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ALKYLATION OF CARBOXYLIC ACIDS BY SOLID–LIQUID PHASE-TRANSFER CATALYSIS FOR DETERMINATION BY GAS CHROMATOGRAPHY

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SUMMARY

A solid–liquid phase-transfer catalysed process has been investigated for the alkylation of carboxylic acids. With tetrabutylammonium as counter ion, the bicarbonate ion was solvated in methylene chloride. In this solution carboxylic acids could be quantitatively alkylated in the presence of alkyl iodide. Benzoic acid and acetylsalicylic acid were used as substrates. The reaction could be governed both by the type of alkyl iodide (number of carbon atoms) and by its concentration. The method was found to be especially suitable for the alkylation of compounds sensitive to hydrolysis. Acetylsalicylic acid was thus quantitatively methylated (>99%) within 7 min without any sign of decomposition.

INTRODUCTION

Alkyl esters of carboxylic acids can be prepared for analytical purpose by several methods, such as alkylation with diazoalkanes[1,2], extractive alkylation[3,4], alkylation with alkyl iodide and sodium carbonate in acetone[5], alkylation with alkyl iodide and tetramethylammonium hydroxide in N,N-dimethylacetamide[6], flash alkylation[7], alkylation with dimethylformamide dialkyl acetals[8–10] and alkylation by solid–liquid phase-transfer catalysis[11–14]. Many of these methods are unsuitable for the alkylation of substances that are sensitive to hydrolytic decomposition, as indometacin[14–16] and acetylsalicylic acid[17–20]. This paper describes a further investigation of a solid–liquid phase-transfer catalysed process which had earlier been used for the alkylation of indometacin[14].

EXPERIMENTAL

Apparatus

The gas–liquid chromatographic (GLC) analyses were performed using a

Varian 1400 instrument equipped with a flame ionization detector. The following temperatures were used: injector, 250°; detector, 250°; column, 130° for the determination of benzoic acid esters and 150° for the acetylsalicylic acid esters. Silanized glass columns (180 cm × 2 mm I.D.) were packed with 3% OV-17 on Gas Chrom Q 100/200 mesh. Nitrogen was used as carrier gas with a flow-rate of 20 ml/min, and the hydrogen and air flow-rates were 20 and 250 ml/min, respectively.

The high-performance liquid chromatographic (HPLC) analyses were performed using a Waters pump model 6000 A, a Waters injector system model U6K and a Perkin-Elmer UV detector model LC-55 at a wavelength of 243 nm. A 250 × 3 mm I.D. stainless steel column packed with 10 μm silica gel particles (Partisil) was used. The mobile phase was acetic acid–chloroform–n-hexane (3:10:87)[21].

In the potentiometric titrations the following equipment was used: a Metrohm EA-404 and a Radiometer calomel electrode K 401 with a saturated potassium chloride solution in ethanol as salt-bridge solution (reference electrodes); an Orion specific ion electrode model 91-01-00, an Ag/AgCl pH electrode (indicator electrode); an Orion 701 potentiometer. The titration vessel was thermostated at 20.0°.

The specific surface area was determined by a light-blocking technique[22,23].

The solvation studies and the studies of the alkylation process method (b) were performed in 50 ml centrifuge tubes (130 × 30 mm I.D.). The alkylation studies according to method (a) were performed in 15-ml centrifuge tubes (120 × 20 mm I.D.).

Chemicals

Tetrabutylammonium (TBA) hydrogen sulphate (Lab Kemi). Sodium bicarbonate with a specific surface area of 420 cm²/cm³ (Merck p.a.). Sodium bicarbonate manually ground immediately before use to a specific surface area of 1200 cm²/cm³ (Merck p.a.). Alkyl iodides (methyl, ethyl, propyl and butyl iodide) (Fluka). Methylene chloride (Merck p.a.). Perchloric acid (Merck p.a.). Dioxane (Merck puriss). Benzoic acid, pharmacopoeical grade. Acetylsalicylic acid, pharmacopoeical grade. Sulphuric acid (1 M), pharmacopoeical grade. Hexadecane (internal standard for the GLC determinations) (Merck).

