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ALKYLATION OF CARBOXYLIC ACIDS BY SOLID-LIQUID PHASE-TRANSFER CATALYSIS FOR DETERMINATION BY GAS CHROMATOGRAPHY. II*

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SUMMARY

The alkylation of benzoic acid was studied in different solvents containing an alkyl halide and tetrabutylammonium bicarbonate. The bicarbonate anion was transferred to the organic solvents by shaking solid sodium bicarbonate with solutions of tetrabutylammonium hydrogen sulphate. The alkylation rate was influenced by the type of solvent used, ketones being the most favourable. The quaternary ammonium bicarbonate was found to be stable in the ketones even at elevated temperatures, but the dissolution was slower than in halogenated solvents. The possibility of controlling the alkylation reaction by a suitable choice of solvent, alkyl halide and reaction temperature was demonstrated. It was also shown that the content of water and ethanol in some solvents drastically affected the alkylation rate.

INTRODUCTION

Extensive work has been carried out on extractive alkylation and phase-transfer catalysis (PTC) in recent years and several surveys have been published¹⁻⁹. Alkyl esters have been prepared for analytical purposes by these techniques^{10,11}. Processes occurring in the presence of solid components, solid-liquid PTC, with crown ethers or quaternary ammonium compounds as dissolution agents, may lead to interesting analytical possibilities¹²⁻¹⁷. This paper describes further studies on a previously employed solid-liquid PTC process^{15,16} with special emphasis on the effect of solvents on the dissolution of the quaternary ammonium bicarbonate and on the rate of the alkylation reaction.

* For Part I, see *J. Chromatogr.*, 170 (1979) 25.

EXPERIMENTAL

Apparatus

The equipment employed in Part I¹⁶ was used.

Chemicals

The following were used: tetrabutylammonium (TBA) hydrogen sulphate (Lab Kemi, Göteborg, Sweden; Fluka, Buchs, Switzerland); sodium bicarbonate (Merck, Darmstadt, G.F.R.; p.a. grade); methyl, ethyl, propyl, butyl and benzyl iodide, butyl bromide and butyl and benzyl chloride (Fluka); chloroform, methylene chloride, 1,2-dichloroethane, acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile and pentanol (Merck, p.a. grade); Perchloric acid (Merck, p.a. grade); dioxane (Merck, puriss grade), benzoic acid (pharmacopoeical grade); sulphuric acid (1 mol/l) (Merck, p.a. grade); *n*-hexadecane (internal standard for the gas chromatographic determinations) (Merck). All solvents were used without any further purification.

Dissolution studies

A 40.00-ml volume of organic solvent containing TBA hydrogen sulphate (0.01 mol/l) was shaken for different periods of time with 1.00, 6.00 or 10.00 g of sodium bicarbonate in a thermostated water bath at $20.0 \pm 0.1^\circ\text{C}$ at a frequency of 80 strokes/min. The suspension was transferred to a filter-paper and 5.00 or 10.00 ml of the clear filtrate were analysed by potentiometric titration with perchloric acid in dioxane (0.0035 mol/l). Titrations in chloroform were performed after addition of methyl isobutyl ketone, which made it easier to read the potential.

Studies on the alkylation process

Preparation of TBA bicarbonate. A 40.00-ml volume of organic solvent containing TBA hydrogen sulphate (0.01 mol/l) was shaken for 20 min with 6.00 g of sodium bicarbonate and filtered. The alkylation reaction was studied in a thermostated water bath at $20.0 \pm 0.1^\circ\text{C}$, except in the experiments where the influence of temperature was studied (in these cases the water bath was thermostated at 10.0, 20.0, 30.0, 40.0 and $50.0 \pm 0.1^\circ\text{C}$). A 20.00-ml volume of the solution of pre-dissolved base was mixed with 10.00 ml of the same organic solvent containing benzoic acid (0.004 mol/l) and *n*-hexadecane (0.008 mol/l). A 10.00-ml volume of a solution of alkylating agent (different concentrations) was added and 1.00 ml of the mixture was removed at various times up to at least 24 h and shaken with 0.2 ml of sulphuric acid (1 mol/l) to stop the reaction. When acetone and acetonitrile were used as solvents the reaction was stopped by adding 1.00 ml of the reaction mixture to a tube containing 1.00 ml of methylene chloride and 0.2 ml of sulphuric acid. The completion of the esterification was checked by determining the content of benzoic acid by liquid chromatography¹⁶ and, in the butylation studies also by gas chromatographic quantification of butyl benzoate.

