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Phase Transfer Catalyzed Reactions of Chloroform with Electrophilic Alkenes. Effect of Solvent on Reaction Course

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Abstract: Reaction of chloroform with acrylic esters **1a-g**, carried out in the presence of 50% aq NaOH, benzyltriethylammonium chloride (TEBACl) as a catalyst in heptane, gives exclusively adducts of trichloromethyl anion **2a-g** with good yields. The same reaction carried out in the absence of solvent yields a mixture of products.

Keywords: carbanions; phase transfer catalysis; solvent and solvent effects; Michael reactions

Reactions of haloforms with concentrated aqueous solution of sodium hydroxide and a quaternary ammonium salt Q^+X^- as a catalyst (phase-transfer catalysis, PTC[1]) generate trihalomethyl anion, which further splits into dichlorocarbene.[2] According to well documented Mąkosza mechanistic picture,[3] deprotonation of haloform occurs at the phase boundary between the organic phase, containing haloform and appropriate reagent, and concentrated aqueous sodium hydroxide phase. Trihalomethyl anion thus formed migrates into organic phase as an ion pair with lipophilic tetraalkylammonium cation Q^+, where it can undergo reversible dissociation to dihalocarbene and Q^+X^-. In such an equilibrating system

$$Q^+CX_3^- \rightleftharpoons Q^+X^- + CX_2 \qquad (1)$$

the final outcome depends on the philicity of the reactant: nucleophilic alkenes react with dihalocarbene, whereas electrophilic ones (Michael acceptors) can react with trihalomethyl anion.

This mechanistic picture describes correctly the general path of catalytic process, however it is somewhat oversimplified. It doesn't take into account the differences in reaction course caused by the structure of ammonium salts. There are many reported cases indicating that reactions of equilibrating system (1) with alkenes,[4-10] especially with electrophilic ones,[11-14] are very sensitive to the kind of tetraalkylammonium cation used, its lipophilicity in particular, and to other reaction parameters (for short reviews see Refs 15-17). For instance reaction of unsubstituted acrylic esters with chloroform, carried out in the presence of typical lipophilic catalysts, such as benzyltriethylammonium chloride (TEBA) lead to trichloromethyl anion addition products (methyl[14,18] and ethyl[19] acrylates) or to mixtures of products (acrylic esters of higher alcohols[11,14]), whereas in the presence of tetramethylammonium (TMA) salts they form dichlorocarbene addition products, with high selectivity.[12-14] (Scheme 1).

