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How iodide anions inhibit the phase-transfer catalyzed reactions of carbanions

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ABSTRACT

The inhibitory effect of iodide anions on the phase-transfer catalyzed reactions of carbanions generated in liquid–liquid two-phase systems by aqueous NaOH is due to preferential location of these anions in the interfacial region of the two-phase system—organic phase/concd aqueous NaOH. In such situation, the basic activity of NaOH in this region is decreased and the equilibrium of deprotonation of the carbanion precursors is disfavoured.

1. Introduction

In a short communication by Jarrousse,[1] it was reported that alkylation of phenylacetonitrile proceeds efficiently in the presence of 50% aqueous NaOH and 20 mol % of benzyltriethyl ammonium chloride (TEBA) with ethyl chloride, much less with ethyl bromide and 'does not proceed' with ethyl iodide. On the basis of this communication, a general catalytic methodology for the alkylation of arylacetonitriles via carbanions generated in an immiscible two-phase system—in the presence of 50% aqueous NaOH and tetraalkylammonium (TAA) salt acting as catalyst, was elaborated[2,3] and applied in industry.[4,5] This two-phase catalytic methodology was subsequently expanded to alkylation and other reactions of carbanions[6] as well as inorganic anions and named Phase-Transfer Catalysis (PTC).[7] The catalytic action of TAA salts in these two-phase systems consists of the continuous formation of lipophilic ion pairs of the lipophilic TAA cations with the reacting anions that then enter the organic phase where further reactions take place. Presently PTC is a well established general methodology applicable to a variety of reactions of inorganic and organic anions, metalloorganic compounds, etc.[8] Contrary to what might be expected, the order of reactivity of ethyl halides namely Et–Cl>Et–Br>Et–I in the alkylation of phenylacetonitrile in this system observed by Jarrousse[1] was confirmed and explained in one of our first papers in this field.[2] It was shown that this is an artefact and that the reaction is inhibited by bromide and particularly iodide anions produced in the reaction, which overrides the intrinsic reactivity of R–X in the two-phase systems. On the other hand, in the reaction of TAA salts of carbanions normal order of activity R–I>R–Br>R–Cl is observed. Similar observation was made for the PTC reaction of alkyl halides with inorganic anions. For example, PTC reactions of alkyl halides with cyanide anions proceed efficiently with R–Cl, more slowly with R–Br, and do not proceed (or are extremely slow) with R–I. Also in these cases, it was shown that the iodide anions produced inhibit the process. They remain as the TAA iodide in the organic phase, hence cyanide anions are not transferred into the organic phase and the catalytic process is arrested.[7]

Consider a reaction of an alkyl halide with an inorganic salt carried out in a two-phase system: an aqueous solution of inorganic salt Na^+Y^-—the nonpolar alkyl halide R–X or its solution in a nonpolar solvent catalyzed by a lipophilic TAA salt Q^+X^- (Eq. 1a). Assuming that all this salt stays in the organic phase—one can show that concentration of inorganic anions X^- and Y^- in the organic phase is governed by the ion-exchange equilibrium presented in Eq. 1b.

$$R{-}X_{org} + Na^+Y^-_{aq} \overset{Q^+X^-}{\rightarrow} R{-}Y_{org} + Na^+X^-_{aq} \quad (1a)$$

$$Q^+X^-_{org} + Na^+Y^-_{aq} \leftrightharpoons Q^+Y^-_{org} + Na^+X^-_{aq} \quad (1b)$$

The position of this equilibrium, and hence the concentration of X^- and Y^- anions in the organic phase is determined by the differences in energy of hydration and energy of solvation by the

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organic solvent of these anions, the former is, as a rule, a much more important factor. On this basis, the explanation of the inhibitory effect of iodide anions on the PTC reactions of inorganic anions is straightforward. The energy of hydration of iodide anions, due to their low charge density, is much smaller than that of majority of other inorganic anions, thus when $X^-=I^-$ the equilibrium (Eq. 1b) is shifted to the left and concentration of Y^- in the organic phase becomes negligible, hence the catalytic reaction of Y^- anions with R–X is inhibited.

The numerous observations of the inhibitory effect of I^- anions on the PTC reactions of carbanions generated in situ from C–H acids in the presence of concentrated aqueous alkali (PTC/OH^- two-phase systems) were rationalized similarly as for the reactions of inorganic anions, namely, because their high lipophilicity iodide anions compete successfully with carbanions for lipophilic TAA cations of the catalyst, hence, concentration of the ion pairs: carbanion–TAA cation ($\geqslant C^-Q^+$) in the organic phase is low and the catalytic process retarded.[8] Although indeed the concentration of these ion pairs in the organic phase in the presence of I^- ions is low, such a rationalization appears insufficient and oversimplified. Obviously, one cannot explain the preference for I^- anions in competition with carbanions for TAA cations in the organic phase on the basis of differences in hydration and solvation energies of I^- and carbanions, similarly as in the case of PTC reactions of inorganic anions governed by the ion-exchange equilibrium (Eq. 1b). Such explanation would be based on the assumption that the lipophilicity of I^- is higher than the lipophilicity of carbanions, which can hardly be accepted.

Moreover there are numerous reports that alkyl iodides can be successfully applied for the PTC alkylation of carbanions.[9] Obviously, in these cases, the iodide anions produced during the reaction do not inhibit the catalytic process.

In this paper, we clarify these controversies and present a mechanistic picture of the inhibitory action of I^- anions on PTC reactions of carbanions.

The key difference between the PTC reactions of inorganic anions and carbanions is due to the fact that in the former case, the catalyst acts simply as an agent transferring inorganic anions located in the aqueous phase into the organic phase, whereas the PTC reactions of carbanions that are generated in situ are more complicated. In the typical PTC systems, the carbanion precursor located in the organic phase is deprotonated by base located in the aqueous phase and the generated carbanions, thanks to the catalyst, are present in the organic phase in the form of lipophilic ion pairs with the catalyst cations. Thus, without mechanistic discussion of how this process proceeds and where the deprotonation takes place, we can write for a given CH acid a general equilibrium, which is responsible for concentration of the carbanions in the organic phase (Eq. 2).

$$\geqslant C{-}H_{org} + Na^+OH^-_{aq} + Q^+X^-_{org} \overset{K(X^-)}{\leftrightharpoons} \geqslant C^-O^+_{org} + Na^+X^-_{aq} + H_2O_{aq} \quad (2)$$

The position of this equilibrium, or in more strict terms, the free energy difference (ΔG^0) between the right and left sides, is a function of many parameters: ΔG^0 of the deprotonation reaction: $\geqslant C{-}H+OH^- \leftrightarrows \geqslant C^- + H_2O$; ΔG^0 of the H_2O transfer: $H_2O_{org} \leftrightarrows H_2O_{aq}$; ΔG^0 of the X^- transfer: $X^-_{org} \leftrightarrows X^-_{aq}$; etc. Keeping all other components and conditions constant, the effect of X^- on the position of the equilibrium, which governs the concentration of the carbanions in the organic phase and is obviously responsible for the inhibitory effect of I^- on the PTC reactions can be easily determined by comparing the equilibrium concentrations of $\geqslant C^-$ according to Eq. 2 for different X^-. Thus, $\Delta\Delta G^0(Br^-/I^-)$, which for a given C–H acid decides on the difference between equilibrium concentrations of $\geqslant C^-Q^+$ in the organic phase for Q^+Br^- and Q^+I^- is in fact equal to the difference of the free energy change for Br^- and I^- anions in the system (Eq. 3),