RESULTS AND DISCUSSION

Influence of the organic solvent

*The dissolution step**. In Part I¹⁶ the dissolution of the bicarbonate anion as

* In Part I¹⁶ solvation was used in the same sense as dissolution in this paper.

the tetrabutylammonium ion pair in methylene chloride was found to be more rapid when the available surface area of sodium bicarbonate was large. This could be achieved by using large amounts of sodium bicarbonate or by grinding the salt. In this study, the influence of the amount of solid sodium bicarbonate on the dissolution procedure was evaluated for methyl ethyl ketone. In methylene chloride an NaHCO_3 : TBAHSO_4 molar ratio (R) of 30:1 was found to be sufficient to achieve equilibrium after 20 min of shaking¹⁶. It is evident from Table I that a larger ratio, R , was necessary in methyl ethyl ketone and it is also clear that the dissolution is slower than in methylene chloride. In practical use, an R value of 180 proved to be most suitable. The effect of the shaking time on the dissolution process was studied for some other solvents, with the results shown in Table II ($R = 180$). In the halogenated solvents equilibrium was attained after 5 min, but in the ketones and acetonitrile 20–120

TABLE I

DISSOLUTION OF BICARBONATE WITH TBA HYDROGEN SULPHATE IN METHYL ETHYL KETONE

$R = \text{NaHCO}_3$: TBAHSO_4 molar ratio. Values given are concentrations of dissolved HCO_3^- (mmol/l).

Shaking time (min)	NaHCO_3 (g)		
	1.00	6.00	10.00
	R		
	30	180	300
5	0.8	4.0	3.3
20	1.7	7.2	4.7
40	3.5	6.6	4.9
60	6.8	9.6	9.6
120	6.6	9.6	9.6

TABLE II

DISSOLUTION OF BICARBONATE WITH TBA HYDROGEN SULPHATE IN DIFFERENT SOLVENTS

NaHCO_3 : TBAHSO_4 molar ratio = 180. Values given are concentrations of dissolved HCO_3^- (mmol/l). Values on the same line were obtained on the same occasion.

Solvent	Shaking time (min)			
	5	20	60	120
Acetone	—	1.9	4.7	—
	—	—	—	7.9
Methyl ethyl ketone	6.0	8.4	8.7	—
	4.0	7.2	9.6	9.6
	—	—	9.6	9.7
Methyl isobutyl ketone	8.8	9.1	9.0	—
	5.0	8.5	—	—
Chloroform	9.0	—	9.1	—
1,2-Dichloroethane	8.3	8.1	7.8	—
Methylene chloride	7.0	7.0	7.0	—
Acetonitrile	—	5.9	—	—
	—	—	—	9.8
Pentanol	—	2.7	—	—

min were necessary. The process was slowest in acetone, and acetonitrile and methyl ethyl ketone gave intermediate values. The last solvent was selected for more extensive studies, which revealed that large differences in bicarbonate concentrations could sometimes be obtained with shorter shaking times. Thus, after 20 min values between 2.7 and 10.1 mmol/l were obtained, and 60 min of shaking produced concentrations of 8.7–9.6 mmol/l. This emphasized that a sufficient shaking time and amount of sodium bicarbonate should be allowed for the dissolution of the bicarbonate ion pair.

Toluene, benzene and ethyl acetate were tested but could not be used since TBAHSO₄ was not sufficiently soluble in these solvents.

