reduction of fluorenone **6** in the presence of alkyl halides (MeCl, $Pr^iCl$ and $Pr^iBr$) yields the O-alkylation products.[67] It was shown by the pulse radiolysis method that the rate of alkylation of RA $(\mathbf{6})^{-\cdot}$ with alkyl bromides in HMPT ($k_{EtBr} = 3.5 \times 10^8$, $k_{Pr^iBr} = 2.5 \times 10^6$, $k_{Bu^tBr} = 1.6 \times 10^6$ litre $mol^{-1}$ $s^{-1}$ at 20 °C) and the contribution of $S_N$ mechanism drastically decrease on transition from the primary alkyl substituent to secondary and tertiary ones. In the latter case, the alkylation follows only the ET mechanism.[68] If the ET mechanism was valid for all the alkyl halides, one could expect an increase in the rate in reverse order of relative reduction ability [$E^\circ_{EtBr} = -2.30$, $E^\circ_{Pr^iBr} = -2.24$, $E^\circ_{Bu^tBr} = -2.02$ V, cyclic voltammetry (CV), disk Pt-electrode, *vs.* Ag/AgI electrode].[68] No information about the structure of obtained products is reported and therefore the ratio of alkylation direction in competing mechanisms is unknown.

## 3. Reactions of benzophenone anionic forms with aryltrimethylammonium salts

The methods of testing the reaction mechanisms described above provide rather uncertain results, the reason is that the same centre of alkyl halides reacts in both the $S_N$- and ET-process. In contrast, the application of aryltrimethylammonium salts as the model reagents where the reaction centre is different for different reaction mechanisms, makes it possible to differentiate the products according to the mechanism of their formation.[69–72] It is known that the reduction of the cations $ArMe_3N^+$ results in cleavage of the N–Ar bond to give an aryl radical and trimethylamine, while in the nucleophilic attack it is the N–Me bond that is cleaved, which is followed by transfer of the methyl group to the nucleophile and formation of aryldimethylamine **23** (Scheme 4).[69–71]

The reactions of potassium salts of ketone **5** AF with $PhMe_3NClO_4$ in THF result in the formation of two sets of compounds (Scheme 4, in this particular case Ar = Ph). The methylated derivatives **12b**, **17b**, **19b**, **20b** (in the ratio 1 : 9 : 2 : 1) are formed from the RA by the $S_N$ mechanism, while the phenylation products **24**, **25**, **26** (1 : 7 : 1) are formed by the ET mechanism; the ratio $S_N$ : ET is ~3 : 2. The structures of the products suggest that not only oxygen atom but also α- and *para*-carbon atoms are the nucleophilic centres in RA $(\mathbf{5})^{-\cdot}$. Only *C*-methylation product (**12b**) and *C*-phenylation products **24**, **25**, **26** (3 : 1 : 1) were obtained from DA $(\mathbf{5})^{2-}$.

The attractiveness of aryltrimethylammonium salts as model reagents is that varying the nature of a substituent in the aryl fragment allows change in its activity as the ET

Scheme 4

$(\mathbf{5})^{-\bullet}$ [or $(\mathbf{5})^{2-}$] $\xrightarrow{ArMe_3N^+}$

$\xrightarrow{S_N}$ $Ph_2MeCOH$ (**12b**) + $p$-$MeC_6H_4Bz$ (**17b**) + $Ph_2HCOMe$ (**19b**) + $Ph_2MeCOMe$ (**20b**) + $ArMe_2N$ (**23**)

$\xrightarrow{ET}$ $Ph_2ArCOH$ (**24**) + $Ph_2ArCOMe$ (**25**) + $p$-$ArC_6H_4Bz$ (**26**) + ArH + $NMe_3$

Ar = Ph, 4-$MeC_6H_4$, 3-$MeC_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-$ClC_6H_4$, biphenyl-4-yl, 1-naphthyl.

reaction centre. This makes possible to study the effect of the nature of the reagent on the ratio of the reaction rates in the $S_N$ and ET mechanisms. It was shown for RA $(\mathbf{5})^{-\bullet}$ that the increase in electron affinity of the aromatic fragment of the ammonium salt decreases the contribution of the $S_N$ mechanism (Table 2).[69] As the increase in the electron affinity of the reagent should accelerate both $S_N$- and ET-processes, the observed behaviour indicates a higher sensitivity of the reaction rate in the ET mechanism to this factor. This agrees with the values of activity coefficients in the Hammett equations for the rates of competing processes: $\rho_{SN}$ is $\sim 1.5-2$ (for the reactions of aryltrimethylammonium salts with nucleophiles) and $\rho_{ET} \approx 8$ (estimated by using the Marcus equation [69]).

**Table 2**. The effect of the aryl fragment of the salt $ArMe_3NClO_4$ on the contribution of the $S_N$ mechanism to the formation of the reaction products with potassium salt of radical anion of benzophenone in THF.[70]

| Ar | $-E_{1/2}$/V | $\sigma^-$ (see [a]) | $S_N$ contribution (%) |
|---|---|---|---|
| 4-$MeOC_6H_4$ | 2.72 | −0.27 | 100 |
| 4-$MeC_6H_4$ | 2.66 | −0.17 | 96 |
| 3-$MeC_6H_4$ | 2.65 | −0.07 | 96 |
| 3-$MeOC_6H_4$ | 2.59 | −0.12 | 69 |
| Ph | 2.56 | 0 | 59 |
| 4-$PhC_6H_4$ | 2.34 | 0.12 | 14 |
| 3-$ClC_6H_4$ | 2.16 | 0.37 | 11 |
| 1-Naphtyl | 2.00 | – | 6 |

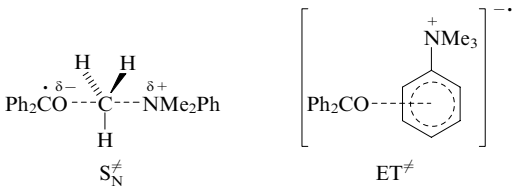
[a] Values for the substituent in the benzene ring.

The contribution of the $S_N$ mechanism correlates better with the values of the half-wave potential ($E_{1/2}$) of polarographic reduction rather than with the $\sigma^-$ constants of substituents in the benzene ring of ammonium salts. Remarkably, the position of the methyl group does not affect this contribution. A possible reason is insensitivity of the rate of the $S_N$ process to this factor, while the reaction centre of the ET process is the benzene ring as a whole.[69, 70]

The conclusion about higher sensitivity of the ET-process rate to the structure of the reagent [69] is consistent with the increase in configuration inversion of oct-2-yl fragment of alcohol **12** in the series I < Br < OMs in the reaction of sodium salt of RA $(\mathbf{5})^{-\bullet}$ with enantiomeric 2-substituted octanes.[59] The ability of 2-OctX (X = I, Br, OMs) to accept an electron [$E_{1/2}$ are equal to −1.69, −2.34 and −2.72 V, respectively, *vs.* normal calomel electrode (NCE) [73]] varies to a greater extent than the nucleofugicity of the X group in this series.[5, 74] Therefore, it is logical to assume that the dependence found is caused first of all by the sensitivity of the transformation rate according to the ET mechanism to the nature of X.

The ratio $S_N$ : ET in the reactions of potassium salts of RA of ketones $RC_6H_4Bz$ (R = 4-Me, 3-Me, 3-OMe, 3-F) with $PhMe_3NClO_4$ in THF is $\sim 1.5-2$ and does not virtually depend on the type of the substituent R.[70] This means that the rates of the reactions that follow different competitive mechanisms are almost equally sensitive to the character of the substituent R. The values of $\rho_{SN} \approx -4.7$ and $\rho_{ET} \approx -3.5$, estimated from the effect of a substituent on the kinetic basicity and oxidation potentials of RA of monosubstituted benzophenone derivatives, agree with this observation.

The character of the cation and the solvation properties of the medium significantly affect the rate and regioselectivity of the reactions of RA salts of ketones with alkyl halides [49–61] and $ArMe_3NClO_4$ salts.[70, 72] Probably, the ratio of various types of ionic associates of metal ketyls [75] as well as that of the nucleophilic and electron-donating components of their reactivity are affected by these factors. The effect of ionic association on the ratio of $S_N$ and ET mechanisms in the reactions of alkali metal salts of RA $(\mathbf{5})^{-\bullet}$ with $PhMe_3NClO_4$ was studied by varying the metal type (Li, Na, K), solvent (THF and HMPT) and addition of compounds that form complexes with a metal cation (dibenzo-18-crown-6 and tetramethylethylenediamine).[70, 72] It was found that the decrease in the counter-ion radius in the RA salt reduces the contribution of the $S_N$ mechanism from 59% to 11% for the reactions in THF. As the transition from potassium ketyl to lithium ketyl in THF is accompanied with stronger ionic association, the initial system becomes more stable than the $S_N$- and ET-transition states ($S_N^{\neq}$ and $ET^{\neq}$, respectively) and both competing processes should be retarded.[5] The decrease in the contribution of the mechanism is probably caused by partial neutralisation of the nucleophile charge in the transition state. As a result, the $S_N$ transition state shows lesser affinity to the metal cation and is less stable than the ET-transition state where the negative charge is delocalised, but not neutralised.[5, 70, 72]



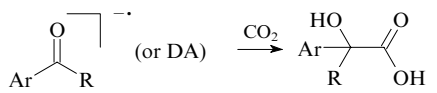

$S_N^{\neq}$ $ET^{\neq}$

Hence the activation energy of the $S_N$ process is more sensitive to the type of the alkali metal.[70, 72] This conclusion is also valid for the reactions of RA $(\mathbf{5})^{-\bullet}$ with alkyl halides.

The increase in solvent polarity on transition from THF to HMPT increases the contribution of the ET pathway up to 83%–87%. In this case, the type of the metal cation does not virtually affect the ratio of the competing pathways in the reaction of RA $(\mathbf{5})^{-\bullet}$ with $PhMe_3NClO_4$, because it is free ions that mainly determine the reactivity in HMPT.[72]

Diaryl ketone RA and DA generated by reduction of ketones with alkali metals in liquid ammonia, dimethoxyethane or THF, and also electrochemically in DMF, acetonitrile, *N*-methylpyrrolidone find diverse applications as nucleophilic synthons. These transformations predominantly involve the keto group and only rarely the aromatic ring.

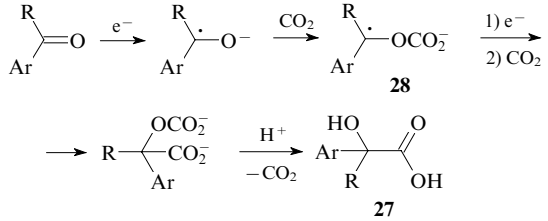
The anionic forms of aromatic ketones add $CO_2$ to the carbonyl carbon atom yielding α-aryl-α-hydroxy carboxylic acids **27**.[76–88]



**27** (6%–90%)

Ar = Ph, biphenyl-4-yl, fluoren-2-yl, 4-$MeC_6H_4$, 3-$MeC_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 2-$FC_6H_4$, 4-$FC_6H_4$;
R = Me, cyclo-$C_6H_{11}$, Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 4-$FC_6H_4$.