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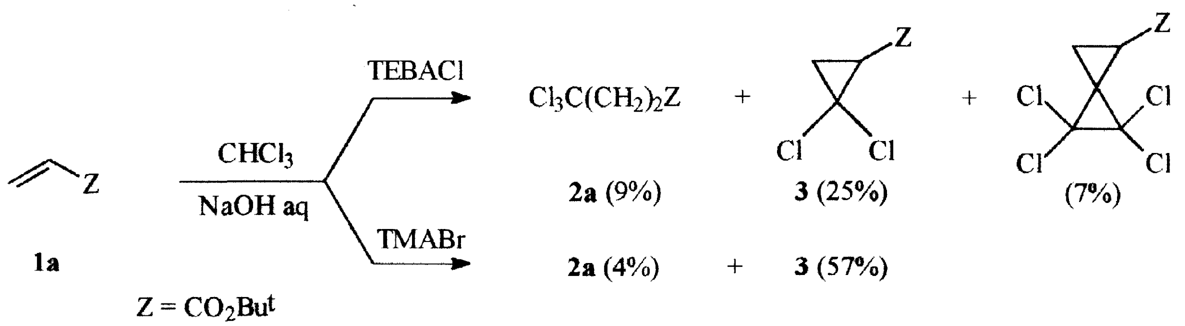
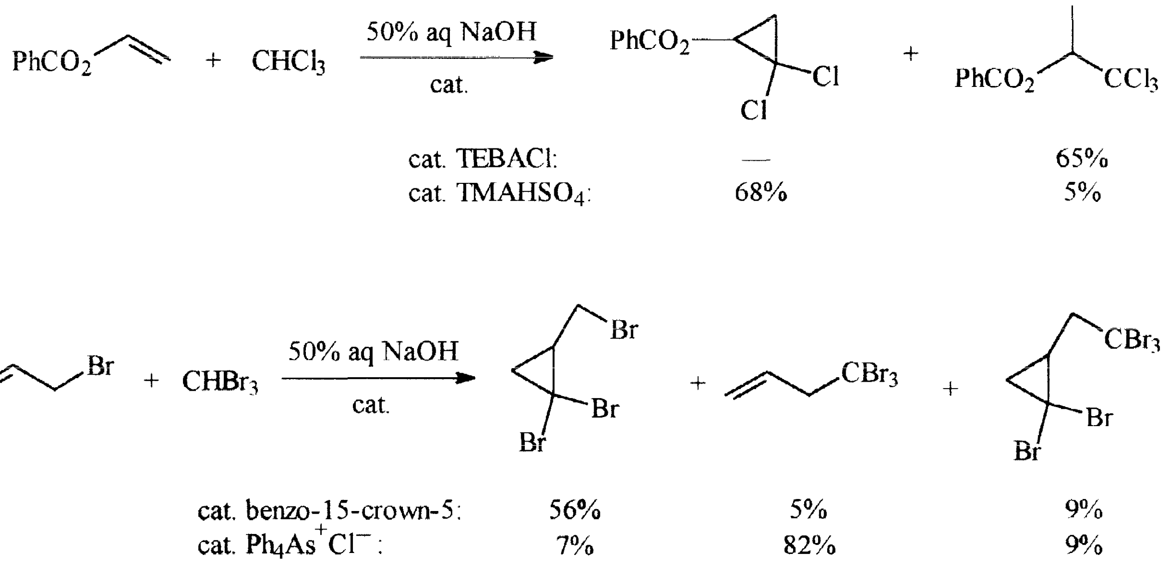


Scheme 1

Other examples of the influence of the catalyst structure on reaction course include: (a) reactions of chlorodibromomethane with alkenes (with TEBACl, mixtures of all possible *gem*-dihalocyclopropanes[4], with dibenzo-18-crown-6[5,6] or TMACl[7] — *gem*-bromochlorocyclopropanes are formed, with high selectivity); (b) reactions of allyl bromides with bromoform (large, or highly delocalized ions favor allylation of tribromomethyl anion,[9] while TMA salts and benzocrown ethers — dibromocarbene addition[9]); (c) reactions of unconjugated di- and polienes with chloroform (with TMACl monoaddition, with lipophilic catalysts — polyaddition products prevail[8]); (d) reactions of alkenyl carboxylates with chloroform (TMA salts promote dichlorocyclopropanation, TEBACl — products of reactions with trichloromethyl anion[10]). Two spectacular examples are given on Scheme 2.

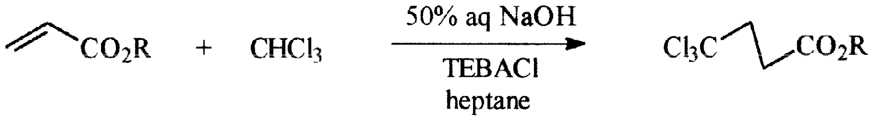


Scheme 2

We suggested previously[13] that TMA salts favor *gem*-dichlorocyclopropanation of some electrophilic alkenes because they are practically devoided of lipophilic properties.[20] Ion pairs $TMA^+CCl_3^-$, formed in low concentration at the interphase, cannot penetrate into the organic phase. Due to small size of TMA cation, these ion pairs are tight, therefore the activity of the trichloromethyl anion is insufficient to add to electrophilic alkenes. On the other hand, dichlorocarbene formed in dissociation process (1) can leave phase boundary and add to double bond with formation of dichlorocyclopropane derivatives.

Now, we wish to report the results of PTC reactions of chloroform with acrylic esters, carried out in the presence of TEBACl and aliphatic hydrocarbon as a solvent. In such system the presence of nonpolar solvent decrease the solubility of $TEBA^+CCl_3^-$ in organic phase, but should not exert strong effect on the tightness of this ion pair.