$$\begin{aligned}\Delta\Delta G^0(Br^-/I^-) &= \Delta G^0(Br^-) - \Delta G^0(I^-) = [\Delta G^0_{hydr}(Br^-) \\ &\quad - \Delta G^0_{solv}(Br^-)] - [\Delta G^0_{hydr}(I^-) - \Delta G^0_{solv}(I^-)] \\ &= \Delta\Delta G^0_{hydr}(Br^-/I^-) - \Delta\Delta G^0_{solv}(Br^-/I^-) \end{aligned} \quad (3)$$

where $\Delta G^0{}_{hydr}$ and $\Delta G^0{}_{solv}$ stand for the standard free energies of hydration and solvation of X^- in the aqueous and organic phases, respectively. In a similar way as presented in Eq. 3, the effect of differences in the C–H acidity of the various carbanion precursors on the equilibrium can be estimated keeping X^- constant: $\Delta\Delta G^0(\geqslant C{-}H'/\geqslant C{-}H'') = \Delta G^0(\geqslant C^{-\prime}/\geqslant C{-}H') - \Delta G^0(\geqslant C^{-\prime\prime}/\geqslant C{-}H'')$. These reasonings were semiquantitatively confirmed by experiments in which the equilibrium contents of carbanions in the organic phase according to Eq. 2. was measured as a function of acidity of the carbanion precursors and kind of X^- in Q^+X^-. Ring substituted phenylacetonitriles $ArCH_2CN$ (pK_a's in the range 16–24 in DMSO[10]) and also phenylsulfonyl acetonitrile (pK_a 12[10]) were used as the model carbanion precursors, they were reacted with equimolar amounts of tetrabutylammonium (TBA) halides in two-phase system, chlorobenzene/50% aq NaOH (Table 1).

The results obtained are presented in a graphical form in Figure 1. The contents of carbanions and halides in the samples of the organic phase taken from the corresponding two-phase systems equilibrated at +35 °C were determined by titration and given in Table 1 as fractions (in %) of the total amount of Q^+, which was considered to be 100%. It is assumed and verified experimentally that when the aqueous phase consists of a 50% solution of NaOH, all TBA cations are in the organic phase in the form of $\geqslant C^-Q^+$ or Q^+X^-. The assumption that all $\geqslant C^-Q^+$ and Q^+X^- are in the organic phase, and that no other anionic species are present in this phase, requires that the sum of the found contents of the carbanions and halides in the organic phase should be 100% in regard to the total starting amount of TBA halides, which is perfectly the case. The basicity of the organic phase determined by acidometric titration was assigned to $\geqslant C^-Q^+$ ion pairs because, if no $ArCH_2CN$ was added to the system, extraction of OH^- anions into the organic phase by Q^+X^- salts was negligible in the case of $X^-=Br^-$, I^- (Table 1, entries 2 and 3) or took place to a very small extent in the case of TBA chloride (entry 1). In a similar way, when no Q^+X^- was added to the system there was no Na^+OH^- or $\geqslant C^-Na^+$ detected in the organic phase by the titration (entries 4, 8, 12, 16, 20 and 23). We have confirmed that the results are related to the truly equilibrated system by an experiment (entry 17 in the brackets) in which a mixture of 50% aq NaOH and chlorobenzene solution of the $ArCH_2CN$ and Q^+Cl^- was treated in a standard way to show 82% content of the carbanions in the organic phase. Subsequent addition to the system of NaI in the amount equimolar to Q^+Cl^- followed by equilibration resulted in decrease of the carbanion contents in the organic phase from 82% to 5%, which was similar to the value obtained when a solution of the $ArCH_2CN$ and Q^+I^- in chlorobenzene was treated with an excess of 50% aq NaOH (Table 1, entry 19).

Thus, it was shown that the equilibrium ratio $\geqslant C^-/X^-$ in the organic phase is a function of acidity of $ArCH_2CN$ and a nature of X^-, decreasing for a given C–H acid in the order $X^-=Cl^-$, Br^-, I^- (Fig. 1). The same picture was observed when 'catalytic' amounts of Q^+X^- (10% molar) in regard to $ArCH_2CN$ was employed, though the fractions of Q^+ accompanied with carbanions were somewhat higher (Table 1, entries 13–15 in the brackets).

On the basis of equation $\Delta G^0 = -RT\ln K$ and Eq. 3 one could express change of the equilibrium constant $\Delta\ln K(X_1^-/X_2^-)$ for a given C–H acid and two different TAA halides $Q^+X_1^-$ and $Q^+X_2^-$ as (Eq. 4).

Table 1
Equilibrium contents of tetrabutylammonium salts of carbanions ($\geqslant C^-Q^+$) and halides (Q^+X^-) in the organic phase and the equilibrium constant $K(X^-)$ in two-phase system: a solution of $ArCH_2CN$ and TBA halides 1:1 molar ratio in chlorobenzene/50% aq NaOH, at 35 °C[a]

$$ArCH_2CN_{org} + Na^+OH^-_{aq} + Q^+X^-_{org} \underset{\text{PhCl/50\% aq NaOH 35 °C, argon}}{\overset{K(X^-)}{\rightleftharpoons}} ArCHCN^-Q^+_{org} + Na^+X^-_{aq} + H_2O_{aq}$$

Entry	Ar	pK_a of $ArCH_2CN$ (DMSO)[b]	X^-	$\geqslant C^-_{org}$ (%)	X^-_{org} (%)	$\geqslant C^-_{org}+X^-_{org}$ (%)	$K(X^-)$
1	No $ArCH_2CN$	—	Cl^-	4(0.6)[c](OH^-)	94(98)[c]	98(99)[c]	—
2			Br^-	<0.5(OH^-)	100	100	—
3			I^-	<0.5(OH^-)	99	99	—
4	4-$MeOC_6H_4$	~23.4	No Q^+X^-	~0	—	—	—
5			Cl^-	22	79	101	$\sim 2.88\times10^{-1}$
6			Br^-	9	92	101	$\sim 3.55\times10^{-2}$
7			I^-	2	97	99	$\sim 1.57\times10^{-3}$
8	4-MeC_6H_4	~22.9	No Q^+X^-	~0	—	—	—
9			Cl^-	36	65	101	$\sim 1.14\times10^{0}$
10			Br^-	11	90	101	$\sim 5.54\times10^{-2}$
11			I^-	4	95	99	$\sim 6.57\times10^{-3}$
12	Ph	21.9	No Q^+X^-	~0	—	—	—
13			Cl^-	56(83)[d]	44(18)[d]	100(101)[d]	$\sim 6.05\times10^{0}$
14			Br^-	16(30)[d]	85(71)[d]	101(101)[d]	$\sim 1.31\times10^{-1}$
15			I^-	5(8)[d]	98(93)[d]	103(101)[d]	$\sim 9.64\times10^{-3}$
16	4-ClC_6H_4	~20.8	No Q^+X^-	~0	—	—	—
17			Cl^-	82(5)[e]	18(I^-–95)[e]	100(100)[e]	$\sim 7.78\times10^{1}$
18			Br^-	33	67	100	$\sim 9.02\times10^{-1}$
19			I^-	10	89	99	$\sim 4.68\times10^{-2}$
20	3-ClC_6H_4	~19.7	No Q^+X^-	~0	—	—	—
21			Br^-	53	47	100	$\sim 4.74\times10^{0}$
22			I^-	14	87	101	$\sim 9.60\times10^{-2}$
23	2,4-$Cl_2C_6H_3$	~18.5	No Q^+X^-	~0	—	—	—
24			Br^-	76	26	102	$\sim 3.20\times10^{1}$
25			I^-	34	68	102	$\sim 9.30\times10^{-1}$
26	C_6F_5	15.8	No Q^+X^-	~0	—	—	—
27			I^-	58	41	99	$\sim 7.47\times10^{0}$
28	$PhSO_2$	12.0	No Q^+X^-	~0[f]	—	—	—
29			I^-	100	1	101	—