METHODS

Solvation studies

40.00 ml of methylene chloride containing TBA hydrogen sulphate (0.10 or 0.01 M) was shaken for 20 min with varying amounts of sodium bicarbonate in a thermostated water bath at 20.0° at a frequency of 80 strokes/min. In some experiments the amount of sodium bicarbonate was kept constant and the shaking time was varied. The suspension was transferred to a paper filter and 10.00 ml of the clear filtrate was analysed by potentiometric titration with perchloric acid (0.0350 or 0.0035 M) in dioxane.

Studies of the alkylation process

Method (a). To 1.00 ml of methylene chloride containing TBA hydrogen sulphate (0.005 M), carboxylic acid (0.001 M), hexadecane (0.002 M) and alkyl iodide (0.5 M), 0.3 g of sodium bicarbonate was added. The mixture was shaken for a certain

time. The reaction was interrupted by shaking the reaction mixture with 0.20 ml of sulphuric acid (1 M). The organic phase was analysed for the ester formed.

Method (b). 40.00 ml of methylene chloride containing TBA hydrogen sulphate (0.01 M) was shaken for 20 min with 6.00 g of sodium bicarbonate at 20.0°. The suspension was transferred to a paper filter and 20.00 ml of the filtrate was mixed immediately with 20.00 ml of methylene chloride containing the carboxylic acid (0.002 M), hexadecane (0.004 M) and the alkyl iodide (various concentrations). The solution was thermostated at 20.0° and 1.00 ml was removed at various times. The reaction was interrupted by shaking the removed reaction mixture with 0.20 ml of sulphuric acid (1 M). The organic phase was analysed by GLC for the determination of alkyl esters and by HPLC for the determination of the underivatized acids.

RESULTS AND DISCUSSION

The following symbols are used:
TBA$^+$ = tetrabutylammonium ion
HA   = carboxylic acid
RX   = alkyl iodide
RA   = alkyl ester
C_x = the concentration of the alkyl ester when no carboxylic acid could be detected in the reaction mixture.
C_t = the concentration of the alkyl ester at time t.
k' = the observed rate constant obtained from the slope of the pseudo first-order plot.

Extensive work has been done in the fields of extractive alkylation[24] and phase-transfer catalysis (PTC) in the past few years, and several review articles have been published[24-28]. In liquid–liquid PTC water of hydration might be co-extracted with the ion pair partitioned from the aqueous to the organic phase[27,29]. This can be avoided by solid–liquid PTC. Analytical applications of this procedure have been worked out for the preparation of carboxylic acid esters[11-14]. In most cases the catalysts have been of the crown ether type, but in this study the quaternary ammonium compound TBA hydrogen sulphate was used.

Solvation studies
        In a previous paper discussing the alkylation of indometacin by PTC[14], it was shown that the anion of sodium bicarbonate, present as a solid, was solvated in methylene chloride containing TBA hydrogen sulphate. Further evidence of this is shown in Table I, where the results of the methylation of acetylsalicylic acid are shown. The second column shows the results from the methylation with sodium bicarbonate present (method a) and the third column with no solid phase present (method b). Sodium bicarbonate and TBA hydrogen sulphate were both necessary for the reaction to proceed: if either was omitted no alkylation was detected.

        The solvation of the anionic base was followed by potentiometric titration of the methylene chloride phase. Fig. 1 shows a typical titration curve. Blank titrations were performed on methylene chloride containing TBA hydrogen sulphate (0.1 M) and on pure methylene chloride shaken with sodium bicarbonate and filtered. Neither of these experiments gave a titration curve with a potential rise, which in-

TABLE I

METHYLATION OF ACETYLSALICYLIC ACID: YIELD OF METHYL ACETYLSALIC-YLATE (%)

Conditions as described under Methods (0.5 M methyl iodide).