Initial investigations were carried out on the reaction of t-butyl acrylate (**1a**). Using five molar excess of chloroform and heptane as a solvent (equal of chloroform volume) we found that only addition of trichloromethyl anion takes place with the formation of **2a**, in good yield and high selectivity. Use of pentane, hexane or isooctane instead of heptane led to the same result. With benzene, toluene, dioxane and anisole however, the mixtures are formed, in which product **2a** prevails. Lowering the amount of heptane results in the formation of three products, as shown on Scheme 1. Other acrylic esters of higher alcohols **1b-g** behave similarly (Scheme 3, Table).



1 **2**

1-2	**a**	**b**	**c**	**d**	**e**	**f**	**g**
R	Bu^t	Bu^s	Bu^i	Bu^n	$(CH_2)_2OCH_3$	Pr^n	2-ethylhexyl
Yield of **2** (%)	53	46	59	64	49	54	30

Scheme 3

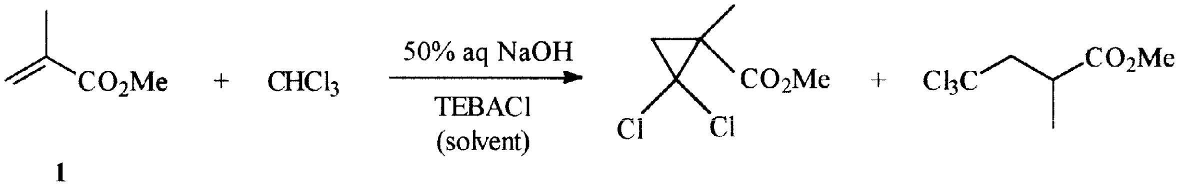
When stirred with chloroform in the absence of solvent, all acrylic esters investigated gave more or less complicated mixtures of products, except **1g**. Reaction of **1g** led to the formation of **2g** exclusively, although in rather low yield. Probably the long aliphatic chain in this substrate mimic the solvent.

We suppose, that the presence of nonpolar solvent shifts the equilibrium (1) to the left. Solubility of $TEBA^+CCl_3^-$ ion pair in chloroform/heptane mixture is probably better as compared with TEBACl. An ion pairs with TEBA cation are less tight than with TMA, therefore trichloromethyl anion is active enough to add to Michael acceptor. The possibility that the solvent influences dichlorocarbene selectivity was ruled out on the basis of competitive experiments.[21] We found the same relative activities with and without the solvent.

Solvent	$k_{2\text{-methyl-2-butene}}/k_{\text{cyclohexene}}$ [a]
—	18.2 ± 0.4
hexane	19.3 ± 0.6
heptane	18.1 ± 0.5

[a] Results obtained from three independent experiments

With less electrophilic (substituted at double bond) acrylates the effect of the solvent was not so pronounced. For instance, in the reaction of methyl methacrylate with chloroform in heptane we obtained a mixture of carbene and anion adducts, in which the former prevails. In the absence of a solvent, under the same reaction conditions, dichlorocyclopropane derivative is formed exclusively (Scheme 4).



1

heptane	26%	5%
—	50%	—

Scheme 4

In 1993 Bieler et al. reported, that diethyl vinylphosphonate with chloroform and TEBACl in PTC reaction gives trichloromethyl anion exclusively[22] (for similar observation see also Refs 23,24); when this reaction was carried out in heptane, product of dichlorocarbene addition to double bond was obtained. The influence of the solvent on reaction course is opposite to that observed in this work for reactions with acrylic esters. However, in our hands experiments performed under the same conditions as described[22], gave in both cases diethyl 3,3,3-trichloropropylphosphonate exclusively (see Experimental).