The *ortho*- and *para*-carboxylation was observed only for dilithium salt of DA of pheny cyclohexyl ketone in THF.[77, 87] The yield of acids **27** increases on going from RA to DA and from chemical to electrochemical generation of these AF. The highest yields (80%–90%) were obtained for 2-acetylfluorene and 4-acetylbiphenyl,[79] benzophenone and a series of its chloro- and fluoro-derivatives [78] in DMF. The presence of the halogen atom in the reaction products indicates that the rate of carboxylation is at least two orders of magnitude larger than that of decomposition of RA even for chloro-derivatives of ketone **5**.[78] The following process was suggested.[86]

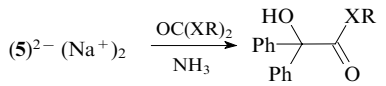


**27**

Ar = Ph, biphenyl-4-yl, fluoren-2-yl, 4-$MeC_6H_4$, 3-$MeC_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 2-$FC_6H_4$, 4-$FC_6H_4$;
R = Me, cyclo-$C_6H_{11}$, Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 4-$FC_6H_4$.

Upon one-electron reduction of a ketone, the RA reacts with $CO_2$ as the O-nucleophile. Then either electrochemical or chemical (under the action of RA) reduction of RA **28** takes place, followed by addition of the second $CO_2$ molecule to the carbonyl carbon atom of the dianion formed. Protonation and decarboxylation occur during workup of the reaction mixture.

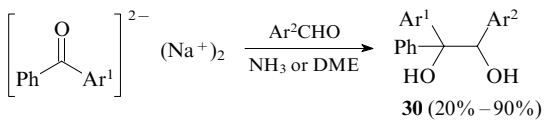
Benzilic acid esters **29** are formed in the reaction of sodium salts of DA $(\mathbf{5})^{2-}$ with dialkyl carbonates and thiocarbonates in liquid ammonia.[76]



**29** (70%–77%)

XR = OMe, OEt, $O(CH_2)_2NEt_2$, $S(CH_2)_2NEt_2$.

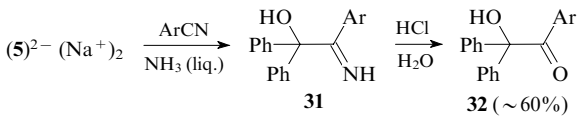
The reaction of DA of diaryl ketones with aromatic aldehydes in DME and liquid ammonia yields glycols **30**.[76]



**30** (20%–90%)

$Ar^1$ = Ph, 4-$MeC_6H_4$, 2-$MeC_6H_4$, biphenyl-2-yl;
$Ar^2$ = Ph, 4-$MeOC_6H_4$.

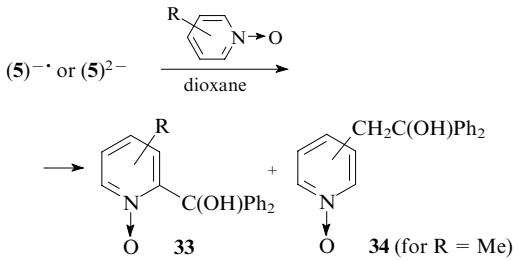
The highest yield of triphenylglycol ($Ar^1 = Ar^2$ = Ph, 91%) was obtained in the reaction of dipotassium salt of DA $(\mathbf{5})^{2-}$ with benzaldehyde in liquid ammonia.[89] The reaction of this DA with aromatic nitriles in liquid ammonia results in ketimines **31**, hydrolysis of which affords α-arylbenzoins **32**.[76]



**31** **32** (~60%)

Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$.

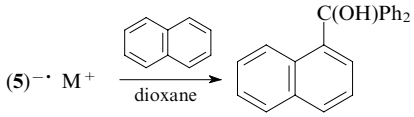
The hydroxydiphenylmethyl group is introduced in the α-position of heterocycles in the reaction of alkali salts of AF of ketone **5** with pyridine, picoline and quinoline *N*-oxides in dioxane [90–94] yielding alcohols **33**. In addition, alcohols **34** are formed from picoline *N*-oxides as a result of hydroxyalkylation of the methyl group. The highest yields were obtained in the reactions of lithium salts of DA.



**33** **34** (for R = Me)
(30%–90%)

R = H, Me, 2,3-benzo.

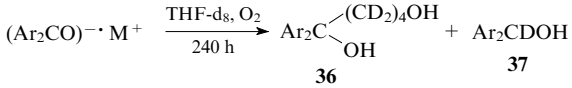
1-Naphthyldiphenylmethanol (**35**) is formed in the reaction of salts of RA $(\mathbf{5})^{-\bullet}$ with naphthalene in dioxane.[95] The highest yield (~50%) was obtained in the reaction with lithium salt, which was explained by the lowest extent of ionic association of the corresponding RA salt.[96]



**35** (15%–50%)

M = Li, Na, K.

Prolonged (more than 200 h) treatment of alkali salts of DA $(\mathbf{5})^{2-}$ and $(\mathbf{6})^{2-}$ with THF-$d_8$ results in *C*-4-hydroxybutylation of the carbonyl carbon atom and formation of alcohols **36** in 75% and 55% yields in the case of most active lithium salts.[97] Noticeable amounts of alcohols **37** were obtained from Na and K salts.



**36** **37**

$Ar_2CO$ = **5** or **6**; M = Li, Na, K.

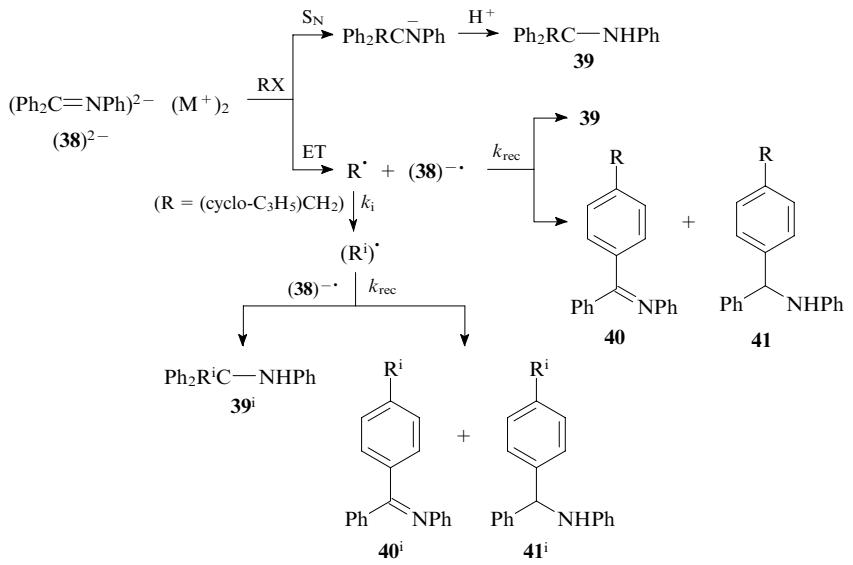
## 4. Alkylation of benzophenone anil dianion

Benzophenone anil dianion (**38**) generated by treatment with an alkali metal in THF, undergoes C-alkylation of azomethine group to yield amine **39** and of the *para*-position of the benzene ring to give anil **40** and aniline **41** (Scheme 5).[98–100]

Obviously, the alkylation of DA $(\mathbf{38})^{2-}$ with *tert*-alkyl and adamantyl halides follows the ET mechanism.[98]

The character of reactivity of DA $(\mathbf{38})^{2-}$ with respect to primary alkyl halides was determined using cyclopropylmethyl halides. The products containing not only cyclopropylmethyl, but also but-3-enyl fragments are formed in these reactions (see Scheme 5). However, their orientation is different and therefore it is unlikely that the same mechanism operates in both cases. Alkylation of the aromatic rings yields only compounds

Scheme 5

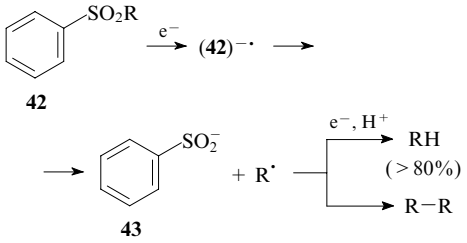


M = Li, Na, K; X = Cl, Br, I; R = Pr$^i$, Bu$^t$, *tert*-$C_5H_{11}$, 1-Ad, 2-Ad, (cyclo-$C_3H_5$)$CH_2$; R$^i$ = $CH_2$=$CH(CH_2)_2$; Ad is adamantyl.

containing the but-3-enyl fragment (**40**$^i$ and **41**$^i$) and therefore proceeds according to the ET mechanism, while the alkylation of the azomethine group affords compounds with both cyclopropylmethyl (**39**) and but-3-enyl (**39**$^i$) fragments, which suggests realisation of both $S_N$ and ET mechanisms. Alkyl chlorides do not produce isomerisation products, which is in favour of the $S_N$ mechanism. However, isomers were obtained in the reactions with bromides and iodides, in a higher yield in the latter case. This supports the conclusion (see above) about higher sensitivity of the reaction rate in the ET mechanism in comparison with the $S_N$ mechanism, to the type of the halogen atom.[57, 59, 69, 73] The increase in the yield of these products was also observed in the series K < Na < Li, which agrees with the hypothesis [57, 72] about higher sensitivity of the reaction rate in the $S_N$ process to the type of counter-ion of AF salt. The results of the reactions of salts of DA $(\mathbf{38})^{2-}$ with Pr$^i$Hal agree with the trends revealed:[100] the yield of amine **39** formed according to the $S_N$ mechanism increases on going from the iodide to chloride and from lithium salts of DA to potassium salts.

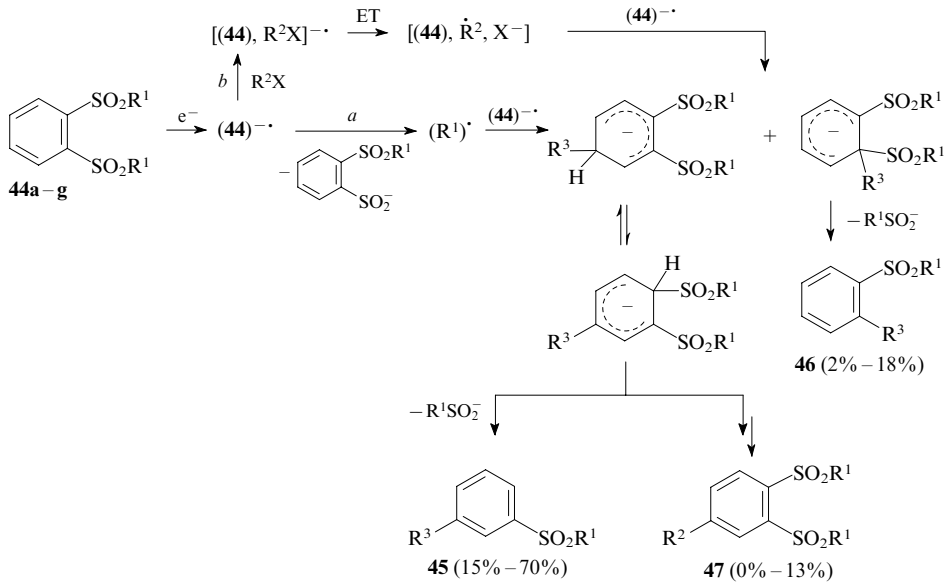
## IV. Reactions of radical anions of alkyl aryl sulfones with alkyl halides

Radical anions generated upon cathode reduction of alkyl aryl sulfones **42** (Refs 101–103) are unstable and dissociate yielding arylsulfinate anion **43** and an alkyl radical, which is predominantly reduced to the alkane.