[a] The 0.12 M solutions each of $ArCH_2CN$ and TBA halides in chlorobenzene were used unless indicated otherwise. Initial ratio $\geqslant$C–H/$OH^-\approx1/100$.
[b] According to Bordwell.[10] Sign ~ denotes an estimated pK_a value that was calculated from the Hammett equation on the basis of pK_a of phenylacetonitrile and ρ values reported by Bordwell[10] and the literature data on σ and σ^- values of substituents.[16]
[c] NaCl (5 equiv) in regard to Q^+ was added to the system.
[d] Initial ratio $\geqslant$C–H/Q^+X^-=10/1, i.e., 1.2 M in regard to the C–H acid and 0.12 M in regard to Q^+X^- solution in chlorobenzene was used.
[e] NaI (1 equiv) in regard to Q^+Cl^- was added to the system, which was equilibrated previously with Q^+Cl^-.
[f] Three-phase system: organic phase, aqueous NaOH and dispersion of white precipitate—$PhSO_2CHCN^-Na^+$.

$$\Delta\ln K(X_1^-/X_2^-) = \ln K(X_1^-) - \ln K(X_2^-) = -\Delta\Delta G^0(X_1^-/X_2^-)/RT$$
$$= [\Delta\Delta G^0_{solv}(X_1^-/X_2^-) - \Delta\Delta G^0_{hydr}(X_1^-/X_2^-)]/RT \quad (4)$$

Assuming that $|\Delta\Delta G^0_{solv}| \ll |\Delta\Delta G^0_{hydr}|$, because of relatively low values of the solvation energy of inorganic anions X^- in an aprotic organic medium of low polarity such as chlorobenzene, Eq. 4 can be substantially reduced to Eq. 5.

$$\Delta\ln K(X_1^-/X_2^-) \cong -[\Delta\Delta G^0_{hydr}(X_1^-/X_2^-)]/RT \quad (5)$$

According to Eq. 5, $\Delta\ln K(X_1^-/X_2^-)$ values should not depend on a kind of a C–H acid that is confirmed by the experimental data shown in Table 1. The average experimental values of $\Delta\ln K(X_1^-/X_2^-)$ for the tested C–H acids calculated on the basis of Eq. 6 were as follows: $\Delta\ln K(Br^-/I^-)=3.3\pm0.7$; $\Delta\ln K(Cl^-/Br^-)=3.4\pm1.6$.

$$K(X^-) \cong ([\geqslant C^-Q^+]_{org}[X^-]_{aq}[H_2O]_{aq}/[\geqslant C{-}H]_{org}[OH^-]_{aq}$$
$$[Q^+X^-]_{org})^{equilibrium} \quad (6)$$

Coe et al.[11] reported the following values of $\Delta\Delta G^0_{hydr}(X_1^-/X_2^-)$ for anions hydrated by one molecule of water as it is in 50 wt % aqueous NaOH: −8.6 kJ/mol for (Br^-/I^-) and −5.3 kJ/mol for (Cl^-/Br^-). The calculated values of $\Delta\ln K(X_1^-/X_2^-)$ according to Eq. 5 (T=308.15 K, R=8.314 J/mol K) and the literature data on $\Delta\Delta G^0_{hydr}(X_1^-/X_2^-)$ are 3.4 (Br^-/I^-) and 2.1 (Cl^-/Br^-) that is in a reasonably good agreement with the experimental results obtained in our studies.

For the carbanion precursors of relatively high C–H acidity, pK_a<10 in DMSO, the position of the equilibrium presented in Eq. 2 is strongly shifted to the right, so the differences $\Delta\ln K(X_1^-/X_2^-)$ cannot be reliably measured in direct experiments. This was confirmed in experiments similar to those presented in Table 1—the determination of the contents of carbanions and halide anions in the organic phase when a solution of much stronger CH acid such as phenylmalononitrile (pK_a=4.2 in DMSO[10]) and equimolar amount of TBA halides (X^-=Br^- or I^-) in chlorobenzene was equilibrated with an excess of 50% aq NaOH. Titrimetric analysis of the organic phase indicated that practically all the Q^+ cations are accompanied with the carbanions regardless of the kind of X^- (I^- or Br^-) anions (Table 2). Similar results gave experiments in which sodium hydroxide solution contained large quantities of dissolved NaI (Table 2 entries 4–6). Phenylmalononitrile being a very strong C–H acid is completely deprotonated with an excess of aqueous NaOH, but the formed sodium salt is not soluble in the organic phase, in our case chlorobenzene, thus are no carbanions or other basic anions in the organic phase unless quaternary ammonium salt Q^+X^- is added (Table 2, entry 1).

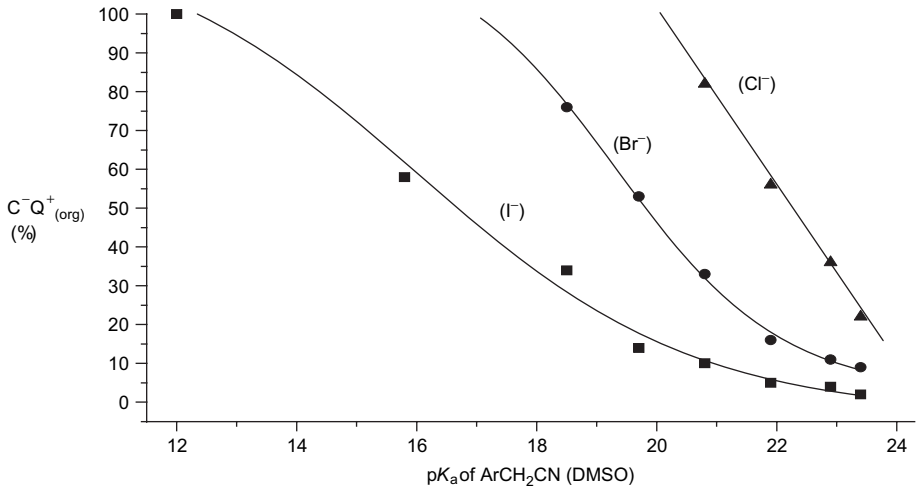


Figure 1. Equilibrium contents of tetrabutyl salts of carbanions ($\geqslant C^-Q^+$) in the organic phase as a function of acidity of $ArCH_2CN$ and a kind of X^- anions in two-phase system: a solution of $ArCH_2CN$ and TBA halides 1:1 molar ratio in chlorobenzene/50% aq NaOH (see also Table 1).

The data presented in Tables 1 and 2 show that the equilibrium concentration of $\geqslant C^-Q^+$ in the organic phase generated from CH acids and Q^+X^- in the two-phase system: nonpolar solvent/50% aq NaOH according to Eq. 2 is determined by two factors: CH acidity of the carbanion precursor and the hydration energy of X^-. However, in the case of CH acids of high acidity, the gain of energy ΔG^0 of the deprotonation $\geqslant C\text{–}H + OH^- \rightleftharpoons \geqslant C^- + H_2O$ is so large that it offsets the differences of the hydration energy of X^-, thus the differences between equilibrium concentrations of carbanions in the organic phase as a function of a kind of X^- become negligible or rather beyond the range of determination by the used method. In this case, the equilibrium content of carbanions in the organic phase is almost 100% in regard to TAA cations regardless of a kind and concentration of X^- anions present in the system (see Table 2).