Table. Characterization Data of **2**

2	Reaction time (h)	Yield (%)	B.p. (°C/ Torr)	^{1}H NMR, δ ($CDCl_3$, 200 MHz), J (Hz)	M. F. M. W.	Analysis (%); Calcd/Found C	 H	 Cl
a	3.5	53	60 – 62/0.4	1.47 [s, 9H, $C(CH_3)_3$], 2.61 – 2.79 and 2.93 – 3.10 (two sym. m, 4H, CH_2CH_2)	$C_8H_{13}Cl_3O_2$ 247.55	38.82 38.73	5.29 5.27	42.97 42.74
b	4	46	74/0.6	0,90 (t, J = 7.4, 3H, $CH_2\mathbf{CH_3}$), 1.21 (d, J = 6.2, 3H, $CH\mathbf{CH_3}$), 1.47 – 1.69 (m, 2H, CH_2), 2.73 – 2.81 and 3.00 – 3.09 (two sym. m, 4H, CH_2CH_2), 4.86 (qt, J = 6.2, J = 6.4, 1H, CH)	$C_8H_{13}Cl_3O_2$ 247.55	38.82 38.99	5.29 5.32	42.97 42.64
c	3	59	68 – 70/0.1	0.94 (d, J = 6.7, 6H, 2 × CH_3), 1.85 – 2.05 (m, 1H, CH), 2.77 – 2.85 and 3.02 – 3.11 (two sym. m, 4H, CH_2CH_2), 3.90 (d, J = 6.7, 2H, OCH_2)	$C_8H_{13}Cl_3O_2$ 247.55	38.82 38.73	5.29 5.35	42.97 43.12
d	3	64	70 – 72/0.12	0.93 (t, J = 7.2, 3H, CH_3), 1.28 – 1.46 (m, 2H, CH_2), 1.55 – 1.70 (m, 2H, CH_2), 2.74 – 2.82 and 3.00 – 3,08 (two sym. m, 4H, CH_2CH_2), 4.11 (t, J = 6.6, 2H, OCH_2)	$C_8H_{13}Cl_3O_2$ 247.55	38.82 38.89	5.29 5.26	42.97 42.60
e	2	49	77 – 78/0.3	2.79 – 2.90 and 2.98 – 3.09 (two sym. m, 4H, CH_2CH_2), 3.37 (s, 3H, OCH_3), 3.56 – 3.61 and 4.23 – 4.28 (two sym. m, 4H, OCH_2CH_2O)	$C_7H_{11}Cl_3O_3$ 249.52	33.70 33.97	4.44 4.48	42.63 42.40
f	2.5	54	62 – 64/0.4	0.94 (t, J = 7.2, 3H, CH_3), 1.57 – 1.74 (m, 2H, $\mathbf{CH_2}CH_3$), 2.74 – 2.82 and 3.00 – 3.08 (two sym. m, 4H, CH_2CH_2), 4.06 (t, J = 6.7, 2H, OCH_2)	$C_7H_{11}Cl_3O_2$ 233.52	36.00 36.26	4.75 4.78	45.55 45.14
g	8	30	125/0.5	0.87 (broad t, 6H, 2 × CH_3), 1.26 – 1.41 [m, 8H, $CH_3\mathbf{CH_2}CH$ and $CH(\mathbf{CH_2})_3CH_3$], 1.47 – 1.62 (m, 1H, CH), 2.73 – 2.81 and 2.99 – 3.08 (two sym. m, 4H, CH_2CH_2), 4.01 (d, J = 5.7, 2H, OCH_2)	$C_{12}H_{21}Cl_3O_2$ 303.65	47.47 47.25	6.97 7.09	35.03 34.81

Our investigations supply further evidence, that there are fine interactions between the catalyst, the solvent and reacting species which affect their reactivity. A proper selection of suitable catalyst, solvent and reaction conditions very often allow for a selective preparation of the desired product from substrates capable of reacting in different ways.

EXPERIMENTAL

Boiling points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 200 spectometer at 200 MHz and 50 MHz, respectively, as solutions in $CDCl_3$. Gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 Series II chromatograph, equipped with HP50+ capillary column (30 m). Commercial acrylates **1a,c,d,g** (Aldrich) and **1b,e,f** (Polysciences) were used.