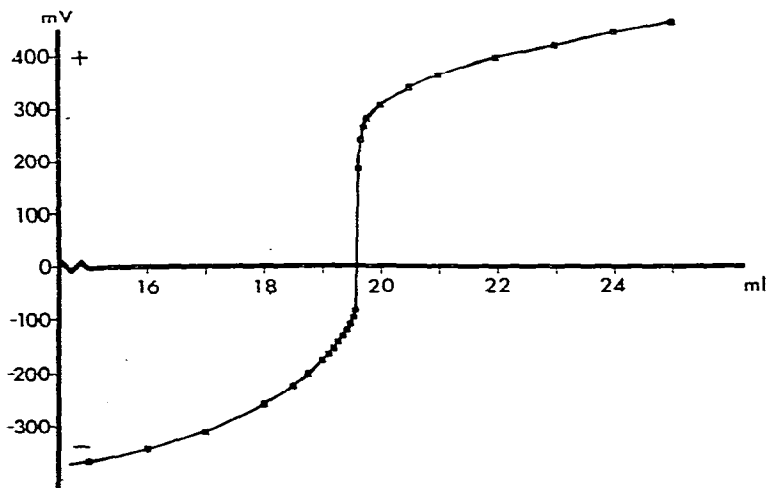| Reaction time (min)	Method (a)	Method (b)
2	42	69
5	67	88
10	89	100
15	99	99
20	99	100
30	100	100

Fig. 1. Titration curve. Conditions as described under Methods. 0.1 M TBAHSO$_4$, 0.0350 M HClO$_4$ in dioxane.

dicates that the quaternary ammonium compound is necessary for the solvation of the base to occur.

The concentration of the solvated base in methylene chloride depended on the concentration of the quaternary ammonium compound and the amount of solid sodium bicarbonate. Table II shows that a tenfold increase in the TBA hydrogen sulphate concentration gave a tenfold increase in the concentration of the solvated base. For both concentrations studied an equilibrium value of $ca.$ 80% solvation was reached when the surface area of the bicarbonate was sufficiently large. A decreased amount of sodium bicarbonate gave a decreased concentration of solvated base.

The specific surface area of the sodium bicarbonate powder was of importance for the solvation (Fig. 2 and Table II). The shaking time necessary to achieve maximum solvation was $ca.$ 20 min for the ground substance (1200 cm^2/cm^3) and $ca.$ 120 min for the unground substance (420 cm^2/cm^3) at a molar ratio of 10:1 (0.33 g NaHCO$_3$, 40.00 ml 0.01 M TBAHSO$_4$).

The available surface area can also be increased by using larger amounts of

TABLE II

SOLVATION OF BICARBONATE IN METHYLENE CHLORIDE WITH TBA HYDROGEN SULPHATE

Conditions as described under Methods. Shaking time, 20 min. Temperature, 20.0°. Each value is the mean of two titrations of each of two solvation experiments.

Amount of NaHCO₃ (g)	Concentration of TBAHSO₄ (mole/l)	Molar ratio NaHCO₃:TBAHSO₄	Concentration of solvated HCO₃⁻ (mmole/l)
3.35	0.100	10:1	74.4
2.52	0.100	7.5:1	69.4
1.68	0.100	5:1	51.6
0.84	0.100	2.5:1	29.3
6.00	0.010	183:1	8.5
3.34	0.010	102:1	8.5
1.00	0.010	29:1	8.6
0.33	0.010	10:1	2.2
0.34*	0.010	10:1	8.0