Since in two-phase systems, nonpolar solvents/50% aq NaOH, the phases might be regarded as completely mutually immiscible[12] assuming that rate of deprotonation and transfer of ion pair is a fast process (equilibrium establishment is a fast process), the observed rate of alkylation for a given of C–H acid can be written down as presented in Eq. 7.

$$\text{Rate of alkylation} = k_{Rx}[\geqslant C^-Q^+]^{eff}{}_{org}[RX]_{org} \quad (7)$$

It is obvious that during the course of the alkylation, the effective concentration of the carbanions is lower than equilibrium concentration $[\geqslant C^-Q^+]^{eff}{}_{org} \leq [\geqslant C^-Q^+]^{eq}{}_{org}$, where the latter stands for the equilibrium concentration of carbanions in the organic phase according to Eq. 2. The alkylation rate constant k_{Rx} increases in the order $k_{RCl} < k_{RBr} < k_{RI}$[13] whereas due to inhibitory effects of produced X^-, the observed rate of PTC alkylation of carbanions generally decreases from R–Cl to R–I,[1,2] because the equilibrium and effective concentration of carbanions in the organic phase in the course of PTC alkylation of a given C–H acid with R–I in the presence of aq NaOH should be significantly lower than in the course of alkylation with R–Br. A similar relation should be observed for the alkylation with R–Br and R–Cl. A rigorous description of the kinetics of PT catalyzed reactions is therefore a complicated task requiring consideration of the mass transfer and chemical reaction steps involved in the process. However, one could suppose that the effective concentration of ion pairs $\geqslant C^-Q^+$ in the organic phase in the course of PTC alkylation should correlate with the equilibrium constant $K(X^-)$ of these ion pairs formation process (Eq. 2).

On the basis of this reasoning, one could assume that the final outcome of PTC alkylation of CH acids with various alkyl halides, R–X, X=Cl, Br, I, should be rather a complicated function of a few parameters: acidity of CH acid, nucleophilicity of the corresponding carbanions, intrinsic activity of R–X, inhibitory effect of X^-, etc.

In order to demonstrate the complication of the system and interplay of these parameters, we have carried out PT catalyzed alkylation of three arylacetonitriles differing in CH acidity with *n*-Pr–X, X=Cl, Br, I, under identical conditions. The results are shown in Table 3.

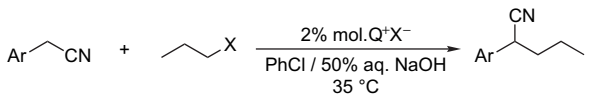
Phenylacetonitrile is the weakest of these three CH acids, so the equilibrium concentration of the corresponding ion pairs $ArCH\text{–}CN^-Q^+$ is the most affected by the nature of X^- anions generated in

Table 2
Equilibrium contents of tetrabutylammonium salts of carbanions ($\geqslant C^-Q^+$) and halides (Q^+X^-) in the organic phase in system: solid sodium salt of phenylmalononitrile–a solution of TBA halides in chlorobenzene–aqueous NaOH, at 35 °C

$$PhC(CN)_2^-Na^+_{solid} + Q^+X^-_{org} \underset{PhCl/aq\ NaOH,\ 35\ ^\circ C,\ argon}{\rightleftharpoons} PhC(CN)_2^-Q^+_{org} + Na^+X^-_{aq}$$

Entry	Aqueous phase	X^-	Ratio $\geqslant C^-/X^-$	$\geqslant C^-_{org}$ (%)	X^-_{org} (%)	$\geqslant C^-_{org}+X^-_{org}$ (%)
1	50% aq NaOH	No Q^+X^-	—	<0.5	—	—
2		Br^-	1:1	100	3	103
3		I^-	1:1	100	2	102
4	NaX (2.0 M) in	I^-	1:11	99	4	103
5	50% aq NaOH	I^-	1:101	85	12	97
6		Br^-	1:101	96	4	100
7	NaX (2.0 M) in 20% aq NaOH	I^-	1:101	98	6	104

Table 3
Influence of C–H acidity of $ArCH_2CN$ on PTC alkylation of $ArCH_2CN$ with *n*-propyl halides in chlorobenzene/50% aq NaOH two-phase system in the presence of 2 mol % of TBA halides (Q^+X^-) at 35 °C[a]



Entry	Ar	pK_a of $ArCH_2CN$ (DMSO)	Time	Conversion of $ArCH_2CN$[a] (%)		
				X=Cl	X=Br	X=I
1	Ph	21.9	1 h	51	13	2
4	2,4-$Cl_2C_6H_3$	18.5	10 min	2	66	20
5	C_6F_5	15.8	24 h	0	4	24

[a] By GLC.

the course of the reaction. On the other hand, its carbanions are strong nucleophiles thus they react satisfactorily with *n*-Pr–Cl. The highest conversion with *n*-Pr–Cl indicates that the process is controlled by the equilibrium concentration of $ArCHCN^-Q^+$ in the organic phase.

Pentafluoroacetonitrile is the strongest CH acid, so the equilibrium concentration of the ion pairs $ArCHCN^-Q^+$ in the organic phase is high, close to the starting concentration of the Q^+X^- regardless of the kind of X^- and is not affected by the produced X^-. On the other hand, carbanions of this nitrile are weak nucleophiles thus the observed conversion, highest for *n*-Pr–I is determined by chemical activity of R–X (value of K_{Rx} in Eq. 7). Due to high acidity of this carbanion precursor, the process is not inhibited by I^- anions.

2,4-Dichlorophenylacetonitrile occupies the intermediate position. It is a stronger CH acid than $PhCH_2CN$, so the equilibrium concentration of $ArCHCN^-Q^+$ in the organic phase is higher but still significantly affected by I^-. On the other hand, *n*-Pr–Br is a more active alkylating agent than *n*-Pr–Cl. The observed conversion is governed partially by the rate constant of alkylation (for *n*-Pr–Cl) and partially by the equilibrium concentration of the ion pairs (for *n*-Pr–I).

First experiments in which degree of PTC alkylation of ring substituted phenylacetonitriles with various alkyl halides was connected with CH acidity of the nitriles and kind of leaving groups were carried out by W. Lasek, Ph.D. thesis, Institute of Organic Chemistry, 1994.

These results indicate unambiguously that the inhibitory effect of the bromide and iodide anions on the PTC alkylation of carbanions with alkyl halides is not connected with the competition between these anions and carbanions for the lipophilic cations of the catalyst. This conclusion is unambiguously confirmed by direct competition between I^- and carbanions of phenylmalononitrile that are less lipophilic than that of phenylacetonitrile. In such a competition, only $\geqslant C^-Q^+$ is transferred to the organic phase (Table 2). Thus, one can conclude that I^- ions exert an inhibitory effect not on the extraction of the carbanions but on deprotonation of the carbanion precursors—hence the inhibitory effect should be correlated with the CH acidity of the latter. For analysis of this question, the crucial equilibrium (Eq. 2) can be divided into two parts: deprotonation of the carbanion precursor and the ion exchange.

$$\geqslant C{-}H_{org} + NaOH_{aq} \leftrightharpoons \geqslant C^-Na^+_{int} + H_2O_{aq} \tag{8a}$$

$$\geqslant C^-Na^+_{int} + Q^+X^-_{org} \leftrightharpoons \geqslant C^-Q^+_{org} + NaX_{aq} \tag{8b}$$

As was already shown, Eq. 8b is shifted to the right regardless of X^- and thus cannot be responsible for the inhibitory effect of iodide anions. On the other hand, X^- is not present in Eq. 8a, thus their effect on the position or the equilibrium 8a should be connected with deprotonation of the CH acids and hence a function of pK_a and concentration of NaOH. Thus, simple thermodynamic consideration does not offer sufficient explanation of the inhibitory effect, because it does not takes into account how the process occurs.