The alkyl radical formed from RA of *ortho*-disulfones **44a–g** [104–106] recombines with the second equivalent of RA

Scheme 6



R$^1$ = Me (**a**), Et (**b**), Pr$^n$ (**c**), Bu$^n$ (**d**), n-$C_5H_{11}$ (**e**), n-$C_6H_{13}$ (**f**), n-$C_8H_{17}$ (**g**); R$^2$X = Pr$^i$Br, Bu$^n$Br, Bu$^n$I, Bu$^i$Br, n-$C_7H_{15}$Br, n-$C_8H_{17}$Br, *sec*-$C_8H_{17}$Br, $CH_2$=$CH(CH_2)_4$Br, n-$C_{18}H_{37}$Br, $Br(CH_2)_4$Br, $Br(CH_2)_4$Cl, $Br(CH_2)_{10}$Br, $BrCH_2CH(Me)CH_2Cl$; R$^3$ = R$^1$ (pathway *a*) or R$^2$ (pathway *b*).

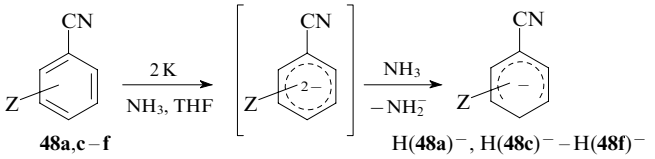
$(\mathbf{44})^{-\bullet}$ entering *ipso*- or *para*-positions in respect of one of the alkylsulfonyl groups to give ultimately alkylated sulfones **45** and **46** with preponderance of the former (Scheme 6). Thus electrolysis of equimolar mixture of disulfones **44b** and **44d** results in the formation of a mixture of all four possible sulfones **45** in approximately equal amounts.

The overall yield of sulfones **45**–**47** in the electrolysis in the presence of excess of an alkyl halide is equal to 60%–80%.[106] The products of *para*-alkylation **45** and **47** are predominant. In the reactions with α,ω-dibromo- and -bromochloroalkanes, the bromine atom is substituted by an aromatic fragment. No products of substitution of the chlorine atom and bisarylation of the haloalkane were detected. Total racemisation occurs with the optically active *sec*-$C_8H_{17}Br$ which rules out the $S_N$ mechanism. The absence of products containing the cyclopentylmethyl fragment upon electrolysis of sulfone **44b** in the presence of hex-5-enyl bromide is explained by the higher rate of recombination of RA $(\mathbf{44b})^{-\bullet}$ with the hexenyl radical in comparison with the rate of isomerisation of the latter (Scheme 6).[1,2,107] The fact that the addition of an alkyl halide in CV of sulfones **44** makes reduction irreversible without increase in the current was regarded[105] as an indication of transient formation of a complex of RA $(\mathbf{44})^{-\bullet}$ with the alkyl halide followed by intracomplex electron transfer (see Scheme 6). Regioselectivity of recombination of the generated alkyl radical with RA is mainly determined by steric factors.[106]

## V. Alkylation and cyanoarylation of anionic reduced forms of aromatic nitriles

The anionic forms of aromatic nitriles differ from AF of nitroarenes and aromatic ketones by more favourable distribution of excess charge density for the molecular skeleton modification: 70%–80% of it is localised in the ring.[108–113] In most detail, the structures of products, the mechanism and regioselectivity of alkylation have been studied for the reactions of alkali salts of AF of benzonitrile (**48a**),[114–117] its 2-methoxy- (**48b**),[118] 2-methyl- (**48c**),[117] 3-methyl- (**48d**),[117,119] 4-methyl derivatives (**48e**),[117,120] 1-naphthonitrile (**48f**),[115–117,121,122] 9-cyanoanthracene (**49**),[123,124] phthalo- (**50**)[125,126] and terephthalonitriles (**51**)[127–130] and 9,10-dicyanoantracene (**52**)[131] with alkyl halides.

In contrast to RA, the dianions of nitriles **48a**–**f** are so basic that if generated in liquid ammonia they are protonated in the *para*-position relative to cyano group furnishing CHDA $H(\mathbf{48a})^-$–$H(\mathbf{48f})^-$. Data from $^{13}C$ NMR spectroscopy and quantum chemical calculations[108,113] show that the main part (~80%) of π-charge of these CHDA is located in the pentadienyl fragment, mainly in the *ipso*-position in respect of the cyano group: the value of π-charges $q_\pi \approx -0.42$ to $-0.44$.




Z = H (**a**), 2-Me (**c**), 3-Me (**d**), 4-Me (**e**), 2,3-benzo (**f**).

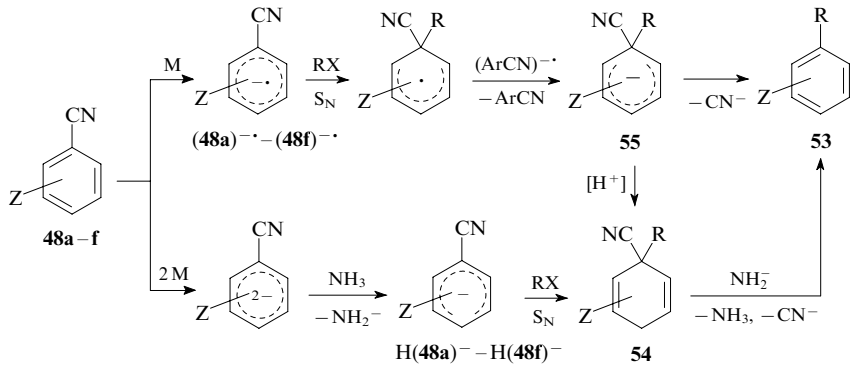
At the same time, DA of nitriles **49**, **51**, **52** are stable in liquid ammonia.[108,128,131] Dianion $(\mathbf{49})^{2-}$ is transformed into CHDA $H(\mathbf{49})^-$ upon treatment with water or methanol.[108]

The reaction of RA and CHDA, generated from nitriles **48a**–**f**, with alkyl halides[114–124,132,133] yields the aromatic alkylation products, *viz*.: alkylarenes **53** as a result of substitution of the alkyl group for the cyano group and cyanoalkyldihydroarenes **54** as a result of *ipso* -addition (Scheme 7).

Thus, both products (**53** and **54**) are formed from the same precursor: anion **55** (see Scheme 7). Radical anions $(\mathbf{48a})^{-\bullet}$–$(\mathbf{48f})^{-\bullet}$ undergo alkylation in the *ipso*-position relative to the cyano group.[114,117,119,120,122] At the same time, dihydroarenes **54** are primary alkylation products of CHDA, and alkylarenes **53** are formed as a result of their dehydrocyanation under the action of the amide ion present in the system.[115–120]

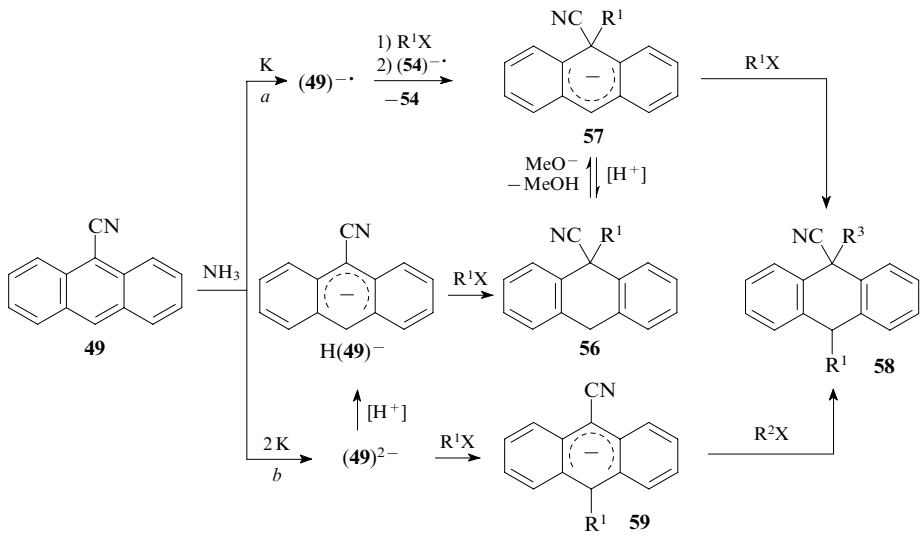
The overall yields of the alkylation products are sufficiently high and may reach 75%–90% in the reactions of doubly reduced nitriles. The addition of alkyl halide to the AF salts ('direct' mixing of the reactants) results in the formation of alkylarene **53** as the main product. The ratio **53** : **54** varies in the range from 90 to 2, the portion of diene **54** being increased if the naphthalene is replaced by the benzene ring,[116] if the methyl group is introduced in *para*-position relative to the cyano group,[116,119,120] if alkyl chlorides are replaced by alkyl iodides[114,116,122] and if linear alkyl fragment is replaced by a branched one,[119] probably due to more effective 'quenching' of the amide ion by alkyl halide or by its ammonolysis product. The addition of a solution of lithium salt of CHDA in a mixture $NH_3$–THF to an excess of a alkyl halide ('reverse' mixing) prevents the dehydrocyanation of diene **54** and makes it the main product.[117,118] Alkylarene **53** may be obtained by treatment of the initially formed mixture of the alkylation products with sodium amide.[120]

Scheme 7




Z = H (**a**), 2-MeO (**b**), 2-Me (**c**), 3-Me (**d**), 4-Me (**e**), 2,3-benzo (**f**); M = Li, Na, K; RX = MeI, $Bu^nHal$ (Hal = Cl, Br, I), $Bu^iBr$, $Bu^sBr$, cyclo-$C_6H_{11}Br$, $CH_2{=}CH(CH_2)_4Br$, BnBr, 3-$MeOC_6H_4CH_2Br$, cyclo-$C_3H_5CH_2Br$.