Stability of TBA bicarbonate. In methylene chloride the quaternary ammonium bicarbonate concentration decreased by about 30% in 20 h at room temperature¹⁶. More extensive degradation was found to occur in 1,2-dichloroethane, 27% disappearing within 6 h at 20°C. At higher temperatures the degradation reaction accelerated; for example, 78% had degraded after 3 h at 40°C. In contrast to the halogenated solvents, there was no decline in the TBA bicarbonate concentration in acetone, methyl ethyl ketone, methyl isobutyl ketone or acetonitrile at room temperature for at least 6 days. At 60°C no degradation of TBA bicarbonate was observed after 3 h in methyl ethyl ketone.

Butylation of TBA benzoate in 1,2-dichloroethane gave 2-chloroethyl benzoate as a by-product (verified by gas chromatography–mass spectrometry). At higher temperatures this compound was often the main product. This indicates that the reason for the instability of the TBA bicarbonate in the halogenated solvents might be that they react with the nucleophilic bicarbonate anion. From this it follows that the alkylating agent might react with the TBA bicarbonate, which emphasizes the importance of adding the alkyl halide after the carboxylic acid has reacted with the pre-dissolved base. If the alkyl halide was added some time before the acid, the halide could in principle begin to consume the necessary excess of bicarbonate (see *Importance of the TBA concentration*).

The alkylation step. The rate of the alkylation reaction was studied in the solvents mentioned in Table II. As in Part I¹⁶ benzoic acid was used as the model substance and the reaction was followed by determination of the product (ester) concentration at suitable time intervals. An excess of alkyl halide was used in this study also. Pseudo-first-order behaviour of the alkylation reaction was assumed, and the observed rate constants (k') were calculated from the slopes of the straight lines obtained by plotting $\log C_{\infty}/C_{\infty} - C_t$ versus time (where C_{∞} is the concentration of the alkyl ester when no carboxylic acid could be detected in the reaction mixture and C_t is the concentration of the alkyl ester at time t).

Halogenated solvents have been used extensively in PTC reactions and extractive alkylation^{7,10}. This study shows, however, that solvents of the dipolar aprotic type such as ketones and acetonitrile are useful and might even be superior (Table III). These solvents are known to solvate cations, whereas anions are poorly solvated^{18,19}. For this reason many reactions can be considerably more rapid in dipolar aprotic solvents, when the reaction involves anions. The observed rate constants, k' , obtained in this study (Table III) are in agreement with these observations. The ketones are the solvents of choice from a reactivity point of view, with methyl ethyl ketone being about 100 times better than methylene chloride.

Addition of water to a concentration of 0.11 mol/l (0.2%, v/v) reduced the k'

TABLE III
 BUTYLATION OF BENZOIC ACID IN DIFFERENT ORGANIC SOLVENTS

<i>Solvent</i>	<i>Butyl iodide concentration (mol/l)</i>	<i>k' · 10² (min⁻¹)</i>	<i>Calculated time for 99% alkylation with 1.0 mol/l butyl iodide (min)</i>
Methyl ethyl ketone	0.1	54	1
Acetone	0.1	49	1
Methyl isobutyl ketone	0.1	16	3
Acetonitrile	0.1	3.1	15
1,2-Dichloroethane	1.0	6.5	71
Methylene chloride	1.0	3.9	118
Chloroform	1.0	0.40	1150

for butylation of benzoic acid in methyl ethyl ketone from 0.54 to 0.15. Hence it is advantageous to use a dry solvent in the alkylation reaction. The use of a solvent such as methyl ethyl ketone as an extractant of acids from aqueous samples is less suitable owing to its ability to dissolve water²⁰; another solvent therefore has to be used for such extractions.

The use of ketones as solvents for alkylation of organic acids was mentioned in 1913 by Claisen and Eisleb²¹, more recently by Kawahara²² and, on the micro-scale, by Dünge²³. These reactions occurred in the presence of potassium carbonate at elevated temperatures. Some alkali metal carbonates have been used recently in methylation reactions of a number of aromatic acids in acetone²⁴. Caesium carboxylates reacted the quickest, followed by rubidium and potassium salts, which shows the effect of the size of the counter ion. The same good effect can be achieved by using the TBA bicarbonate ion pair as described in this paper. With the TBA cation excluded, *i.e.*, only sodium bicarbonate present, no alkylation of benzoic acid in methyl ethyl ketone occurred within 24 h at 20°C. The alkylation of hydantoins performed with acetone or methyl ethyl ketone as solvents required a stronger base (potassium hydroxide) in order to go to completion²⁵.