* Ground to a specific surface area of 1200 cm^2/cm^3. In all other cases the bicarbonate was unground and the specific surface area was 420 cm^2/cm^3.
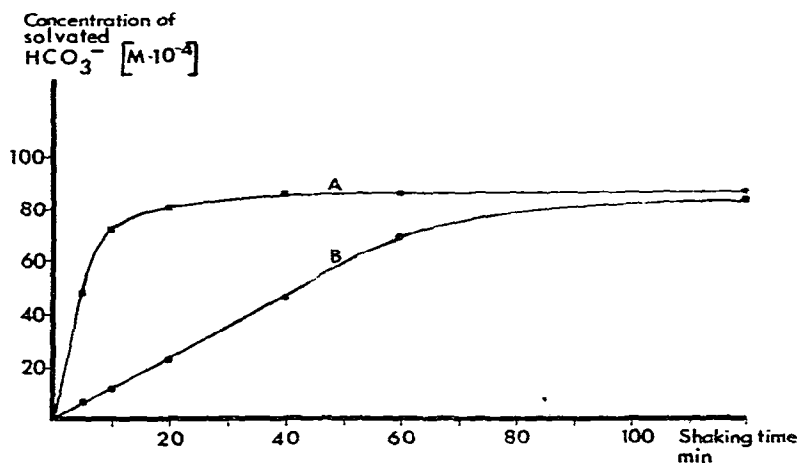

Fig. 2. Solvation of bicarbonate from ground and unground sodium bicarbonate *versus* time at a molar ratio of NaHCO₃–TBAHSO₄ 10:1 (0.01 M TBAHSO₄). Sodium bicarbonate with a specific surface area of (A) 1200 cm^2/cm^3, (B) 420 cm^2/cm^3.

sodium bicarbonate. A molar ratio of 180:1 gave a very rapid solvation of the bicarbonate. Fig. 3 shows that a shaking time of 20 min is sufficient to achieve equilibrium. As can be seen from Table II, a molar ratio of 30:1 could be used in practical work as well. This suspension was less difficult to agitate. However, in practice, presolvation according to method (b) is preferable.

The concentration of the solvated bicarbonate decreased by *ca.* 30% after 20 h and by 43% after 44 h at room temperature. This means that the solvated bicarbonate ion pair as a reagent has to be prepared fresh each day. Titration experiments were carried out using thermostated vessels to decrease the influence from the heat developed from the stirring equipment.
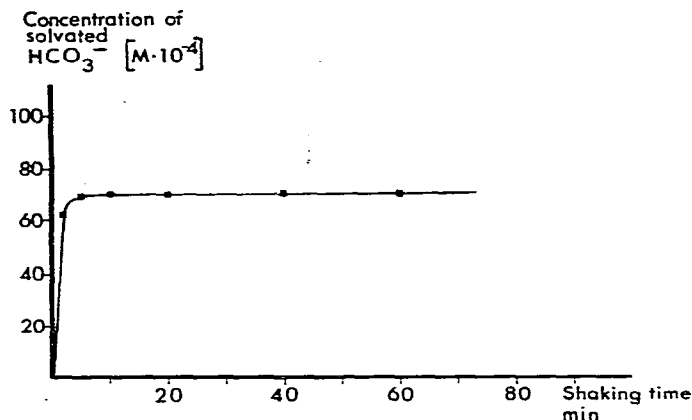
Concentration of
solvated
HCO_3^- $[M \cdot 10^{-4}]$

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100
 80
 60
 40
 20
        20      40      60      80   Shaking time
                                        min
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Fig. 3. Solvation of bicarbonate from unground sodium bicarbonate *versus* time at a molar ratio of $NaHCO_3$-$TBAHSO_4$ 180:1 (0.01 M TBAHSO$_4$).

Studies of the alkylation process

The solid–liquid PTC alkylation could be a three-step reaction, as demonstrated in Fig. 4. The consecutive steps might be solvation (I), protolysis of the acid and the simultaneous formation of an ion pair (II) and alkylation of the ion pair with the alkyl iodide (III). The solvation of the basic anion was proved (1) by the filtration procedure (method b), (2) by the experiments where in alternate sequences one of the participants in reaction I was removed, and (3) by the titration experiments.
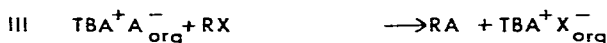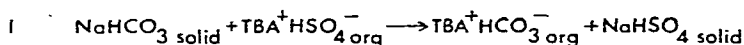
I $NaHCO_{3\ solid} + TBA^+HSO_{4\ org}^- \longrightarrow TBA^+HCO_{3\ org}^- + NaHSO_{4\ solid}$

II $TBA^+HCO_{3\ org}^- + HA \longrightarrow TBA^+A_{\ org}^- + H_2CO_3$

III $TBA^+A_{\ org}^- + RX \longrightarrow RA + TBA^+X_{\ org}^-$

Fig. 4. Reaction scheme for solid–liquid PTC alkylation.