Scheme 8

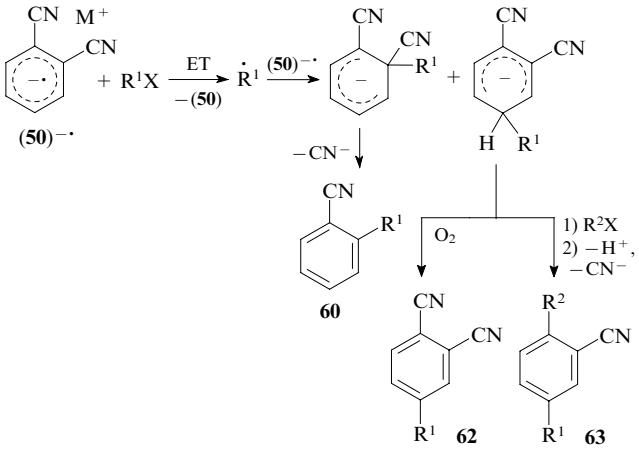


$R^1X$ = MeI, $Bu^nBr$, $Bu^nI$, cyclo-$C_3H_5CH_2Br$; $R^2X$ = MeI; $[H^+]$ = $NH_4Cl$, MeOH; $R^3$ = $R^1$ (pathway *a*) or $R^2$ (pathway *b*).

Radical anion $(\mathbf{49})^{-\bullet}$ is alkylated in the *ipso*-position yielding diene **56** because its precursor, anion **57,** cannot be decyanated. The reactions of DA $(\mathbf{49})^{2-}$ result in the formation of 9,10-dialkyl-9,10-dihydroanthracenes **58,** including those containing different alkyl fragments (the yields 70%–80%)[124] (Scheme 8). The structure of products obtained by consecutive treatment of DA $(\mathbf{49})^{2-}$ with alkyl halides $R^1X$ and $R^2X$ indicates that DA is alkylated in the *para*-position in respect of the cyano group, yielding anion **59**.

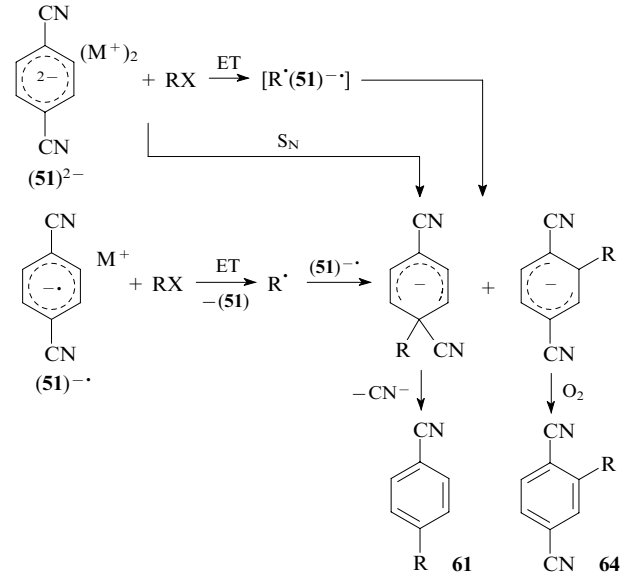
Alkyldihydroanthracenes **56** are formed selectively upon alkylation of CHDA $H(\mathbf{49})^-$ prepared from DA $(\mathbf{49})^{2-}$ by the treatment with $NH_4Cl$ (see Scheme 8). The absence of alkyl anthracenes among the reaction products shows that the decyanation of CHDA **57** does not take place due to a very small gain in energy provided by the core aromatisation. This makes this process different from alkylation of AF of benzo- and naphthonitriles (see Scheme 7) or dinitriles **50** and **51** (Schemes 9, 10).

Scheme 9



M = Na, K; $R^1X$ = $Bu^nHal$ (Hal = Br, I), $Bu^iBr$, $Bu^sBr$, $Bu^tHal$ (Hal = Br, I), $CH_2{=}CH(CH_2)_4Br$, n-$C_8H_{17}Br$, cyclo-$C_3H_5CH_2Br$, $R^2X$ = $R^1X$ (if $R^1$ is primary alkyl) or $Bu^nBr$.

Scheme 10



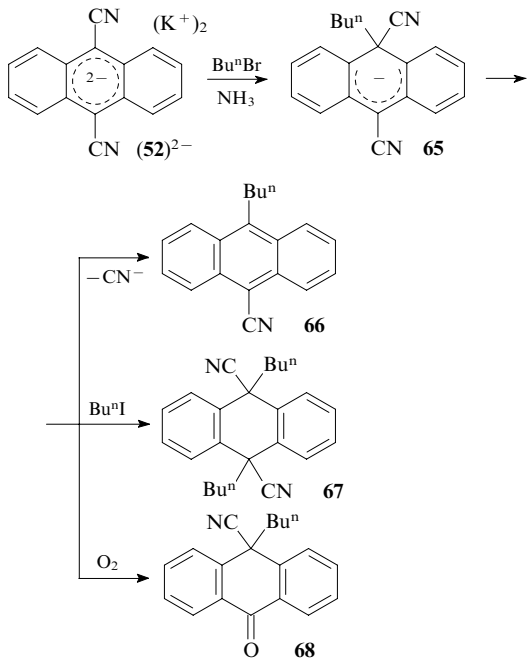
M = Li, Na, K; RX = $Bu^nHal$ (Hal = Cl, Br, I), $Bu^sBr$, $Bu^tHal$ (Hal = Br, I), n-$C_5H_{11}Br$, n-$C_8H_{17}Br$, cyclo-$C_6H_{11}Br$, AllBr, $(CH_2{=}CMeCH_2)Br$, $CH_2{=}CH(CH_2)_2Br$, $CH_2{=}CH(CH_2)_3Br$, $CH_2{=}CH(CH_2)_4Br$, cyclo-$C_3H_5CH_2Br$.

The reactions of AF of dinitriles **50** (Refs 125, and 126) and **51** (Refs 127–130) with alkyl halides afford substitution products of the cyano group (**60** and **61**) and hydrogen atoms (**62**–**64**) (see Schemes 9 and 10) in overall yields of up to 90%. The ratio of the alkylation products in *ipso*- and unsubstituted positions varies in the range 0.8–5. In the reactions of DA $(\mathbf{51})^{2-}$, this ratio increases in the range 4–100 for the series tertiary < secondary < isoalkyl < normal alkyl fragments and halogen atoms I < Br < Cl.

Radical anion $(\mathbf{52})^{-\bullet}$ does not react with alkyl halides in liquid ammonia at −33 °C, and DA $(\mathbf{52})^{2-}$ is alkylated in the *ipso*-position with $Bu^nBr$.[131]

The thus generated CHDA **65** is decyanated in an argon atmosphere yielding 10-butyl-9-cyanoanthracene (**66**), and is transformed into dibutylcyanodihydroanthracene **67** upon treatment with $Bu^nI$. The same reaction in air results in the

formation of anthrone **68**. The yields of the products are 80%–84%.




With the help of mechanism-testing agents it was found that the direction of alkylation of AF of mono- and dicyanarenes is directly associated with the reaction mechanism.[114, 116, 119, 122–124, 132] Thus the *ipso*-alkylation of RA of nitriles **48a**,**c**–**f**, **49** and the corresponding CHDA generated by protonation of the respective DA with primary alkyl halides in liquid ammonia at −33 °C proceeds according to the $S_N$ mechanism. In this case, the direction is determined by predominant localisation of the excess electron density on the carbon atom bearing the cyano group (spectroscopic and quantum chemical data).[108, 113, 124, 134] The contribution of the ET mechanism starts to appear in the alkylation of RA $(\mathbf{48e})^{-\bullet}$ on going from $Bu^nBr$ to cyclopropylmethyl bromide due to higher reduction potential of nitrile **48e** in comparison to those of nitriles **48c** and **48d** ($E^\circ$ are equal to −2.34, −2.23 and −2.26 V, respectively, *vs.* SCE[135, 136]) and the increase in the electron affinity of the alkyl halide.[137]

The $S_N$ mechanism is prevailing in the reactions of RA $(\mathbf{48a})^{-\bullet}$ with primary alkyl halides. This was confirmed by the pulse radiolysis method in a study of the temperature dependence of the rate constant for the reaction of this RA with $Bu^nI$ in *N*-methylpyrrolidone.[13] In contrast to $(\mathbf{48a})^{-\bullet}$ the mechanism of the reaction of RA $(\mathbf{48d})^{-\bullet}$ and $(\mathbf{48e})^{-\bullet}$ with alkyl bromides changes from $S_N$ in $NH_3$ at −33 °C (Ref. 132) to ET in DMF at 20 °C.[11] It was found by the method of estimation of the contribution of the $S_N$ mechanism, based on the comparison of electrochemical parameters of studied and a model (proceeding totally according to the ET mechanism) reactions[12] that in reactions of RA $(\mathbf{48d})^{-\bullet}$ and $(\mathbf{48e})^{-\bullet}$ electrochemically generated in DMF with primary and secondary alkyl halides RX (R = Me, Et, $Bu^n$, $Bu^s$, *neo*-$C_5H_{11}$, 1-Ad; X = Cl, Br, I) both mechanisms operate. The contribution of the $S_N$ mechanism increases (Table 3) on going from branched to normal alkyl groups and from iodides to chlorides as well as from RA $(\mathbf{48e})^{-\bullet}$ to a relatively weaker reducing agent RA $(\mathbf{48d})^{-\bullet}$ (see the values of $E^\circ$ above).[11]

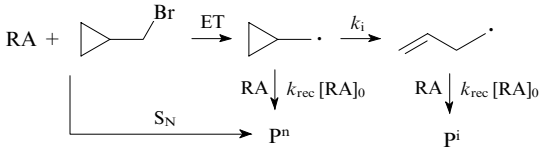
The dependence of reactivity of RA on the reaction conditions may be explained by a higher sensitivity of the reaction rate in the ET mechanism to the temperature change provided that the solvation effects in $NH_3$ and DMF are similar and relatively small. The observation[121, 122] that the transition from $NH_3$ or THF saturated with $NH_3$ to neat THF does not change the orientation and the mechanism of alkylation of RA $(\mathbf{48f})^{-\bullet}$ supports this explanation.