In order to clarify the situation, mechanistic concepts should be included in the consideration. There are two accepted distinct mechanisms of operation of PTC: extraction[7] and interfacial[14] mechanisms. In application to the reactions of carbanions, the extraction mechanism comprises transfer of TAA hydroxides to the organic phase where they act as base abstracting protons from CH acids Eq. 9.

$$Q^+X^-_{org} + Na^+OH^-_{aq} \leftrightharpoons Q^+OH^-_{org} + Na^+X^-_{aq} \tag{9a}$$

$$\geqslant CH_{org} + Q^+OH^-_{org} \leftrightharpoons \geqslant C^-Q^+_{org} + H_2O_{org\rightarrow aq} \tag{9b}$$

The position of the ion-exchange equilibrium when $X^-{=}Br^-$ and I^- is very unfavourable for formation of Q^+OH^- and the concentration of OH^- anions in the organic phase is negligible. In fact, the difference of this concentration between Br^- and I^- is meaningless.

According to the interfacial mechanism the crucial step—deprotonation of the CH acids—proceeds in the interfacial region. It is followed by the ion exchange of interfacially located $\geqslant C^-Na^+$ with Q^+X^- to produce lipophilic ion pair that enters subsequently the organic phase Eq. 10, Figure 1.

$$\geqslant CH_{int} + NaOH_{int} \leftrightharpoons \geqslant C^-Na^+_{int} + H_2O_{int} \tag{10a}$$

$$\geqslant C^-Na^+_{int} + Q^+X^-_{int} \leftrightharpoons \geqslant C^-Q^+_{int} + NaX_{int} \tag{10b}$$

$$\geqslant C{-}H_{org} \rightarrow \geqslant C{-}H_{int} \quad NaOH_{aq} \rightarrow NaOH_{int} \tag{10c}$$

$$\geqslant C^-Q^+_{int} \rightarrow \geqslant C^-Q^+_{org} \text{ etc.} \tag{10d}$$

The chemical steps 10a and 10b are connected with transfer processes 10c and 10d.

For reactions proceeding according to the extraction mechanism, the reason for the inhibitory effect of iodide and bromide anions is obvious—the unfavourable equilibrium 10a for the extraction of OH^- anions into the organic phase. However, this explanation is inconsistent with significant differences between effect of Br^- and I^- anions and also differences of these effects for CH acids of different pK_a. On the other hand, the explanation of the inhibitory effect of iodide (and bromide) anions on PT catalyzed reactions of carbanions and also results presented in Tables 1 and 2 are reasonably rationalized by the interfacial mechanism.

In 50% aqueous NaOH there is about one molecule of water per each ion of Na^+ or OH^- that is much less than normal hydration number of these ions.

The low hydration energy of X^- compared with that of OH^- (Table 4) suggests that X^- anions (especially I^-) would preferentially occupy the surface (interfacial region) of the aqueous phase, hence they would significantly reduce the interfacial concentration (activity) of OH^- anions in the two-phase systems. This phenomenon that can be expressed as in Eq. 11, should strongly affect the deprotonation equilibrium (8a).

$$X^-_{aq} + OH^-_{int} \rightleftarrows X^-_{int} + OH^-_{aq} \tag{11}$$

Adsorption of lipophilic I^- anions at the interface has been already suggested in order to explain the observed inhibitory effect of I^- anions on the rate of hydroxide ion promoted interfacial deuterium exchange and alkylation reactions of phenylacetonitrile carried out in the unagitated two-phase systems ('flat' interface) in the absence of a phase-transfer catalyst.[15] However, in such a system, the measured (observed) rate of the deuterium exchange does not reflects rate of deprotonation because deuteration of the intermediate carbanions can be the rate limiting step. Therefore, we have studied effect of iodide anions on the rate of the isotope exchange of arylacetonitriles in the vigorously stirred two-phase systems under conditions that assure that observed rate is indeed determined by the rate of deprotonation (Eq. 12).

$$\geqslant C{-}D_{int} + OH^-_{int} \underset{K_D}{\overset{K_{-D}}{\rightleftarrows}} \geqslant C^-_{int} + HOD_{int}(H_2O_{int}) \underset{K_{-H}}{\overset{K_H}{\rightleftarrows}} \geqslant C{-}H_{int} + OD^-_{int}(OH^-_{int}) \tag{12}$$

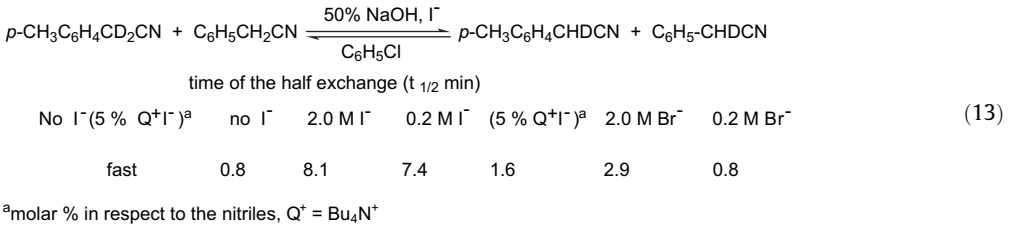
It should be stressed that experimental verification of the above-mentioned effect in the D/H exchange model reaction (Eq. 12) is straightforward only under the condition $k_H \gg k_D \gg k_{-D}$. If so,

Table 4
Bulk average differences of enthalpies and free energies of hydration of OH^- and X^- anions (kJ/mol)[11]

X^-	$\Delta H^0_{aq}(OH^-)-\Delta H^0_{aq}(X^-)$	$\Delta G^0_{aq}(OH^-)-\Delta G^0_{aq}(X^-)$
Cl^-	−152.7	−126.6
Br^-	−183.7	−153.4
I^-	−224.9	−190.8

then for a C–H acid such as, for instance, phenylacetonitrile (pK_a=21.9 in DMSO[10] when $k_D \gg k_{-D}$) the observed rate of deuterium exchange is determined by the step of proton (deuteron) abstraction from the substrate (rate=$k_{-D}[\geqslant C–D]_{int}[OH^-]_{int}$) and therefore directly depends on the interfacial concentration of hydroxide. If $k_H \ll k_D$, then the effective concentration of carbanions in the course of the reaction is almost as in equilibrium (rate=$k_H[\geqslant C^-]^{eq}_{int}[H_2O]_{int}$) and generally should be reduced with a decrease of the interfacial concentration of OH^- anions, if X^- anions would occupy the interface. However, such adsorption should also increase the activity of water in the interfacial area because bonding of H_2O with OH^- anions is much stronger than with X^- anions (Table 4). That should in turn increase the rate of protonation of the formed carbanions and therefore the observed rate of the isotope exchange reaction in such a case might not be practically affected by eventual adsorption of X^- at the interface. For experimental verification of these suppositions, we have chosen as a model the CH acid 4-methylphenylacetonitrile (pK_a 22.9 in DMSO) fully deuterated in the methylene group. The progress of deuterium exchange was determined using an ^1H NMR technique following the change of intensity of signal of the methylene group protons in relation to the protons of the methyl group of 4-methylphenylacetonitrile (δ 2.4 ppm) used as the internal standard. When a 2.8 M solution of *p*-methylphenylacetonitrile-α-d_2 ($pK_a \cong 22.9$ in DMSO[10]) in chlorobenzene was vigorously stirred with excess of 50% aq NaOH (saturated or not saturated with NaI), we did not observe any significant effect of the iodide anions on the rate of isotope exchange ($t_{1/2}$=51.4 min in the absence of NaI and $t_{1/2}$=67.8 min in the case of 2.0 M NaI in 50% aq NaOH).

The absence of the effect of iodide anions in this model system indicates that the rate of the exchange is determined by the rate of protonation of the generated carbanion ($k_H \ll k_D$). In such a system, I^- at the interface can affect both deprotonation and protonation steps, thus observed results of these controversial effects could be meaningless. In order to avoid these difficulties, we measured the effect of I^- and Br^- anions on the interfacial D–H exchange between two CH acids of similar acidity: phenylacetonitrile (pK_a 21.9) and 4-methylphenylacetonitrile, Eq. 13.