The alkylation process was studied with benzoic acid as model substance using the presolvated ion pair according to method (b). With TBA hydrogen sulphate (0.01 M) and a molar ratio of sodium bicarbonate to quaternary ammonium salt of 180:1, a concentration of *ca.* 0.008 M of solvated base in methylene chloride was obtained. A pseudo-first-order reaction was assumed, and experiments were performed with the alkylating reagents in large excess. The reaction was followed by analysis of the product (ester) at various times. No other product from the carboxylic acid was found, and the reaction was regarded as complete when there was no more carboxylic acid present in the reaction mixture. (Less than 0.5 % of the total amount of carboxylic acid could be detected by HPLC.) With the concentration of the ester at this time set as C_x and the concentration of the ester at time t, C_t, a plot
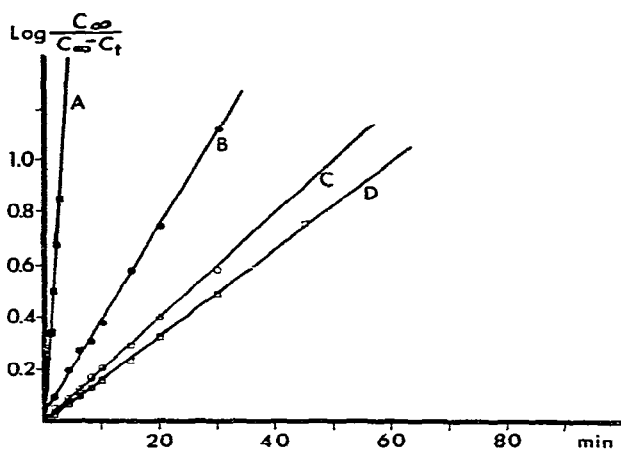
Fig. 5. Pseudo-first-order plot for the alkylation of benzoic acid. Conditions as described under *Method* (*b*), using 1.0 *M* alkyl iodide. Formation of (A) methyl benzoate; (B) ethyl benzoate; (C) propyl benzoate; (D) butyl benzoate.

of log $C_\infty/(C_\infty - C_t)$ against time gave straight lines, which indicates that the reaction is first order (Fig. 5). As expected[30] the rate constant decreased with increasing length of the carbon chain of the alkyl iodides.

The methyl ester was quantitatively formed (>99%) within 6 min and the butyl ester within 120 min. The pentafluorobenzyl ester was quantitatively formed within 2 min. This ester, which has electron capture properties[4], is of special interest for analyses in the low concentration range.

