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Remarks on the Mechanism of Phase-Transfer Catalyzed Carbanion Generation in Two-Phase Systems

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Abstract: Competitive of addition of CCl^-_3 anions to N-alkyl-pyridinium salts and to vinyl acetate, t-butyl acrylate and benzaldehyde was studied in a two-phase system, chloroform / conc. aqueous NaOH, and in a homogeneous medium. The results support an interfacial mechanism for generation of carbanions and indicate that chloroform is deprotonated by NaOH at the interface.

Key words: phase-transfer catalysis, N-alkyl pyridinum salts, interfacial reactions, carbanions

Phase-Transfer Catalysis, PTC, is presently one of the most widely used methodologies in organic synthesis.[2,3] The main application of this catalytic procedure is to be found in numerous reactions of organic and inorganic anions with a variety of partners. This methodology offers particularly great benefits for reactions of carbanions and dihalocarbenes promoted by strong bases.[2,3] These reactive intermediates are very efficiently generated in two phase systems in the presence of conc. aqueous sodium hydroxide and catalysts - tetraalkylammonium salts such as triethyl benzyl ammonium chloride TEBA or tetrabutyl ammonium chloride TBA.

Due to the effectiveness of these systems in numerous reactions of carbanions and dihalocarbenes soon after publication of the first papers[4,5] this methodology become widely used. On the other hand from the beginning there was substantial controversy concerning mechanistic features of this catalytic process.

Initially the extraction mechanism proposed by C.M.Starks for nucleophilic substitution and some other reactions of inorganic anions[6] and suggested earlier in our paper on dichlorocarbene generation[5] was commonly accepted. However, soon this extraction mechanism was found to be inadequate because the partition coefficient is very unfavourable for extraction of OH^- anions into the organic phase. Additionally, the high efficiency of the PTC dichlorocarbene reactions and the low degree of

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hydrolysis were inconsistent with presence of OH^- anions and water in the organic phase.

In order to rationalize these observations an interfacial mechanism was proposed,[2] eq.1 according to which the deprotonation of CH acids takes place at the interface between two immiscible phases - organic phase containing CH acid and an aqueous conc. NaOH solution. The ion pair $R_3C^-Na^+$ generated at the interface is unable to leave the phase boundary because Na^+ cannot be extracted into nonpolar organic solvents, whereas carbanions do not enter highly conc. NaOH solution. The ion-exchange with a tetralkylammonium salt, e.g. chloride Q^+Cl^-, results in the formation of lipophilic ion pairs $R_3C^-Q^+$ which migrate into the organic phase, and sodium chloride which goes to the aqueous phase.

$$R_3CH_{org} + Na^+OH^-_{aq} \rightleftharpoons R_3^-CNa^+_i + H_2O_{aq} \quad a$$

$$R_3C^-Na^+_i + Q^+X^-_{org} \rightleftharpoons R_3C^-Q^+_{org} + Na^-X_{aq} \quad b \qquad \text{eq.1}$$

i - denotes the interfacial region, aq and org - aqueous and organic phase

This mechanism was subsequently supported by numerous experimental results and is now generally accepted.[3,7-9]

In the recent monograph by C.M. Starks, C. Liotta and M. Halpern this mechanism was considered inadequate and a new "modified interfacial mechanism" MIM proposed.[10] According to this mechanism the interfacial region is considered as a third phase in which free ion exchange processes proceed unaffected by extractibilities of various ion-pairs. Thus, in this third phase the equilibrium ion-exchange between tetraalkylammonium halide and sodium hydroxide produces tetraalkyl ammonium hydroxide, which actually acts as the base for deprotonation of CH acids in the interfacial region. This mechanistic proposal can be presented by eq.2:

$$Q^+Cl^-_i + Na^+OH^-_i \rightleftharpoons Q^+OH^-_i + Na^+Cl^-_i \quad a$$

$$R_3CH_i + Q^+OH^-_i \rightleftharpoons R_3C^-Q^+_i + H_2O_i \quad b \qquad \text{eq.2}$$

$$R_3C^-Q^+_i \longrightarrow R_3C^-Q^+_{org} \quad c$$

In order to evaluate this interesting hypothesis one should analyze whether formation of $R_3C^-Q^+$ ion-pairs is possible in this way and, if so, is it necessarily the way on which $R_3C^-Q^+$ ion pairs are produced. First, one should consider that when the interfacial region is defined as a new (third) phase, which by definition should be homogeneous and in which ions exchange freely, then a distinction between OH^- associated with Q^+ or Na^+ as in eq 2a should not be possible. Similarly, one cannot distingish between NaCl and KBr and NaBr and KCl in an aqueous solution of these salts according to eq.3, unless one component is precipitated or extracted.

$$K^+Cl^- + Na^+Br^- \rightleftharpoons K^+Br^- + Na^+Cl^- \qquad \text{eq. 3}$$

This statement is obviously somewhat oversimplified, because there could be various degrees of association between the ions and also the solvation of ions in this third phase cannot be evaluated. Nevertheless this simplification can be accepted because it comes directly from the concept of the third phase.