**Table 3**. The contribution of the $S_N$ mechanism to the alkylation reactions of radical anions $(\mathbf{48d})^{-\bullet}$ and $(\mathbf{48e})^{-\bullet}$ in DMF at 20 °C.[11]

| Alkyl halide | $S_N$ contribution | | Alkyl halide | $S_N$ contribution | |
|---|---|---|---|---|---|
| | $(\mathbf{48d})^{-\bullet}$ | $(\mathbf{48e})^{-\bullet}$ | | $(\mathbf{48d})^{-\bullet}$ | $(\mathbf{48e})^{-\bullet}$ |
| MeI | 0 | 0 | $Bu^nBr$ | 29 | 26 |
| MeBr | 6 | 5 | $Bu^nCl$ | 38 | 29 |
| MeCl | 31 | 23 | $Bu^sI$ | 0 | 0 |
| EtI | 5 | 2 | $Bu^sBr$ | 18 | 2 |
| EtBr | 26 | 13 | $Bu^sCl$ | 21 | 11 |
| EtCl | 41 | 23 | *neo*-$C_5H_{11}$Hal | – | 0 |
| $Bu^nI$ | 23 | 5 | (Hal = I, Br, Cl) | | |

The reactivity of RA $(\mathbf{50})^{-\bullet}$, $(\mathbf{51})^{-\bullet}$ and DA $(\mathbf{51})^{2-}$ with respect to alkyl halides in liquid ammonia differs significantly from predominantly nucleophilic activity of RA of monocyanoarenes **48a**–**f**, **49**. The formation of the products (P) with both cyclopropylmethyl ($P^n$) and but-3-enyl fragments ($P^i$) in the reactions of RA $(\mathbf{50})^{-\bullet}$ and $(\mathbf{51})^{-\bullet}$ with cyclopropylmethyl bromide suggests the ET mechanism (Schemes 9, 10 and 11).

Scheme 11




$$P^n : P^i = \frac{k_{rec}[RA]_0}{k_i \ln(1 + k_{rec}[RA]_0/k_i)} - 1$$

The ratios $P^n : P^i$ are equal to 20 and 4 in the reaction of RA $(\mathbf{50})^{-\bullet}$ and to 16 and 3 in the reaction of RA $(\mathbf{51})^{-\bullet}$ (for $[RA]_0$ = 0.1 and 0.009 mol litre$^{-1}$, respectively)[126, 127, 138] and are in reasonable agreement with the values $P^n : P^i$ = 39 and 3 calculated for the ET mechanism.

The recombination rate constant of the alkyl radical and RA in Scheme 11 is given as $k_{rec} = 1/4\,k_{dif} = 1/4(8\,RT/3000\,\eta) = 5 \times 10^9$ litre mol$^{-1}$ s$^{-1}$,[38] where $\eta$ is the viscosity of liquid ammonia and is equal to 0.26 cP at 238 K,[139] $k_i$(−33 °C) = $4.8 \times 10^5$ s$^{-1}$ (Ref. 140).

The direction of recombination of RA $(\mathbf{51})^{-\bullet}$ with non-isomerised and isomerised alkyl radicals is identical ($\mathbf{61}^n : \mathbf{64}^n = \mathbf{61}^i : \mathbf{64}^i = 2$), which indicates the formation of all products according to the same mechanism. The ability of RA $(\mathbf{51})^{-\bullet}$ to react according to the ET mechanism is confirmed by the kinetic study of its reaction with substituted benzyl bromides in DMF and acetonitrile.[141] The direction of alkylation of RA $(\mathbf{50})^{-\bullet}$ resulting in addition of cyclopropyl and butenyl fragments is slightly different ($\mathbf{60}^n : \mathbf{63}^n = 2$, $\mathbf{60}^i : \mathbf{63}^i = 0.8$), probably due to the contribution of the $S_N$ mechanism to the formation of compound $\mathbf{60}^n$.

The dianion $(\mathbf{51})^{2-}$ possesses dual reactivity with respect to alkyl halides. Whereas the ratio $\mathbf{61}^i : \mathbf{64}^i = 2$ is typical of the ET pathway, and only nitrile $\mathbf{61}^n$ is formed by the $S_N$ mechanism ($\mathbf{61}^n : \mathbf{64}^n = 13$), the contribution of the $S_N$ mechanism in this reaction may be estimated as 77%. The ET mechanism is

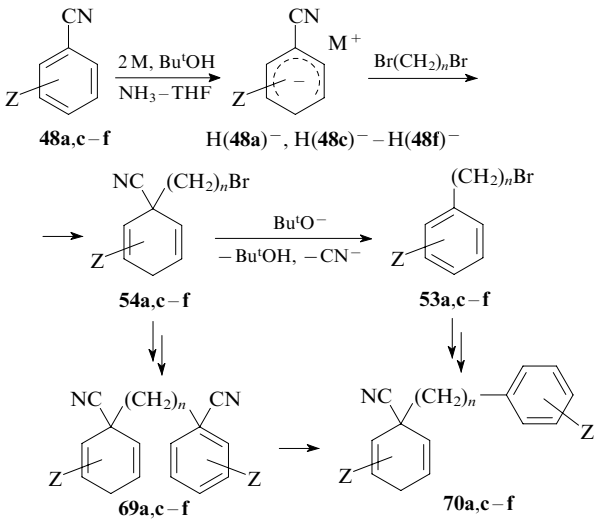
predominant in the reactions of this dianion with secondary and tertiary alkyl halides and also with primary alkyl iodides. It is rather non-selective: the amounts of *ipso*- and *ortho*-alkylation products are comparable (*ipso* : *ortho* = 2–6). On the contrary, DA $(\mathbf{51})^{2-}$ reacts with primary alkyl chlorides and bromides as a nucleophile to give *ipso*-alkylation products in high yield and selectivity. It makes this reaction a general method for the synthesis of *p*-alkyl [128] and *p*-(ω-alkenyl)benzonitriles.[130]

The introduction of an additional cyano group in *ortho*- or *para*-position relative to the already existing cyano group (transition from nitrile **48a** to dinitriles **50** and **51**) results in switching the mechanism of the reaction of RA with primary alkyl bromides from $S_N$ to ET. On the contrary, the increase in the extent of reduction of the substrate [the transition from RA $(\mathbf{51})^{-\bullet}$ to DA $(\mathbf{51})^{2-}$] makes the $S_N$ mechanism predominant. According to the results of PM3/RHF calculations of energetic parameters of the $S_N$ and ET processes in the reactions of RA $(\mathbf{48a})^{-\bullet}$, $(\mathbf{51})^{-\bullet}$ and DA $(\mathbf{51})^{2-}$ with MeBr as a model reagent and electronic structure of these AF,[127, 128] the ratio of the heats of formation of initial products of the $S_N$ (the cyclohexadienyl radical for RA and CHDA for DA) and ET (alkyl radical and a product of one-electron oxidation of AF) processes corresponds to kinetic preferability of the $S_N$ process due to the bond formation (*cf.* with the data from Refs 15, 16 and 142). Its decrease on going from DA $(\mathbf{51})^{2-}$ to RA $(\mathbf{48a})^{-\bullet}$ and further to RA $(\mathbf{51})^{-\bullet}$ corresponds to the decrease in difference of enthalpies of parallel reactions in this series: $\Delta H_{S_N} - \Delta H_{ET}$ are equal to −37, −18, −13 (in all cases ±8) kcal mol$^{-1}$, respectively. The calculations show that in the case of RA $(\mathbf{48a})^{-\bullet}$ the energy gaps between each of its two HOMO and the LUMO of MeBr are comparable. In such a situation a significant binding in the transition state of the $S_N$ mechanism should make it preferential. The transition from nitrile **48a** to dinitrile **51** is associated with the decrease in energies of the MO of the RA due to the introduction of the electron-withdrawing group. At the same time, the energy of MO of the RA occupied by a pair of electrons (MOPE) is farther from that of the LUMO of MeBr, which reduces the rate and contribution of the $S_N$ process. On the contrary, the MO of unpaired electron approaches the LUMO of MeBr, which favours the ET mechanism provided that the mechanism is inner-sphere to some extent.[143–146] This is supported by the observation of the secondary kinetic isotope effect,[144] for example in the reaction of RA $(\mathbf{51})^{-\bullet}$ with MeI,[63] and also by the fact that the activation entropy of the ET process in the reactions of RA may be negative and comparable with that of the $S_N$ process ($\Delta S^{\neq}_{S_N} - \Delta S^{\neq}_{ET}$ is equal ~4–10 cal mol$^{-1}$ deg$^{-1}$).[16, 144] The energy of MOPE increases and becomes closer to the energy of LUMO of MeBr on going from RA $(\mathbf{51})^{-\bullet}$ to DA $(\mathbf{51})^{2-}$. This again makes the $S_N$ mechanism more favourable than ET.

The following facts demonstrate the connect between the derection of reductive alkylation of aromatic nitriles and the mechanism. The $S_N$ alkylation of RA and CHDA with primary alkyl bromides proceeds selectively in the *ipso*-position where the maximum of the electron density is located. This corresponds to the realisation of the earlier transition state.[114–116, 121–124] The *para*-alkylation of DA $(\mathbf{49})^{2-}$ and *ipso*-alkylation of DA $(\mathbf{51})^{2-}$ proceed according to the $S_N$ mechanism corresponding to both the position of the maximum electron density localisation in these DA and the formation of the most stable CHDA in each case.[124, 128] Lower selectivity of the ET alkylation of RA $(\mathbf{50})^{-\bullet}$, $(\mathbf{51})^{-\bullet}$ and DA $(\mathbf{51})^{2-}$ is caused by comparable rates of recombination of RA with alkyl radical in *ipso*- and unsubstituted positions. This better agrees with the distribution of spin density in RA rather than with the relative stability of the CHDA formed.

The reactivity of AF of mononitriles **48a–f** and dinitrile **51** with respect to the primary alkyl bromides remains the same in the reactions of these AF with dibromoalkanes [$Br(CH_2)_nBr$, $n$ = 3–5]. The 'direct mixing' reaction of lithium salt of CHDA H(**48d**)$^-$ with dibromopentane yields products **54** and arene **53** (50% and 11%, respectively) as well as compounds **69** and **70**, corresponding to the substitution of bromine in the primary products2 (18% and 7%, respectively).[117] Under the same conditions the reaction of CHDA H(**48b**)$^-$ with 1-bromo-3-chloropropane results in a single product of the type **54**, containing chlorine in the alkyl fragment.[118] Dienes **54** containing geminal cyano group and ω-bromoalkyl fragment were obtained in 55%–90% yields in the 'reverse mixing' reaction of CHDA generated from nitriles **48a,c–f** by reduction with lithium in a mixture $NH_3$–THF in the presence of Bu$^t$OH, with an excess of dibromoalkane (Scheme 12).[117] This makes it possible to minimise dehydrocyanation and substitution of both bromine atoms and thus to use this reaction as a convenient one-step method of synthesis of cyclohexadienes of the type **54**.