Preparation of reference sample of methyl 2-methyl-4,4,4-trichlorobutyrate. To a vigorously stirred mixture of methyl methacrylate (336 g, 3.36 mol), chloroform (50.4 g, 0.42 mol) and TEBACl (1.84 g, 8.1 mmol), 50% aq NaOH (67.2 g, 0.84 mol) was added dropwise at 20 – 22 °C. Reaction was carried out at this temperature for 4 h, diluted with water (100 ml), the phases were separated. The organic phase was washed with 2% HCl (200 ml), then water (200 ml) and dried ($MgSO_4$). After removal of the solvent on rotary evaporator the residue was distilled on a "Fisher Spaltrohr" rectification apparatus to give methyl 2,2-dichlorocyclopropanecarboxylate, b.p. 96 – 97 °C/21 Torr (lit.[18] b.p. 74 °C/8 Torr), 12.2 g (16%) and methyl 2-methyl-4,4,4-trichlorobutyrate, b.p. 100 – 103 °C/21 Torr, 18.0 g (20%), purity (GC) 99.3%. ^{1}H NMR, δ 1.33 (d, $J = 7.2$ Hz, 3H, $CHCH_3$), 2.65 (dd, $J_{gem} = 14.9$ Hz, $J = 2.9$ Hz, 1H, CH_2), 2.98 (ddq, $J = 7.2$ Hz, $J_{gem} = 14.9$ Hz, $J = 2.9$ Hz, 1H, CH), 3.46 (dd, $J_{gem} = 14.9$ Hz, $J = 8.1$ Hz, 1H, CH_2), 3.75 (s, 3H, OCH_3). Anal. Calcd. for $C_6H_9Cl_3O_2$ (219.49): C, 32.83; H, 4.13; Cl, 48.85; found: C, 32.79; H, 3.93; Cl, 48.23.

Reactions of chloroform with acrylates 1 and methyl methacrylate carried out in the presence of TEBACl in heptane. General procedure. To a vigorously stirred mixture of acrylate **1** or methyl methacrylate (0.1 mol), chloroform (60 g, 0.5 mol, 40 ml), TEBACl (0.46 g, 2 mmol) and heptane (40 ml), 50% aq NaOH (60 g, 0.75 mol) was added dropwise at 40 °C (30 °C in the case of **1e** and methyl methacrylate). Reaction was carried out at this temperature for the time given in Table. The mixture was cooled to r.t., diluted with water (100 ml) and chloroform (50 ml) and filtered through a pad of celite. The phases were separated and the aqueous phase was extracted with chloroform (2 × 30 ml). The combined organic phases were washed with 2% HCl (40 ml), then water (100 ml) and dried ($MgSO_4$). After removal of the solvents the products were distilled under reduced pressure (GC analysed in the case of methyl methacrylate). Their yields, b.p.s and analytical data are given in Table.

Competition experiments. Cyclohexene (2.05 g, 25 mmol, reference alkene), 2-methyl-2-butene (10 – 20 mmol), chloroform (24.00 g, 0.2 mol), 50% aq NaOH (0.40 g, 5 mmol), TEBACl (0.057 g, 0.25 mmol) and, in the experiments with the solvent, hexane or heptane (16 ml) were vigorously stirred at 25 °C for 2 h. The product mixtures were evaluated by GC (the flame ionization detector was calibrated with the products). Relative reactivities were calculated from the molar ratios of initial alkenes and product cyclopropanes according to the expression $k_1/k_2 = (O_2/O_1)(P_1/P_2)$, where O_i represents alkene and P_i represents cyclopropane.[21]

Diethyl 3,3,3-trichloropropylphosphonate. (a) To a vigorously stirred mixture of diethyl vinylphosphonate (9.0 g, 55 mmol), chloroform (66 g, 0.55 mol), TEBACl (0.75 g, 3.3 mmol) and heptane (70 ml), 50% aq NaOH (90 g, 1.13 mol) was added at 25 – 30 °C. Reaction was carried out at r.t. for 10 h, then worked up as described in General Procedure. 3,3,3-Trichloropropylphosphonate was isolated by vacuum distillation, b.p. 105 – 108 °C/1 Torr (lit.[23] b.p. 108 °C/3 Torr, lit.[22] b.p. 104 – 106 °C/0.1 Torr), 9.7 g (62%), purity (GC) 99.2%. ^{1}H NMR, δ 1.31 (t, $J = 7.15$ Hz, 6H, 2 × CH_3), 2.09 – 2.67 (m, 2H, CH_2), 2.84 – 2.96 (m, 2H, CH_2), 4.02 – 4.18 (m, 4H, 2 × OCH_2). (b) In the reaction carried out without heptane, after 24 h 3.7 g (24%) of diethyl 3,3,3-trichloropropylphosphonate was isolated, identical (NMR, GC) with the product obtained in (a).

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