Accordingly, deprotonation of a CH acid with OH^- anions in this third phase would proceed irrespectively whether OH^- is associated with Q^+ or Na^+. Thus, deprotonation with Q^+OH^- in this third phase should be of course a feasible process, but undistinguishable from deprotonation with Na^+OH^-. For the same reason it should not matter whether $R_3C^-Q^+$ is formed directly according to eq. 2b, or via ion exchange as in eq.1, because the driving force for formation of this lipophilic ion pair is its departure from the interfacial region, or the third phase, into the organic phase so, irrespective of the mechanisms shown in eq.1 and 2, the overall process can be pictured, by eq.4.

$$R_3CH_{org} + Na^+OH^-_{aq} + Q^+Cl^-_{org} \rightleftharpoons R_3C^-Q^+ + Na^+Cl^-_{aq} + H_2O_{aq} \qquad \text{eq.4}$$

On the other hand, undoubtedly deprotonation of CH acids to form carbanions can occur without Q^+OH^-. There are numerous papers in which interfacial deprotonation and further reactions of carbanions are described in the absence of Q^+X^-.[7-9] Thus, generally speaking, the modified interfacial mechanism, MIM[10] is possible but not always necessary.

In order to gain additional insight into this problem we have studied interfacial reactions of N-alkylpyridinium salts, in which the liphophilic N-alkylpyridinium cations are simultaneously active electrophilic reactants. In 1973 F. Kröhnke reported that treatment of a chloroform solution of alkylpyridinium salts with conc. aqueous NaOH results in the formation of CCl_3 adducts in the 2- and 4- positions of the pyridine ring.[11] These adducts, N-alkyldihydropyridines, are of moderate stability and the 2-CCl_3 adducts tend to rearrange to the 4-isomers.A studies of this reaction could answer a few questions: 1. Does generation of CCl^-_3 proceed via initial formation of $C_5H_5N^+R\ OH^-$ in the interfacial region according to MIM as shown in eq. 5:

$$C_5H_5\overset{+}{N}R\ Cl^-_i + NaOH_i \rightleftharpoons C_5H_5\overset{+}{N}R\ OH^-_i + NaCl_i \qquad a$$

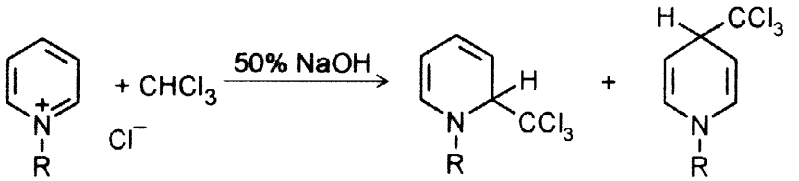
$$C_5H_5\overset{+}{N}R\ OH^-_i + CHCl_{3i} \longrightarrow C_5H_5\overset{+}{N}R\ CCl^-_{3i} + H_2O \qquad b \qquad \text{eq. 5}$$

$$C_5H_5\overset{+}{N}R\ CCl^-_{3i} \longrightarrow CCl_3C_5H_5NR \qquad c$$

2. Is formation of the new C-C bond between the ring carbon of the pyridinium salts and CCl_3^- preceeded by the formation of liphophilic ion-pairs which can subsequently enter the organic phase?

3. What is electrophilic activity of $C_5H_5N^+R$ cations?

For these studies we have selected N-2,4,6-trimethylbenzyl and N-benzhydryl pyridinium chlorides **1** and **2** which form CCl_3 adducts sufficiently stable to be isolated without loss of the material. When chloroform solutions of both these salts were treated with conc. NaOH the adducts **1a** + **1b** and **2a** + **2b** were formed in yields exceeding 90% and purity exceeding 95% Ratio **1a**:**1b** as estimated by ^{1}HNMR was ca. 28:1 and **2a**:**2b** ca 23:1, eq.6.



eq. 6

R = 2,4,6-Me_3PhCH_2 **1**	**1a**	**1b**	93%	23:1
R = Ph_2CH **2**	**2a**	**2b**	92%	28:1
			from NMR	

Further purification of the mixtures of the adducts resulted in partial isomerisation **1a**, **1b** into **2a, 2b**.