Scheme 12

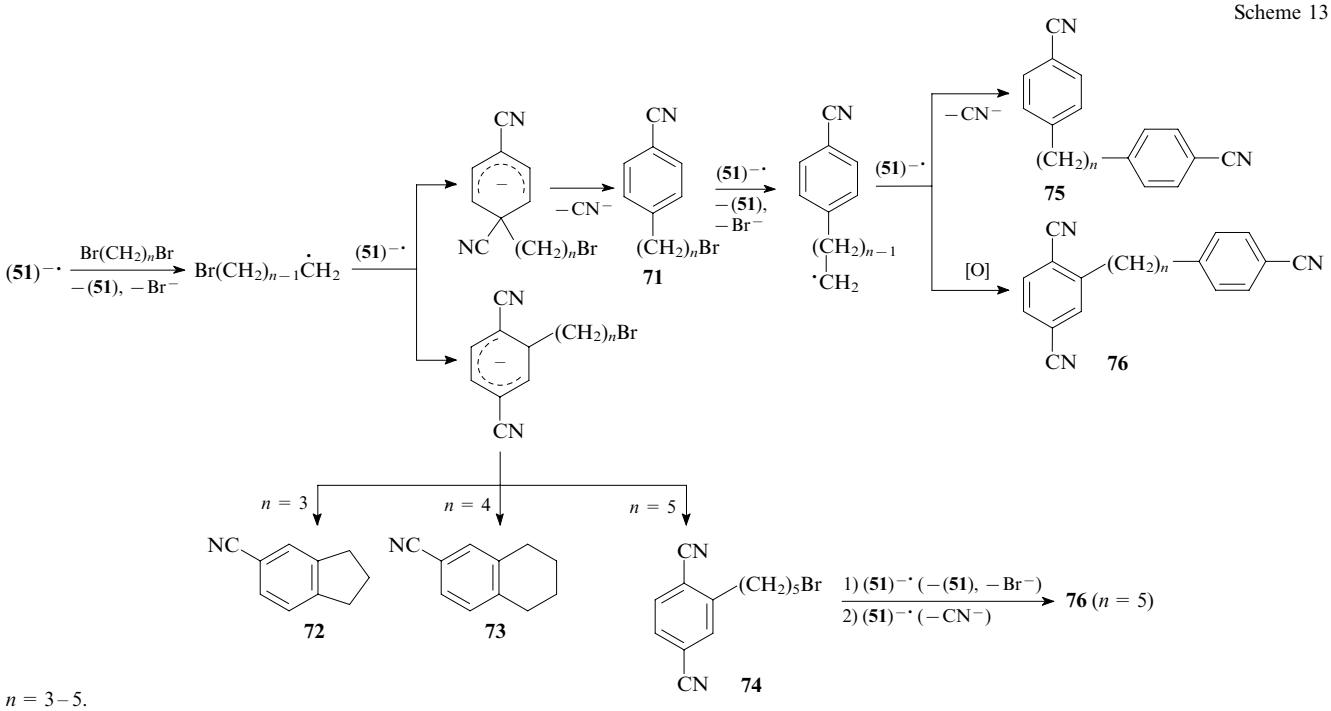



Z = H (**a**), 2-Me (**c**), 3-Me (**d**), 4-Me (**e**), 2,3-benzo (**f**); $n$ = 3–5; M = Li, Na, K.

The reaction of sodium salt of RA $(\mathbf{51})^{-\bullet}$ with $Br(CH_2)_nBr$ in liquid ammonia, which proceeds according to the ET mechanism, results in a mixture of products of primary alkylation of RA in *ipso*- (**71**) and unsubstituted positions (**72–74**) (30%–40%, the ratio ~2 : 1), and also substitution products of bromine in nitriles **71** and **74** *viz.*, diarylalkanes **75** and **76** (10%–15%, the ratio ~2 : 1) (Scheme 13).[147] The application of 'reverse mixing' effectively prevents the formation of 'secondary' products **75** and **76**.

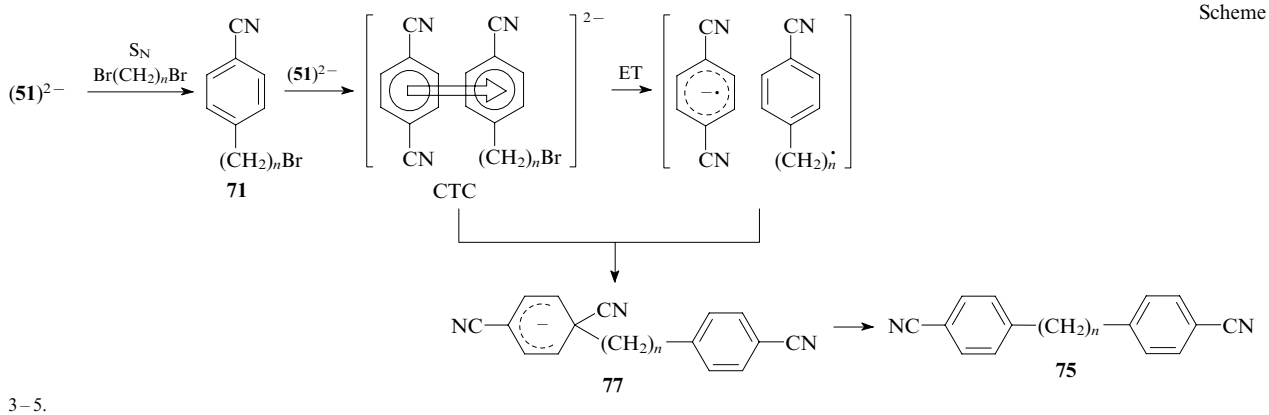
At the same time, compounds **71** and **74** are absent among the reaction products of sodium salt DA $(\mathbf{51})^{2-}$ with dibromoalkanes. Mainly bis-*para*-cyanophenylation of dibromoalkanes takes place, producing compounds **75** (through CHDA **77**) in high yields (80%–90%).[147] This means that the rate of the reaction of DA $(\mathbf{51})^{2-}$ with (bromoalkyl)benzonitriles **71** is higher than that with the starting dibromoalkanes. This rate ratio was confirmed by competitive reactions of DA $(\mathbf{51})^{2-}$ with nitriles **71** and corresponding alkyl bromides and cannot be attributed to realisation of the $S_N$ mechanism in both parallel reactions. Therefore, the mechanism involving the

Scheme 13



$n = 3-5$.

Scheme 14



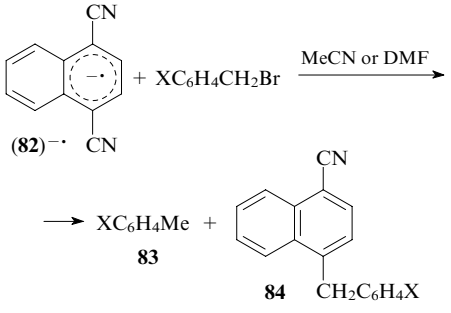
$n = 3-5$.

formation of a charge-transfer complex (CTC) as a key intermediate was suggested for the reaction of $(\mathbf{51})^{2-}$ with nitriles **71** (Scheme 14).[147] This suggestion is in agreement with the formation of CTC between arenes and their anionic reduced formes [148, 149] and identification of CTC as intermediates of ET reactions.[150–152]

The formation of CTC as a key intermediate was also suggested for the arylation of DA $(\mathbf{51})^{2-}$ with nitriles **48a** and **48d**, which affords dicyanobiphenyls **78** (the yield is 60%–90%)[153] (Scheme 15). According to the proposed scheme, the CTC is transformed into dianion **79**, which undergoes easy decyanation to give CHDA **80** stable in an inert atmosphere. For the reaction with nitrile **48a**, this was demonstrated by alkylation of CHDA **80** with $Bu^nBr$, which resulted in cyano(butyl)biphenyl **81** as the final product. Aromatisation of cyclohexadienyl fragment takes place, when CHDA **80** is oxidised upon contact with air, being converted into biphenyl **78**.

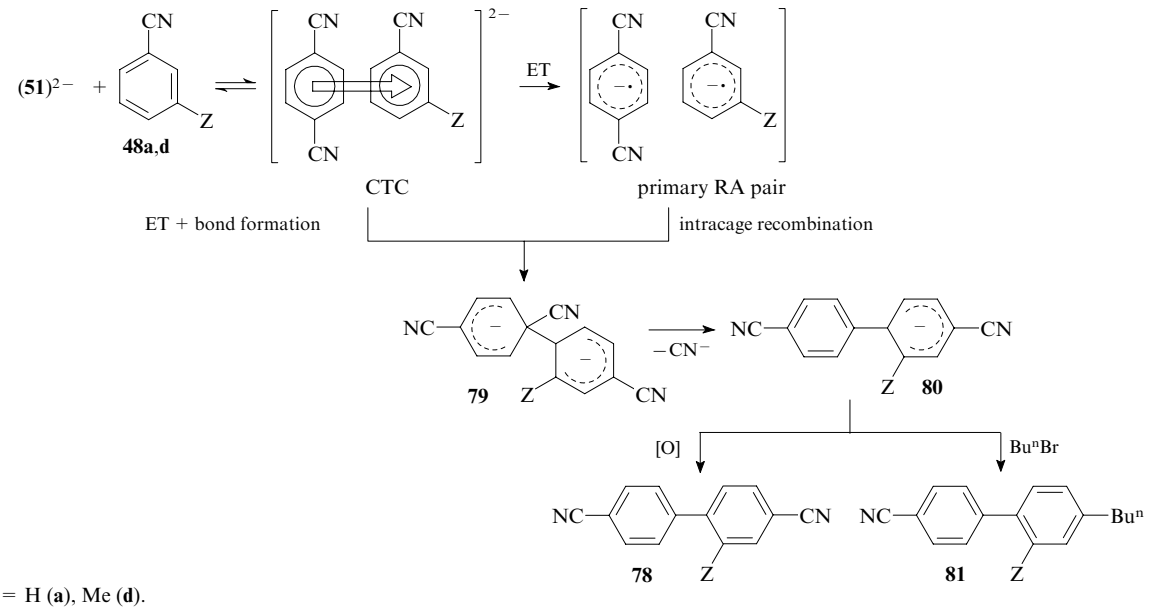
The MP2/6-31+G* calculations show that the plane-parallel and coaxial approaching of DA $(\mathbf{51})^{2-}$ and nitrile **48a** to each other decreases the total energy of the system, which reaches its minimum at the distance of 3.15 Å. This corresponds well to the CTC formation because the interplanar distances in such complexes, formed by radical cations[151] or RA [148, 149] and their precursors, are in the range of 2.9–3.6 Å.

A linear dependence of $\log k$ on $\sigma^-$ of the substituent X ($\rho = 2.6$) common for electron-withdrawing and electron-donating substituents was observed for the reaction of electrochemically generated RA of 1,4-dicyanonaphthalene $(\mathbf{82})^{-\bullet}$ with substituted benzyl bromides in acetonitrile, which yields substituted toluenes **83** and naphthalenes **84**. This value is in good agreement with the value $\rho = 2.5$ calculated for the outer-sphere dissociative ET process.[141]



X = 4-MeO, 4-Me, 4-Bu$^t$, H, 4-Br, 3-CN, 4-CN, 3-$CF_3$, 4-$CF_3$.

Scheme 15




Z = H (**a**), Me (**d**).