Fig. 6 shows the plot of log $C_\infty/(C_\infty - C_t)$ against time at various concentrations of butyl iodide. When the pseudo-first-order rate constants obtained from these experiments were plotted against the concentrations of butyl iodide a straight line was obtained (Fig. 7). This shows that the reaction is first order with respect to the
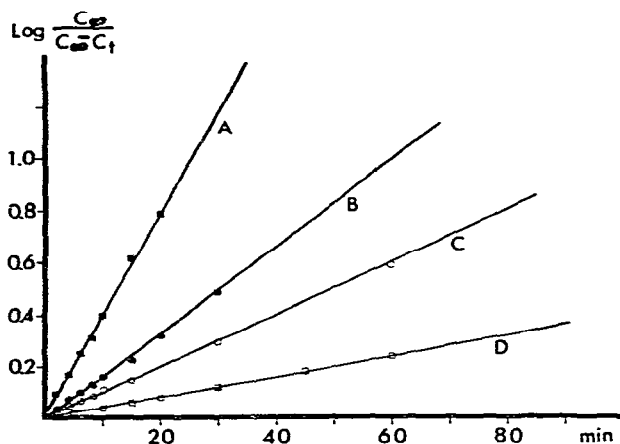
Fig. 6. Influence of butyl iodide concentration on the butylation of benzoic acid. Conditions as described under *Method* (*b*). Butyl iodide concentration: (A) 2.0 *M*; (B) 1.0 *M*; (C) 0.5 *M*; (D) 0.2 *M*.
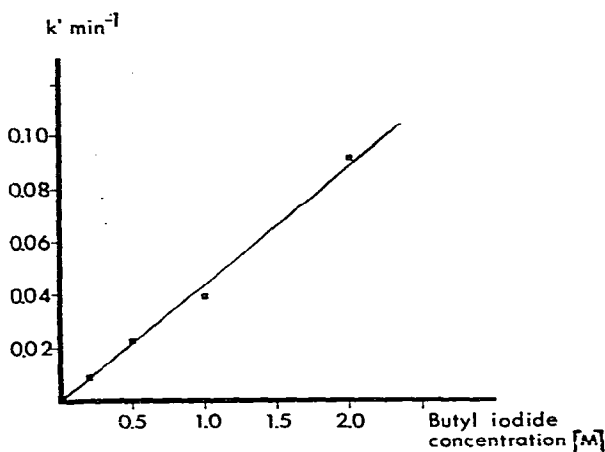
Fig. 7. Relationship between rate constant and alkyl iodide concentration in the butylation of benzoic acid.

alkyl iodide, which means that it is possible to control the reaction by changing the concentration of the alkyl iodide. The calculated times for quantitative butylation ($>99\%$) of benzoic acid were 50 min with 2 M butyl iodide and 475 min with 0.2 M butyl iodide.

The process described in this paper using the solvated tetrabutylammonium–bicarbonate ion pair has proved to be more suitable than liquid–liquid PTC (or extractive alkylation) in the alkylation of acetylsalicylic acid. Extractive methylation of this substance was investigated earlier in our laboratories. This approach was, however, less attractive owing to decomposition of acetylsalicylic acid into salicylic acid. Under the mildest conditions (0.1 M tetrapentylammonium at pH 7.0), $ca.$ 15% of the acetylsalicylic acid was converted into methylsalicylate and $ca.$ 85% methyl acetylsalicylate was formed after 1 h. The results from the methylation of acetyl-salicylic acid according to method (b) were much more favourable, as shown in
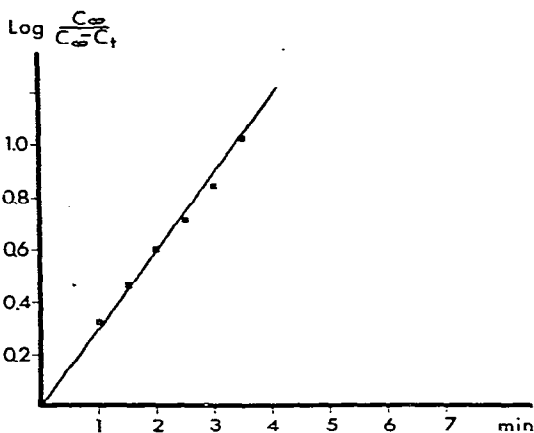

Fig. 8. Pseudo-first-order plot for the methylation of acetylsalicylic acid. Conditions as described under *Method* (*b*). using 1.0 M methyl iodide.

Fig. 8. The methyl ester was quantitatively formed ($>99\%$) within 7 min (1 M methyl iodide) without any noticeable side-reactions (checked both by GLC and HPLC, according to the experimental details above).

The formation of the ethyl, propyl and butyl esters was also studied (1 M alkyl iodide). In these cases small amounts of salicylic acid esters were formed (0.5–2%), probably owing to the longer reaction time (50–200 min). It was shown that underivatized acetylsalicylic acid was sensitive to degradation in a solution containing all the components in the reaction mixture except the alkyl iodide (method b). After 95 min 10% had been degraded. On the other hand, the alkyl esters of acetylsalicylic acid were stable for several days in the reaction mixture.

ACKNOWLEDGEMENTS

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