(13)

The rate of protonation (migration of proton between the carbanion and the nitrile) is not affected by the iodide anions adsorbed at the interface. The results of the isotope exchange between 4-methylphenyl-acetonitrile-α-2D and phenylacetonitrile in the presence of 50% aq NaOH and some anions are shown under Eq. 13. In such a system, we observed strong inhibition of D/H exchange between the nitriles even when the aqueous phase contains a small amount of NaI. Introduction of catalytic amounts of PT catalyst Q^+I^- strongly accelerates the rate of the exchange, apparently due to an increase of the effective concentration of carbanions in the system via formation of the $\geqslant C^-Q^+$ ion pairs, though addition to such system of iodide anions inhibits the rate of the isotope exchange. This indicates that the rate of the formation of $\geqslant C^-Q^+$ ion pairs in two-phase systems containing 50% aq NaOH is significantly reduced when the aqueous phase contains even small amounts of iodide anions. A similar inhibition effect, though much less profound, was observed in the case of bromide anions.

These results support the hypothesis that the effective concentration of carbanions of such C–H acids as phenylacetonitrile in the course of PTC alkylation in the presence of aqueous NaOH depends on the interfacial concentration of OH^- anions (see Eq. 11), which in turn depends on a kind of X^- anions produced in the reaction, being the lowest for iodide anions.

It must be noted that the adsorption of iodide anions at the interface generally should result in a high effective concentration of I^- anions involved in the processes of the ion-exchange equilibria (e.g., $\geqslant C^-/I^-$ competition for TAA cations), which take place between the phases. Entries 5 and 7 from Table 2 clearly demonstrate this effect. The only parameter varied in these two entries was concentration of aqueuos NaOH (50 and 20 wt %, respectively). Whereas in the case of diluted NaOH, for which effect of interfacial adsorption of I^- anions might be neglected, the equilibrium content of carbanions in the organic phase was almost 100%, in the case of highly concentrated NaOH this value was significantly lower. However, this effect apparently is not important for explanation of the inhibition in PTC/OH^- alkylation with R–I, since it becomes considerable only with high conversion of the substrates, so that the ratio $I^-/\geqslant C^-$ becomes very high in the system.

The results and discussion presented in this paper unambiguously shows that the inhibitory effect of iodide anions and much weaker of bromide anions on PTC alkylation of carbanions in two-phase liquid–liquid system containing concd NaOH as the aqueous phase is not due to competition of these anions with carbanions for the lipophilic TAA cations. As it could be supposed a priori, and we have shown experimentally, direct competition between carbanions and iodide anions is always favourable for the more lipophilic anions, that is, carbanions. Since the degree of inhibition is a function of CH acidity of CH acids, iodide anions undoubtedly hinder deprotonation of the CH acids. Thus inhibition of PT catalyzed reactions of carbanions in liquid–liquid two-phase systems containing 50% aq NaOH is due to accumulation of iodide anions at the interface. In such a situation, the activity of OH^- anions in the interfacial regions is decreased and acid–base equilibrium for generation of the carbanions disfavoured.

2. Experimental

2.1. General

GLC analyses were performed on Shimadzu GC-14A gas chromatograph. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in chloroform-d_1 on Varian Gemini spectrometer (200 MHz for ^1H, 50 MHz for ^{13}C and 375 MHz for ^{19}F). Chemical shifts were assigned using signals from $CHCl_3$ (7.26 and 77.0 ppm for ^1H and ^{13}C, respectively) or $CFCl_3$ (0 ppm for ^{19}F) as internal standards. MS spectra were recorded on AMD 604 mass-spectrometer. Elemental analyses were performed on Perkin–Elmer 240 instrument. Melting points

were not corrected. All experiments were carried out using magnetic stirrer equipped with a temperature-controlled oil bath.

2.2. Reagents and substrates

Chlorobenzene, methanol, sodium chloride, bromide, iodide and hydroxide were analytical reagent grade, 50 wt % aqueous NaOH was prepared using distilled water and kept as a stock solution. Substituted phenylacetonitriles (assay 97–99%) were purchased from Aldrich®. Tetrabutylammonium (TBA) bromide, iodide and hydrogen sulfate (assay≥98%) were purchased from Fluka®. Commercial *n*-propyl halides and *n*-dodecane were distilled before use.

Tetrabutylammonium chloride (assay Cl^-≥98% by potentiometric titration with aq $AgNO_3$) was synthesized from TBA hydrogen sulfate according to published procedure.[17]

Phenylacetonitrile (assay ≥99.9% by GLC) was obtained by distillation of the commercially available product (assay 98%, Aldrich®).

2,4-Dichlorophenylacetonitrile (assay ≥99.9% by GLC) was obtained by recrystallization of the commercially available product (assay 98%, Aldrich®) from EtOH. Mp 61.5–62.5 °C (lit.[18] 62–62.5 °C). Calculated for $C_8H_5NCl_2$ (%): C 51.65, H 2.71, N 7.53, Cl 38.11. Found (%): C 51.74, H 2.84, N 7.59, Cl 38.25.

Pentafluorophenylacetonitrile was obtained from hexafluorobenzene and ethyl cyanoacetate according to published procedure.[19] The sample obtained after distillation of the crude product contained ~2 mol % (by ^{1}H NMR) of $C_6F_5CH_2CO_2Et$. The ester impurity was removed by hydrolysis with 50% aq NaOH according to following procedure. A solution of the contaminated sample (5 g) in benzene (20 mL) was mixed with excess of 50% aq NaOH (20 mL) and vigorously stirred at 40 °C for 7 h. The organic phase was separated. The aqueous phase was diluted with water (5–10 mL) and extracted with benzene (3×10 mL). The combined organic extracts were washed with saturated Na_2CO_3 (4×10 mL), water (10 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give 4.0 g of the pure pentafluorophenylacetonitrile as colourless oil. Bp 89–90 °C/~12 Torr (lit.[19] 105 °C/8 Torr). ^{1}H NMR: δ 3.8 (m, CH_2). ^{13}C NMR: δ 10.9 (α-C), 104.5 (td, Ar(C1), $^2J_{C1F2}$=17.8 Hz, $^{n>2}J_{C1Fn}$=4.2 Hz), 114.4 (CN), 137.6 (dm, Ar, $^1J_{CF}$=254.8 Hz), 141.6 (dm, Ar, $^1J_{CF}$=256.1 Hz), 144.9 (dm, Ar, $^1J_{CF}$=250.4 Hz). ^{19}F NMR: δ −160.9 (m, 2F, F3), −152.7 (t, 1F, F4, $^3J_{ortho}$=20.8 Hz), −141.8 (m, 2F, F2). Calculated for $C_8H_2F_5N$ (%): C 46.40, H 0.97, N 6.76. Found (%): C 46.31, H 0.79, N 6.65.

Phenylsulfonylacetonitrile was synthesized on the basis of published procedure for alkylation of sulfinates under PTC conditions.[20] A mixture of $PhSO_2Na$ (8.21 g, 0.05 mol), chloroacetonitrile (3.78 g, 0.05 mol), TBA chloride (0.7 g, ~2.5 mmol, ~5 mol %) in DME (10 mL) was stirred at 90–95 °C for 2 h. After cooling the intensively coloured reaction mixture was passed with Et_2O through a thin (1–2 cm) layer of SiO_2. After removal of the solvents the crude product was recrystallized twice from EtOH (20 mL and 10 mL, respectively) to give 4.91 g (54%) of the product as bright grey crystals. Mp 113–114 °C (lit.[20] 113–114 °C). ^{1}H NMR: δ 4.1 (s, 2H, CH_2), 7.7 (m, 2H, Ph), 7.8 (m, 1H, Ph), 8.1 (m, 2H, Ph). ^{13}C NMR: δ 45.7 (CH_2), 110.4 (CN), 128.8 (Ph), 129.8 (Ph), 135.4 (Ph), 136.6 (Ph). Calculated for $C_8H_7NO_2S$ (%): C 53.03, H 3.89, N 7.73, S 17.69. Found (%): C 53.01, H 4.03, N 7.70, S 17.90.