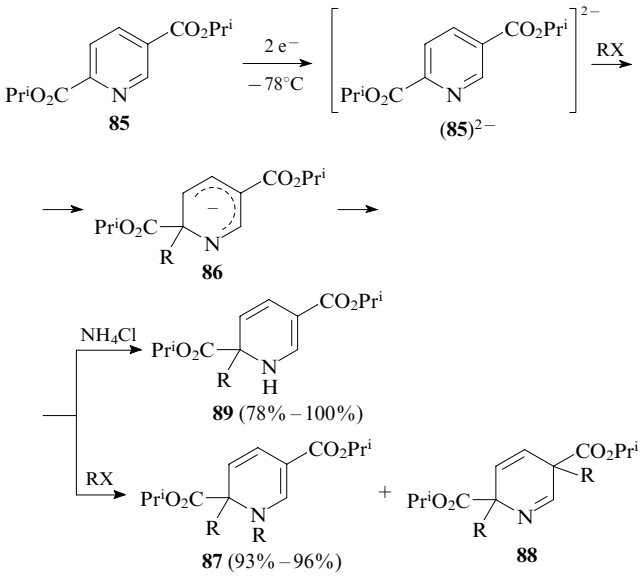
For the same reaction in DMF a similar dependence was observed for the reagents with electron-withdrawing substituents X ($\rho = 2.7$), however, for electron-donating substituents (Me, Bu$^t$, MeO) the sign of parameter $\rho$ changes, and the reaction rate is less sensitive to the character of the substituent X ($\rho = -2.1$). These data were interpreted [141] as an indication of change in the reaction mechanism from ET to $S_N$ caused by higher sensitivity of the $S_N$ process rate to solvation, because the reaction rates with electron-deficient benzyl bromides (the ET mechanism) in these solvents are the same. Radical anion $(\mathbf{51})^{-\bullet}$ ($E^\circ = -1.55$ V relative to NCE in DMF), is more electron-donating than RA $(\mathbf{82})^{-\bullet}$ ($E^\circ = -1.30$ V) and reacts with substituted benzyl bromides in DMF entirely by ET mechanism. In contrast, the mechanism of alkylation of RA $(\mathbf{82})^{-\bullet}$ switches from ET to $S_N$ on going from benzyl bromide to benzyl tosylate due to the change in the nature of the leaving group of the electrophile. This reaction selectively produces 4-benzyl-1-cyanonaphthalene **84** whereas toluenes **83** that are obtained only by ET mechanism are absent from the reaction products.

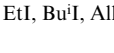
The reductive activation of mono- and dicyanoarenes with respect to alkylating (mono- and dihaloalkanes) and arylating (monocyanoarenes) reagents is extremely important because it makes possible convinient one-step syntheses of hardly accessible compounds: cyanocyclohexadienes functionalised on a saturated carbon atom, 4-alkylbenzonitriles, bis(*p*-cyanophenyl)alkanes, 4-alkylphthalonitriles, 4,4′-dicyanobiphenyls. All these compounds are of interest as potential precursors of analogues of natural biologically active compounds (repellents, herbicides, drugs) [154–160] and of the materials with a wide variety of useful properties (liquid crystals,[161–167] supramolecular complexes,[168–170] phthalocyanine pigments for photodynamic diagnostics and therapy of cancer [171–177]).

## VI. Reactions of anionic reduced forms of nitrogen-containing heterocycles with C-electrophiles

The Birch reduction [178] and the reductive alkylation [179–187] of nitrogen-containing heterocycles, which proceeds *via* AF, are used for the synthesis of precursors of biologically active compounds. The type of AF depends on the acceptor properties of the substrate. Among the pyridine derivatives, high yields of 1,2- and 2,5-dialkyldihydro derivatives were obtained in the reactions of 2,5-di(isopropoxycarbonyl)pyridine (**85**) (Scheme 16).[179, 180]

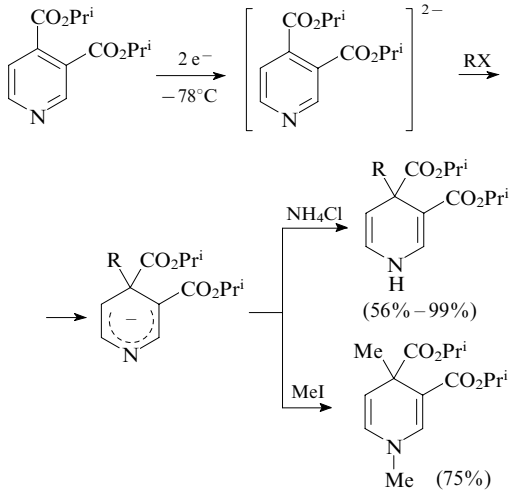
Scheme 16



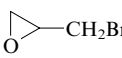

2 e$^-$: Na/NH$_3$; (Na/naphthalene) – THF;
RX = MeI, EtI, Bu$^i$I, AllBr, , I(CH$_2$)$_n$Cl ($n = 3-5$).

On the basis of the structure of products, the authors suggested that DA $(\mathbf{85})^{2-}$ is alkylated in the position 2 to form CHDA **86**, which undergoes further alkylation giving a mixture of isomeric products **87** and **88**. Significantly lower reactivity of CHDA **86** in comparison with DA $(\mathbf{85})^{2-}$ makes it possible to obtain selectively monoalkyldihydro derivative **89** using an excess of protonating agent for 'quenching' CHDA in the next few seconds after the addition of RX. The reductive alkylation of 3,4-di(isopropoxycarbonyl)pyridine produces similar results (Scheme 17).[181] The reactions of other isomers of esters of pyridinecarboxylic acids are non-selective and yield complex mixtures.

Scheme 17



2 e$^-$: Na/$NH_3$; (Na/naphthalene)–THF;

RX = MeI, EtI, , $CH_2Br$, $Ph(CH_2)_2Br$, $I(CH_2)_3Cl$,

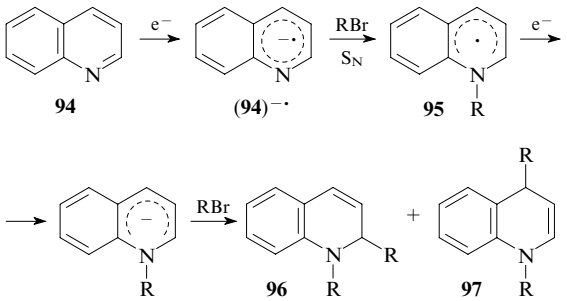
$Br(CH_2)_nBr$ ($n$ = 3, 4), 2-$BrC_6H_4CH_2Br$, 2-$BrC_6H_4(CH_2)_2Br$.

Among the esters of isomeric pyridinecarboxylic acids, only the ester of nicotinic acid is reductively alkylated, the yields of 3-alkyl-3,6-dihydro-derivatives being 20%–40%.[180]

The reductive alkylation of *N*-alkyl- and *N*-benzoylethoxycarbonyl pyridinium salts **90**–**92** is used as a key step in the synthesis of functionalised piperidines (yields 45%–90%) (Scheme 18).[182–184] Salt **90** is selectively γ-alkylated to give benzyldihydro derivative **93**. The reductive alkylation of salts **91** and **92** is less selective. The formed dihydropyridines were not isolated due to their instability and their structures were deducted from the structures of hydrogenated products and by analogy with the reaction of salt **90**. The γ-isomer is the main reaction product of both salts (its content in the mixture is 60%–80%). The nature of AF of pyridinium salts or the mechanism of their alkylation has not been studied.

The conditions of reductive alkylation of *N*-substituted pyridinium salts were optimised[185] and the most suitable protective groups and substituents were chosen, which enabled conversion of unstable dihydro products into stable compounds, valuable for further use in synthesis.

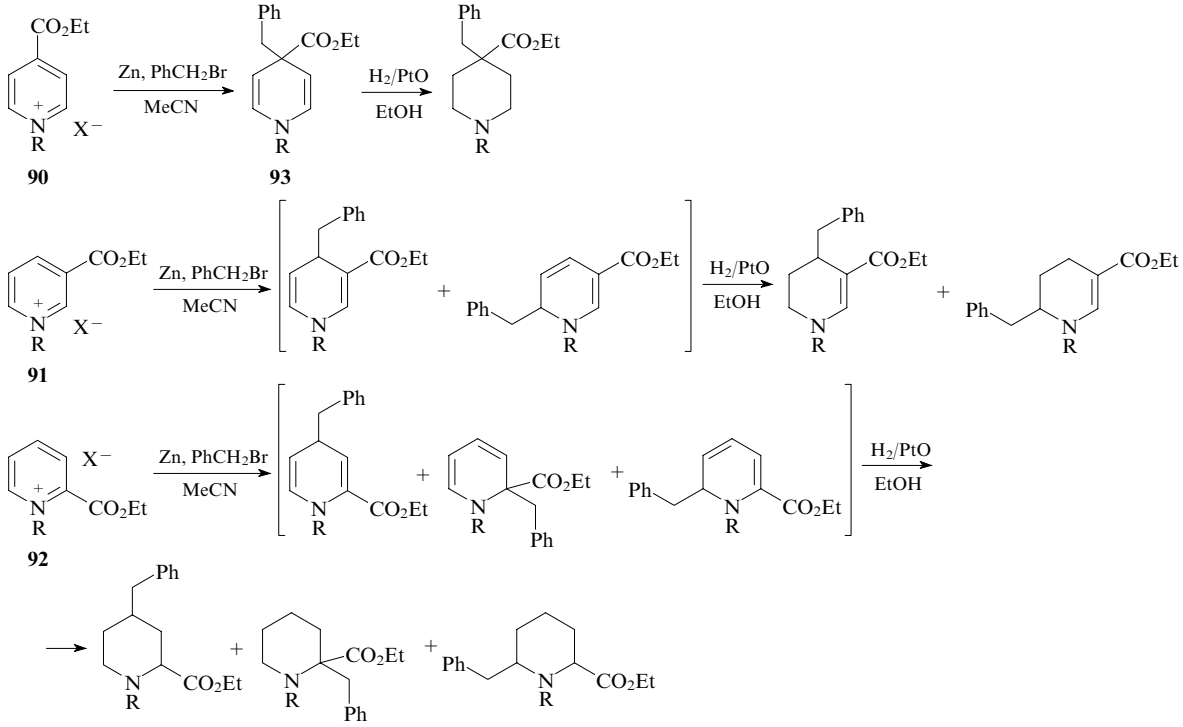
The radical anion of quinoline, $(\mathbf{94})^{-\bullet}$, electrochemically generated in liquid $NH_3$, is *N*-alkylated with EtBr or $Bu^nBr$. Subsequent reduction of radical **95** produces an anion, which is further converted into 1,2- and 1,4-dialkyldihydro derivatives **96** and **97**.[186]



R = Et, $Bu^n$.

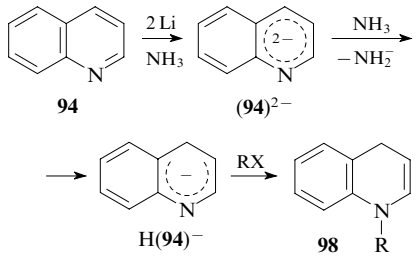
The ECEC mechanism shown above suggested on the basis of electrochemical characteristics, implies that RA $(\mathbf{94})^{-\bullet}$ serves as a nucleophile in respect of primary alkyl bromides.