It should be stressed that the addition was a "clean" reaction, the reaction mixture was pale yellow and no tars were formed. On the other hand when a solution of **1** or **2** in an inert solvent, where deprotonation was not possible, such as toluene, o-dichlorobenzene or tetramethyl urea, was treated with conc. aqueous NaOH in absence of $CHCl_3$, rapid consumption of the salts resulted in formation of unidentified dark tarry materials. Apparently addition of OH^- anion to **1** and **2** gave unstable N-alkyl-2-hydroxydihydropyridines which decompose during the reaction. Results of these simple experiments indicate that N-alkyl pyridinium hydroxides are not involved in deprotonation of $CHCl_3$. Moreover the results show that when in the two-phase system: organic solvent - conc. aqueous NaOH, a CH acid which can be deprotonated at the phase boundary is present it apparently prevents the ion - exchange and formation of alkyl pyridinium hydroxides $C_5H_5N^+$-R OH^- in the interfacial region. Thus, in general one can assume that in the studied system not only are Q^+OH^- ion pairs not intermediates in the formation of R_3C^- Q^+ in the interfacial region but *in the presence a CH acid such as chloroform they are not formed at all.*

In order to clarify whether formation of the CCl_3 adducts **1a,b** and **2a,b** is preceeded by formation of lipophilic ion pairs $C_5H_5N^+$-R CCl_3^- able to enter the organic phase, that is whether the pyridinium salts **1** or **2** can behave as phase transfer catalysts for reactions of CCl_3^- anions, the experiments as shown in eq.6 were repeated in the presence of additional carbanion acceptors, **A**, such as vinyl acetate **3**, t-butyl acrylate **4** and benzaldehyde **5**. It is well known that under the PTC conditions these compounds efficiently add CCl^-_3 anions with the formation 1,1,1-trichloroisopropylacetate **3a**,[12] t-butyl 4,4,4-trichlorobutyrate **4a**[13] and 2,2,2-trichloro-1-phenylethanole **5a**[14] respectively. In all these experiments

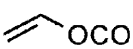
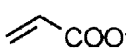
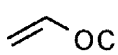
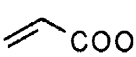
we have observed that only the adducts of CCl_3^- to the pyridinium salts **1a,b** and **2a,b** are formed. No adducts of CCl^-_3 to **A** were detected in the reaction mixtures using ^1H NMR. Similar competition experiments were performed in a homogeneous medium in which a solution of $Bu_4N^+OH^-$ in tetramethyl urea TMU, prepared in advance via ion-pair extraction, according to eq. 7 was used for generation of CCl^-_3 anions.

$$Bu_4N^+HSO^-_{4\,org} + NaOH_{aq} \xrightarrow{TMU} Bu_4N^+OH^-_{org} + Na_2SO_4 \qquad \text{eq.7}$$

Addition of CCl_3^- to the pyridinium salts proceeded efficiently also in this homogeneous system giving **1a,b** and **2a,b** in high yields. On the other hand when solutions of **1** or **2** with equimolar amounts of **3**,**4** or **5** in TMU containing excess of chloroform were treated with a solution of $Bu_4N^+OH^-$ in TMU, besides the expected **1a,b** and **2a,b** substantial amounts of the CCl_3^- adducts **3a**, **4a** and **5a** to competing carbanion acceptors **A** were formed. The results are presented in table 1.

Table 1

1 or 2 + $CHCl_3$ + A (**3**, **4** or **5**) $\xrightarrow{B^-}$ **1a,b** or **2a,b** + A–CCl_3 (**3a**, **4a** or **5a**)

		B^- = NaOH aq, two-phase		$Bu_4N^+OH^-$, TMU, homogeneous systems	
Salt	A	yields %		yields %	
		1a,b or **2a,b**	A-CCl_3	**1a,b** or **2a,b**	A-CCl_3
1	none	93	none	84	none
1		98	-	45	**3a**,13
1		88	-	74	**4a**, 7
2	none	92	none	97	
2		92	-	64	**3a**, 15
2		70	-	58	**4a**, 15
2	PhCHO	90	-	60	**5a**, 46

These results indicate that in the competition for the reaction with CCl_3^- anions generated in a homogeneous medium between the pyridinium salts and carbanion acceptors **A**, the former were more active than t-butyl acrylate and vinyl acetate and of similar activity compared to benzaldehyde. This is

in a good correlation with our early observations that vinyl acetate and t-butyl acrylate are less active electrophiles than benzaldehyde and are unable to react with interfacially located carbanions when Q^+Cl^- catalyst is absent, whereas some reactions of benzaldehyde with such carbanions occur.[7] On the other hand the pyridinium cations, being charged species, are much more efficient in the reaction with carbanions located at the interface than uncharged electrophiles.