Phenylmalononitrile was obtained in 78% yield on the basis of published procedure[21] via the reaction of iodobenzene with malononitrile in DMSO/K_2CO_3 at 120 °C catalyzed by CuCl (20 mol %). The crude product contained ~5 mol % of $CH_2(CN)_2$ and some amounts of tars was sufficiently purified by passing with toluene through a thin (1–2 cm) layer of SiO_2. Mp 66–67 °C (lit.[21] 67–68 °C). ^{1}H NMR: δ 5.1 (s, 1H, H2), 7.5 (m≈s, 5H, Ph). ^{13}C NMR: δ 28.1 (C2), 111.7 (CN), 126.1 (Ph), 127.1 (Ph), 129.9 (Ph), 130.3 (Ph). $C_9H_6N_2$ Calculated: for C 76.04, H 4.25, N 19.71. Found: C 76.17, H 4.04, N 19.82.

p-Methylphenylacetonitrile-α-d$_2$ was obtained by stirring a mixture of neat *p*-methylphenylacetonitrile with ~2 wt % solution of NaOD in D_2O (prepared by careful dissolving of Na in D_2O under argon) for 12 h at room temperature, which assures complete equilibration of the hydrogen atoms on the α-carbon of the nitrile with deuterium. After two such exchanges with a 20:1 ratio of D_2O per nitrile in each exchange, more than 99% of the α-carbon hydrogens of the nitrile (^{1}H NMR δ 3.7 ppm) were replaced by deuterium.

2.3. Determining of equilibrium contents of carbanions and halides in the organic phase generated from equimolar mixtures of $ArCH_2CN$, $PhSO_2CH_2CN$ or $PhCH(CN)_2$ and TBA halides (Q^+X^-) in chlorobenzene/50% aq NaOH two-phase system at 35 °C (Table 1)

A 50 mL three-neck round-bottom flask, equipped with a gas inlet and a magnetic stirring bar, connected to a source of argon and an oil pump (~1 Torr), was charged with a solution of equimolar mixture of corresponding nitrile and TBA halide in chlorobenzene prepared in a volumetric flask (~25 mL, 0.012–0.12 M, 0.3–3 mmol each of the components). In the case of TBA chloride and iodide, which generally were not completely soluble in chlorobenzene at room temperature to give a 0.12 M solution, the solution in volumetric flask was warmed up to 35–40 °C prior to addition to the flask. Under cooling with a dry ice–acetone bath the flask was degassed in vacuum and filled with argon (three times). In the stream of argon, 50% aq NaOH (15 mL, ~300 mmol NaOH) or a solution of NaX (X=I, Br) in 50% aq NaOH (15 mL, 0.2–2 M, 3–30 mmol NaX) was added and the flask was additionally degassed in the same manner and finally filled with argon. Then the cooling bath was replaced with an oil bath and the flask was allowed to warm up to +35 °C for 1 h period time. The mixture was then vigorously stirred for 15min at 35±1 °C. After short separation of the phases (2–3 min), three samples (2×3–5 mL, 1×5–10 mL) of the clear upper organic layer were taken by a volumetric pipette. The use of centrifuge for accurate separation of the phases was not necessary since the phases were well separated by gravitation. Two samples were mixed with methanol (3–5 mL) and titrated with 0.05 M HCl using bromophenol blue as the indicator. Chlorobenzene was evaporated under reduced pressure from the third sample. The residue was dissolved in methanol (10.0 mL total volume) and potentiometrically titrated with 0.01 M $AgNO_3$ in order to determine the content of X^- in the organic phase.

2.4. Comparative experiments on alkylation of $ArCH_2CN$ (Ar=Ph, 2,4-dichlorophenyl or pentafluorophenyl) with *n*-propyl halides carried out in chlorobenzene/50% aq NaOH two-phase system in the presence of 2 mol % of TBA halides (Q^+X^-) at 35 °C (Table 3)

A 10 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with 50% aq NaOH (1.0 g, 12.5 mmol). The flask was thermostated at 35 °C and additionally charged with a homogeneous mixture of $ArCH_2CN$ (4 mmol) and 5.0 mL of chlorobenzene solution containing *n*-propyl halide (1.6 M, 8 mmol), Q^+X^- (0.016 M, 0.08 mmol, 2 mol %) and *n*-dodecane (0.16 M, 0.8 mmol, 20 mol %)—internal standard. The three chlorobenzene solutions, each containing corresponding *n*-PrX, Q^+X^- and the internal standard, were prepared once in 25 mL volumetric flasks and used for alkylation of all nitriles. Since some TBA salts (X^-=Cl^- and I^-) partially crystallized from the chlorobenzene solutions upon storage at ambient temperature, the solutions were warmed up to 35–40 °C to ensure complete dissolving of Q^+X^- salt crystals prior

to addition to the reaction flask. After mixing the reagents, the mixtures were vigorously stirred at 35±1 °C. Small samples of the organic phases were periodically taken after short stops of stirring (see Table 4). The samples were diluted with CH_2Cl_2 and analyzed by GLC. Assigned conversions of $ArCH_2CN$ were confirmed by isolation of the alkylation products and unreacted nitriles by column chromatography (SiO_2, hexane→hexane/EtOAc (20/1)).

The following products of alkylation were isolated:

2-Phenylvaleronitrile: ^{1}H NMR δ 1.0 (t, 3H, H5, $^3J_{H5H4}$=7.2 Hz), 1.5 (m, 2H, H4), 1.9 (m, 2H, H3), 3.8 (dd, 1H, H2, $^3J_{H2H3}$=8.2 Hz, $^3J_{H2(H3)'}$=6.6 Hz), 7.3–7.4 (m, 5H, Ph) is consistent with the literature data.[22] ^{13}C NMR: δ 13.4 (C5), 20.2 (C4), 37.1 (C3 or C2), 37.8 (C2 or C3), 120.8 (CN), 127.1 (Ph), 127.9 (Ph), 128.9 (Ph), 136.0 (Ph). MS (EI, 70 eV) *m*/*z* (%): 159(30, $[M]^+$), 117(100, $[M-C_3H_6]^+$). Calculated for $C_{11}H_{13}N$ (%): C 82.97, H 8.23, N 8.80. Found (%): C 82.81, H 8.42, N 8.64.

2-(2,4-Dichlorophenyl)valeronitrile: ^{1}H NMR δ 1.0 (t, 3H, H5, $^3J_{H5H4}$=7.2 Hz), 1.6 (m, 2H, H4), 1.8 (m, 2H, H3), 4.3 (t (dd), 1H, H2, $^3J_{H2H3} \approx {}^3J_{H2(H3)'} \approx 7.2$ Hz), 7.3 (dd, 1H, Ar(H5), $^3J_{ortho}$=8.4 Hz, $^4J_{meta}$=1.9 Hz), 7.4 (d, 1H, Ar(H3), $^4J_{meta}$=1.9 Hz), 7.5 (d, 1H, Ar(H6), $^3J_{ortho}$=8.4 Hz). ^{13}C NMR: δ 13.2 (C5), 20.3 (C4), 33.9 (C3 or C2), 36.0 (C2 or C3), 119.8 (CN), 127.8 (Ar), 129.6 (Ar), 129.7 (Ar), 132.4 (Ar), 133.2 (Ar), 134.5 (Ar). MS (EI, 70 eV) *m*/*z* (%): 229(24, $[M]^+$), 227(37, $[M]^+$), 187(67, $[M-C_3H_6]^+$), 185(100, $[M-C_3H_6]^+$), 43(28, $[C_3H_7]^+$). Calculated for $C_{11}H_{11}NCl_2$ (%): C 57.92, H 4.86, N 6.14, Cl 31.08. Found (%): C 57.78, H 4.70, N 6.00, Cl 31.41.