Scheme 18



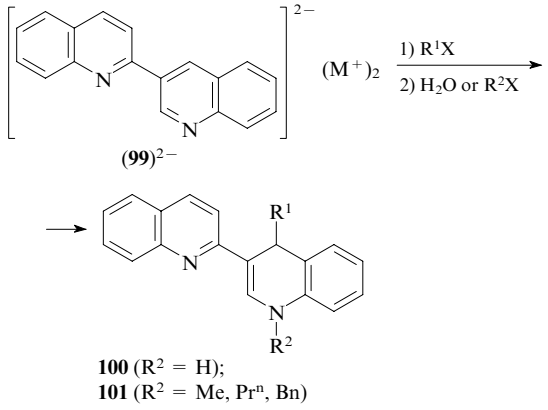
R = Me, X = I; R = $PhCH_2$, X = Br; R = Bz, X = Cl.

Reduction of quinoline with lithium in liquid $NH_3$ and subsequent alkylation result in the formation of 1-alkyl-1,4-dihydro derivatives **98** in high yields.[187] The suggested scheme of the reaction includes protonation of sufficiently basic DA $(\mathbf{94})^{2-}$ by a solvent and alkylation of CHDA $H(\mathbf{94})^-$ formed.




X = Br: R = Me, Et, $Pr^n$, $Pr^i$, $Bu^n$, $CH_2Ph$;
RX = $MeOCH_2Cl$, $(MeO)_2CO$, $(MeO)_2SO_2$.

The dianion of 2,3′-biquinoline $(\mathbf{99})^{2-}$ obtained upon treatment of precursor **99** with lithium or potassium in THF,[188] reacts with alkyl halides, allyl and benzyl phenyl ethers yielding after hydrolysis 4′-alkyl-1′,4′-dihydro-2,3′-biquinolines **100**, and after treatment with alkyl halide, 1′,4′-dialkyl-1′,4′-dihydro-2,3′-biquinolines **101** in 78%–86% yields.[189]



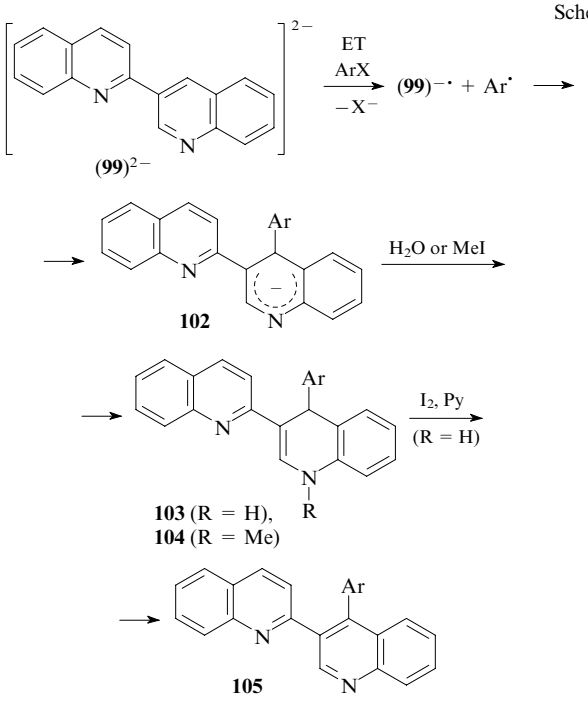

**100** ($R^2$ = H);
**101** ($R^2$ = Me, $Pr^n$, Bn)

$R^1$ = Me, $Pr^n$, $Bu^n$, All, Bn; X = Cl, Br, OPh; M = Li, K.

The direction of alkylation corresponds to the position of the maximum spin density in RA $(\mathbf{99})^{-\bullet}$ and on the basis of this observation the ET mechanism of the reaction was suggested.[190] The increase in the yield of the alkylation products on going from alkyl bromides to alkyl iodides does not contradict this suggestion. However, this mechanism does not correspond to the effect of the type of the counter-ion of the DA salt on the product yield (it increases from $Li^+$ to $K^+$) and also to the relatively low electron affinity of phenyl ethers.

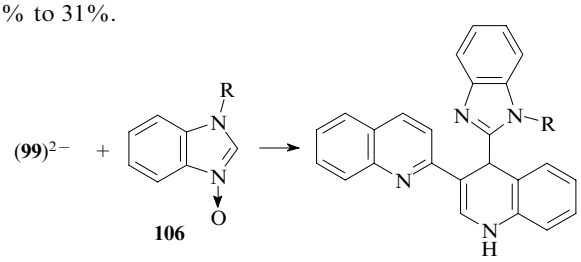
Dianion $(\mathbf{99})^{2-}$ reacts with aryl and hetaryl halides yielding the arylation and dihydroarylation products, which was regarded as an indication of the ET mechanism of the reaction.[190, 191] Radical anion $(\mathbf{99})^{-\bullet}$ and aryl radical formed in the reaction recombine in the position of the maximum spin density of the RA resulting in anion **102**, which undergoes protonation and produces 4′-aryl-1′,4′-dihydro-2,3′-biquinoline **103** in 64%–78% yield. Anion **102** is *N*-alkylated with MeI to give 1′-methyl-4′-aryl-1′,4′-dihydro-2,3′-biquinoline **104** (yield 72%–75%). The dihydro derivative **103** is quantitatively aromatised upon oxidation with iodine in pyridine yielding 4′-aryl-2,3′-biquinoline **105** (Scheme 19).

Scheme 19



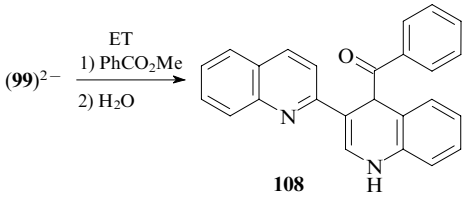

ArX = PhBr, 1-$BrC_{10}H_7$, 2-$FC_5H_4N$, 1-Me-2-Cl-benzimidazole, 1-$Pr^i$-2-Cl-benzimidazole.

Not only aryl halides but also 3-alkylbenzimidazole 1-oxides **106** react with DA $(\mathbf{99})^{2-}$. The reaction produces 4′-(1-alkylbenzamidazol-2-yl)-1′,4′-dihydro-2,3′-biquinolines **107**;[192] the yields depend on the size of the substituent R in *N*-oxide **106** and increase on transition from $Pr^i$ to Me from 23% to 31%.



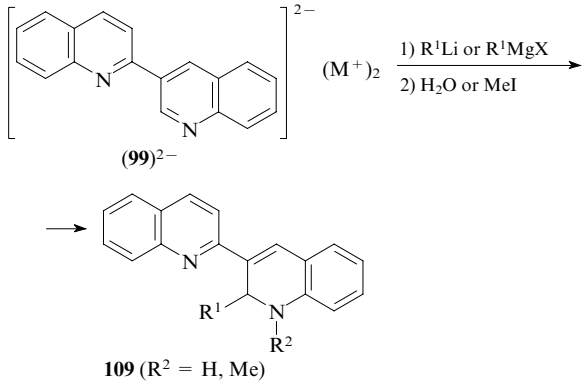

R = Me, Et, $Pr^i$.

The reaction of disodium salt of DA $(\mathbf{99})^{2-}$ with methyl benzoate, resulting in the formation of 4′-benzoyl-1′,4′-dihydro-2,3′-biquinoline **108** in 61% yield, is a rare example of the application of an ester as an acylating reagent for arene AF.[193] Presumably,[193] the electron transfer from DA $(\mathbf{99})^{2-}$ to $PhCO_2Me$ is a key step of the process, because the replacement of the latter by $PhCO_2Pr^i$ or $PhCO_2Bu^t$ does not produce any significant changes in the reaction yield or time.




The reaction of DA $(\mathbf{99})^{2-}$ with organolithium or organomagnesium compounds is rare for DA of arenes. The corresponding 2′-alkyl-1′,2′-dihydro derivatives **109** were obtained

after the treatment with water or MeI, their yields depend on the character of counter-ion of the salt of DA and increase on going from $K^+$ to $Li^+$ from 60%–68% to 79%–84%.[194]

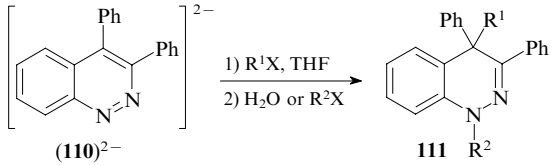



**109** ($R^2$ = H, Me)

$R^1$ = Me, $Bu^n$, Ph; X = Cl, I; M = Li, K.

The suggested mechanism of this reaction includes the formation of a complex of DA with the organometallic reagent followed by intra-complex attack by the nucleophile $(R^1)^-$ on the 2′-position of the dianion with simultaneous electron transfer to the solvent molecule.[194] The following experimental observations provided the basis of the suggested mechanism: the reaction of neutral biquinoline **99** with organolithium and organomagnesium compounds proceeds on position 4′; the lithium salt of DA $(\mathbf{99})^{2-}$ reacts with organometallic compounds much slower than the potassium salt and the reaction does not take place in the presence of a crown ether.

The stable DA $(\mathbf{110})^{2-}$ was obtained by the reduction of 3,4-diphenylcinnoline (**110**) with sodium in THF. Its reaction with water as well as with alkylating and acylating reagents results in the formation of the corresponding 1,4-dihydro derivatives **111** (the yields are 40%–90% depending on the electrophile).[195]




$R^1X$ = $H_2O$, $R^1$ = $R^2$ = H (95%); $R^1X$ = BnCl: $R^1$ = $R^2$ = Bn (51%); $R^1$ = Bn, $R^2$ = H (42%); $R^1X$ = MeI, $R^1$ = $R^2$ = Me (64%); $R^1X$ = $MeO_2CCl$: $R^1$ = $R^2$ = $CO_2Me$ (57%); $R^1$ = H, $R^2$ = $CO_2Me$ (38%); $R^1X$ = $Cl(CH_2)_nCl$, $R^1$ = $(CH_2)_nCl$, $R^2$ = H ($n$ = 3, 62%; $n$ = 4, 82%).

Generally, the DA of electron-deficient azaheterocycles are highly reactive synthons for the carbon–carbon bond formation in the reactions with various carbon-centred electrophiles. High yields and regioselectivity are typical of their reactions, however the mechanisms of these reactions are not comprehensively studied as yet.

* * *

The data presented in the review show that stable anionic reduced forms of functionalised arenes are potentially important organometallic reagents. Their application is a special area of fine organic synthesis and enables short synthetic routes to otherwise hardly accessible precursors of compounds and materials with valuable properties. At the same time, they are important models in studies of a problem of competition between polar and one-electron mechanisms general for organic chemistry. Although the fundamentals in this area already exist, the problems related to structural dependences and shedding light into both the nature of the process and its possible application in the control of chemical transformations are still at early stages of the development. The authors believe that for these reasons further studies in this area are required.

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