Results and discussion presented in this paper strongly support the original interfacial mechanism of phase transfer catalyzed reactions of carbanions and dihalocarbenes - namely deprotonation of the CH acids at the phase boundary with aqueous NaOH followed with formation of the lipophilic ion pair $R_3C^-Q^+$ at the interfacial region as in eq. 1.

It appears that the "modified interfacial mechanism", although possible, does not represent the major pathway of generation of carbanions and formation of the lipophilic ion pairs in PTC reactions of carbanions and halocarbenes.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were taken on a Varian Gemini instrument (200 Mhz for ^1H and 50.3 Mhz for ^{13}C) in $CDCl_3$. Signals of CH atoms obtained from DEPT- experiments are marked with an asterix. Mass spectra were obtained on AMD-604 spectrometer.

t-Butyl acrylate, vinyl acetate, benzaldehyde, chlorodiphenylmethane, $Bu_4N^+HSO_4^-$ and tetramethylurea TMU were commercial compounds. $CHCl_3$, CH_2Cl_2, CH_3CN were distilled over P_2O_5; pyridine was distilled before use. 2,4,6-Trimethylbenzylchloride was prepared according to described procedure.[15] Salt **1** was prepared by refluxing equimolar amount of reagents in acetone for 3h, salt **2** was obtained by refluxing chlorodiphenylmethane in pyridine for 1h.

Reaction of the pyridinium salt 1 in two-phase systems.

To a solution of salt **1** (0.99 g, 4 mmol) in $CHCl_3$ (18 mL) was added 50% aq. solution of NaOH (6 mL) at 0°C and the mixture was vigorously stirred for 15 min at this temperature. Then the mixture was poured into ice-cooled water the, organic phase was separated, washed twice with cold water and dried over $MgSO_4$. The solvent was evaporated and the residue was analysed by ^1H NMR spectroscopy with anisole as an internal standard. Overall calculated yield of adducts **1a** and **1b** were ca. 93%, ratio **1a**:**1b** ca. 23:1. In order to isolate individual **1a** the residue was dissolved in acetone and cooled with dry ice, the precipitate was filtered and analyzed was pure **1a**.

SThe filtrate was concentrated and the brown residue was analysed by ^1H NMR spectroscopy. It was a mixture of **1a** and **1b** in ratio ca. 4:1.

Reaction of pyridinum salt 2 in two-phase system.

To a solution of **2** (1.13 g, 4 mmole) in $CHCl_3$ (8 mL) was added 50% aq solution of NaOH (6 mL) at 0°C. The reaction was carried out as for **1**. Overall yield of adducts **2a** and **2b** was 92% ratio **2a**:**2b** ca. 28:1.

1a. M.p. 80-81°C (dec.). ^1H NMR ($CDCl_3$): δ = 6.90 (s,2H),6.31 (dd, J=5.9,9.2 Hz, 1H), 5.93 (dm, J = 1.0,7.1 Hz) 1H), 5.39 (dd, J = 1.0, 5.9, 9.2 Hz, 1H), 5.24 (d, J = 13.8 Hz, 1H, H of CH_2), 4.93 (ddd, J = 1.2, 5.9, 7.1 Hz, 1H), 4.85 (dd, J = 1.2, 5.9 Hz, 1H), 4.15 (d, J = 13.8 Hz, 1H, H of CH_2), 2.31 (s, 3H), 2.29 (s, 6H). ^{13}C NMR ($CDCl_3$): σ = 138.06, 137.79, 134.93*, 127.86*, 107.12, 106.63*, 98.39*,76.72*, 55.85 (CH_2), 21.04 (CH_3), 19.99 (CH_3). MS (70 eV), m/z (%): 212 [$M^+ - CCl_3$] (18), 133 [$Me_3C_6H_2CH_2^+$] (100), 117 [CCl_3^+] (7), 105 (7), 91 (7), 79 (3). LSIMS: 329 [M^+]. EIHR: calcd. For [$M^+ - CCl_3$] $C_{15}H_{18}N$

212.1439; found 212.1437. $C_{16}H_{18}Cl_3N$ (330.69): calcd. C 58.11, H 5.48, Cl 32.16, N 4.23; found C 58.14, H 5.44, Cl 32.20, N 4.23.