2-Pentafluorophenylvaleronitrile: ^{1}H NMR δ 1.0 (t, 3H, H5, $^3J_{H5H4}$=7.3 Hz), 1.5 (m, 2H, H4), 1.8 (m, 1H, H3), 2.1 (m, 1H, (H3)′), 4.1 (t (dd), 1H, H2, $^3J_{H2H3} \approx {}^3J_{H2(H3)'} \approx 7.9$ Hz). ^{13}C NMR: δ 13.1 (C5), 20.5 (C4), 25.7 (C3 or C2), 34.6 (C2 or C3), 109.8 (td, Ar(C1), $^2J_{C1F2}$=15.9 Hz, $^{n>2}J_{C1Fn}$=4.3 Hz), 117.4 (CN), 138.0 (dm, Ar, $^1J_{CF}$=253.5 Hz), 141.3 (dm, Ar, $^1J_{CF}$=256.3 Hz), 144.7 (dm, Ar, $^1J_{CF}$=250.3 Hz). ^{19}F NMR: δ −155.8 (m, 2F, F3), −148.2 (tt, 1F, F4, $^3J_{ortho}$=21.0 Hz, $^4J_{meta}$=2.1 Hz), −136.9 (m, 2F, F2). MS (EI, 70 eV) *m*/*z* (%): 249(19, $[M]^+$), 207(100, $[M-C_3H_6]^+$), 43(72, $[C_3H_7]^+$), 41(31, $[C_3H_5]^+$). HRMS (EI) 249.05870; calculated for $C_{11}H_8NF_5$: 249.05769. Calculated for $C_{11}H_8NF_5$ (%): C 53.02, H 3.24, N 5.62. Found (%): C 53.14, H 2.87, N 6.10.

2.5. Measurements of rate of D/H exchange in *p*-methylphenylacetonitrile-α-*d*$_2$ in chlorobenzene/50% aq NaOH two-phase system (Eq. 13)

A solution of *p*-methylphenylacetonitrile-α-d_2 in chlorobenzene (0.67 mL, 4.24 M, 2.8 mmol) was rapidly added with vigorous stirring to a 10 mL flask charged with 50% aq NaOH (1.0 mL, 1.52 g, ~19 mmol) and phenylacetonitrile (0.33 mL, 2.8 mmol, 100 mol %) or chlorobenzene (0.33 mL) to keep constant the total volume of the organic phase (1.0 mL), if phenylacetonitrile was not added. When effect of X^- anions (X^-=I^-, Br^-) or Q^+ cations on the rate of deuterium exchange was studied, corresponding salt NaX (0.2–2.0 mmol, 7–70 mol %) and/or TBA iodide (0.052 g, 0.14 mmol, 5 mol %) had been dissolved in 50% aq NaOH (1.0 mL, 1.52 g, ~19 mmol) before addition of *p*-methylphenylacetonitrile-α-d_2. The mixture was vigorously stirred at 25±1 °C. Small samples of the organic phases were periodically taken after short stops of stirring (e.g., 0.5 min, 1 min, 2 min, 5 min, 10 min, 20 min), rapidly mixed with excess of 5% aq HCl and vigorously shaken. After separation from the aqueous phase the samples were mixed with $CDCl_3$ and placed in an NMR tube by passing through a thin layer of $MgSO_4$ in a Pasteur pipette. The degree of deuterium exchange was determined by ^{1}H NMR technique on the basis of intensity of H signal of the methylene group using signal of *p*-methylphenylacetonitrile (δ 2.4 ppm) used as the internal standard. Chemical shifts (ppm) of the methylene protons in $ArCH_2CN$: δ 3.8 (Ar=Ph) and 3.7 (Ar=*p*-methylphenyl).

References and notes

1. Jarrousse, J. *Compt. Rend. Hebd. Seances Acad. Sci. Ser. C* **1951**, *232*, 1424–1426.
2. Mąkosza, M.; Serafinowa, B. *Rocz. Chem.* **1965**, *39*, 1223–1231; *Chem. Abstr.* **1966**, *64*, 12595h.
3. Mąkosza, M.; Serafinowa, B. *Rocz. Chem.* **1965**, *39*, 1401–1408; *Chem. Abstr.* **1966**, *64*, 17474g.
4. Urbański, T.; Beżecki, C.; Lange, J.; Mąkosza, M.; Piotrowski, A.; Serafinowa, B.; Wojnowska, H, Polish Patent 46030, 1962.
5. Mąkosza, M.; Serafin, B.; Urbański, T. *Chim. Ind.* **1965**, *93*, 537–539.
6. Mąkosza, M. *Tetrahedron Lett.* **1966**, 4621–4624; Mąkosza, M. *Tetrahedron Lett.* **1969**, 673–676, 677–678; Mąkosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659.
7. Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.
8. Mąkosza, M.; Fedoryński, M. *Advances in Catalysis*; Academic: New York, NY, 1987; Vol. 35, 375–422; Mąkosza, M.; Fedoryński, M. *Catal. Rev.* **2003**, *45*, 321; Dehmlow, E. V.; Dehmlow, S. S. *Phase-Transfer Catalysis*, 3rd ed.; Chemie: Weinheim, 1993; Starks, C. M.; Liotta, C.; Halpern, M. *Phase Transfer Catalysis. Fundamentals, Applications and Industrial Perspectives*; Chapman & Hall: New York, NY, 1994.
9. Masuyama, Y.; Keno, Y.; Okawara, M. *Tetrahedron Lett.* **1976**, 2967; Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann.* **1988**, 203; Diez-Barra, E.; De La Hoz, A.; Sanchez-Migallon, A.; Sanchez-Verdu, P.; Bram, G.; Loupy, A.; Pedoussant, M.; Pigeon, P. *Synth. Commun.* **1989**, *19*, 293.
10. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
11. Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V.; Tuttle, T. R., Jr. *J. Phys. Chem. A* **1998**, *102*, 7787–7794.
12. Mąkosza, M.; Białecka, E. *Tetrahedron Lett.* **1977**, 183–186.
13. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New York, NY, 2001; pp 445–449.
14. Mąkosza, M. *Pure Appl. Chem.* **1975**, *43*, 439–462; Mąkosza, M.; Lasek, W. *J. Phys. Org. Chem.* **1993**, *6*, 412.
15. Sawarkar, C. S.; Juvekar, V. A. *Ind. Eng. Chem. Res.* **1996**, *35*, 2581–2589.
16. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
17. Brandstrom, A. *Preparative Ion Pair Extraction: An Introduction to Theory and Practice*; Apotekarsocieteten Hassle, Lakemedel: Stockholm, 1974; p 144.
18. Reeve, W.; Pickert, P. E. *J. Am. Chem. Soc.* **1957**, *79*, 1932–1934.
19. Filler, R.; Woods, S. M.; Ferring, A. E.; Sheppard, W. A. *Org. Synth.* **1977**, *57*, 80–83.
20. Wildeman, J.; van Leusen, A. M. *Synthesis* **1979**, 733–734; Bram, G.; Loupy, A.; Sansoulet, M. C.; Strzałko, T.; Seyden-Penne, J. *Synthesis* **1987**, 56–59.
21. Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606–7607.
22. Freerksen, R. W.; Selikson, S. J.; Wroble, R. R.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 4087–4096.