1b. ^1H NMR ($CDCl_3$) δ = 6.90 (s, 2H), 6.15 (dm, J = 8.0 Hz, 2H), 4.80 Hz, 2 H), 4.80 (m, 2 H), 4.37 (s, 2H, CH_2), 4.09 (t, J = 4.3 Hz, 1H), 2.31 (s, 3H, CH_3), 2.30 (s, 6H, 2 CH_3).

2a. M.P. 105-6°C (dec.). ^1H NMR ($CDCl_3$): δ = 7.4 (m, 10H, 2 Ph), 6.46 (dd, J = 5.8, 9.2 Hz, 1H) 6.33 (s, 1H), 6.21 (dm, J = 7.3 Hz, 1H), 5.43 (ddm, J= 1.1, 5.9, 9.2 Hz, 1H), 5.14 (ddd, J = 1.1, 5.8, 7.3 Hz, 1H), 4.91 (dm, J = 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 141.67, 138.89, 133.91*, 129.94*, 128.76*, 128.57*, 128.03*, 127.90*, 127.70*, 108.19*, 106.83, 99.59*, 74.15*, 72.70*, MS (70 eV) m/z (%): 246 [M^+ - Ccl3] (13); 167 [Ph_2CH^+] (100), 152 (12). LSIMS: 386 [M^+ + Na], 364 {M^+ + H]. EIHR: calcd. for [M^+ - CCl_3] $C_{18}H_{16}N$ 246.1282; found 246.1293. $C_{19}H_{16}Cl_3N$ (364.71): calcd. C 62.57, H 4.42, Cl 29.16, N 3.84, found C 62.69, H 4.50, Cl 28.92, N 3.69.

2b. ^1H NMR ($CDCl_3$): σ = 7.5-7.15 (m, 10H, 2 Ph), 6.32 (dm, J = 8.0 Hz, 2 H), 5.71 (s, 1H), 4.87 (m, 2H), 4.14 (t, J = 4.2 Hz, 1H).

Reaction of 1 and 2 with NaOH in two-phase system in absence of $CHCl_3$

A solution of **1** or **2** in CH_2Cl_2 or tetramethyl urea was stirred with 50% aqueous solution of NaOH at 0°C, the mixtures immediately turned dark brown. Analysis of the mixture indicated that **1** and **2** were totally converted into unidentified dark tars.

Competition experiments in two-phase systems. To a solution of salts **1** or **2** (4 mmol) and competing substrate **3**, **4** or **5** (4 mmol) in $CHCl_3$ (18 mL) was added 50% aq. solution of NaOH (6 mL) at O°C. Further manipulations were as described above. In these experiments only products of the addition of CCl_3^- to pyridine ring **1a**, **1b** and **2a**, **2b** were observed.

Reactions in TMU under homogeneous conditions. To a solution of $Bu_4N^+HSO_4^-$ (3.39 g, 10 mmol) in TMU (20 mL) 50% aq. solution of NaOH (10 mL) was added at 0-5°C and the mixture was stirred for 15 min at this temperature. Then organic layer was separated and used in further reactions. The concentration of $Bu_4N^+OH^-$ determined *via* titration with 0.1 HCl was 0.42 M. This solution (2.2 mmol, 5.2 mL) was added to a solution of salt **1** or **2** (2 mmol) in $CHCl_3$ (3 mL) cooled to 0°C. The mixture was stirred for 15 min, then poured into ice-cooled water and extracted with ether. The organic phase was washed with water, dried over $MgSO_4$ and the solvent evaporated. The residue was analysed by ^1H NMR spectroscopy with anisole as an internal standard.

For **1**: the dark brown residue was the mixture of **1a** and **1b** in ratio 16:1, calculated overall yield of **1a** and **1b** was 84%

For salt **2**: the dark brown residue was the mixture of **2a** and **2b** in ratio 3.3 : 1, calculated overall yield of **2a** and **2b** was 97%.

Competition experiments in TMU under homogeneous conditions. A solution of $Bu_4N^+OH^-$ in TMU (2.2 mmol, 5.2 mL) was added to a solution of equimolar amount of the pyridinium salt **1** or **2** and competing substrate **3, 4** or **5** (2 mmol) in $CHCl_3$ (3 mL), cooled to 0°C and the mixture was stirred for 15 min at this temperature. All further manipulations were as described above. The residue was analysed by ^1H NMR spectroscopy using anisole as an internal a standard.

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