The reaction was slower in halogenated solvents than in the ketones. 1,2-Dichloroethane and methylene chloride gave rate constants of the same magnitude. Chloroform gave a considerably lower reaction rate, however, which may be due to the ethanol preservative. Addition of ethanol to methylene chloride reduced *k'* considerably, as can be seen in Table IV. A further illustration of this effect was given by an attempt to butylate benzoic acid in pentanol. In this experiment no ester was formed even after 24 h.

Some problems were encountered with the reproducibility of the observed rate constant, *k'*, in methylene chloride. The variations in the magnitude of *k'* were found to depend on different concentrations of ethanol and water in the solvent (Table IV). Methylene chloride saturated with water produced a *k'* of about one sixth of the value obtained in batches of this solvent containing small amounts of ethanol and water, which indicates that a direct reaction in methylene chloride extracts from aqueous samples is less favourable.

The probable reason for the influence of ethanol and water on the alkylation is the solvation of the nucleophilic benzoate anion by these hydrogen donors^{18,19}

TABLE IV

INFLUENCE OF WATER AND ETHANOL ON THE BUTYLATION OF BENZOIC ACID

Organic solvent: methylene chloride. Alkylating agent: butyl iodide (1.0 mol/l). The content of water was determined by Karl Fischer titration and the ethanol was determined by gas chromatography using a Porapak Q column.

Water concentration (mol/l)	Ethanol concentration (mol/l)	$k' \cdot 10^2$ (min ⁻¹)
0.107*	—	0.70
0.107*	—	0.70
0.034	—	2.9
0.026	—	2.8
0.012	0.001	4.0
0.012	0.001	4.1
0.012	0.001	4.4
0.007	0.002	4.1
0.006	0.002	3.7
0.006	0.82**	0.14***
0.005	0.161	2.9

* Saturated with water.

** Added to the reaction mixture.

*** In this instance the reaction was not followed to completion but k' was calculated by assuming $C_\infty = 1.00 \cdot 10^{-3}$ mol/l.

The solvents in this study were used without any purification. As demonstrated in Table IV, this can influence the values of k' , which therefore have to be regarded as approximate.

Dissociation of ion pairs is likely to occur in solvents with higher dielectric constants²⁶⁻²⁹. No attempts have been made to determine dissociation constants or to evaluate possible differences in the alkylation rates between the benzoate anion as an ion pair with TBA or present as a dissociated ion.

Importance of the TBA concentration

In the solid-liquid PTC alkylation of indometacin¹⁵ it was found that the concentration of quaternary ammonium compound had to be at least equivalent to the concentration of carboxylic acid in order to achieve quantitative derivatization. The concentration of dissolved bicarbonate was about 80% of the TBA hydrogen sulphate concentration initially present when methylene chloride was used as a solvent¹⁶, which means that there was a four-fold excess of dissolved bicarbonate in relation to carboxylic acid in the reaction mixture. This proved to be sufficient for the quantitative alkylation of benzoic acid and also acetylsalicylic acid.

An attempt was made to alkylate benzoic acid in methylene chloride, in which the TBA concentration was 50% of the benzoic acid concentration. In this solution the concentration of dissolved bicarbonate could be expected to be about 40% of the benzoic acid concentration. The results were compared with an alkylation in which a five-fold excess of TBA was used (Fig. 1). The alkylation in the presence of excess TBA was quantitative within 120 min, whereas only about 47% of the benzoic acid had reacted after 3 days in the system with a deficit of TBA. The concentration of ester found is close to the expected concentration of dissolved bicarbonate mentioned above, and it is obvious that a slight excess of TBA bicarbonate com-

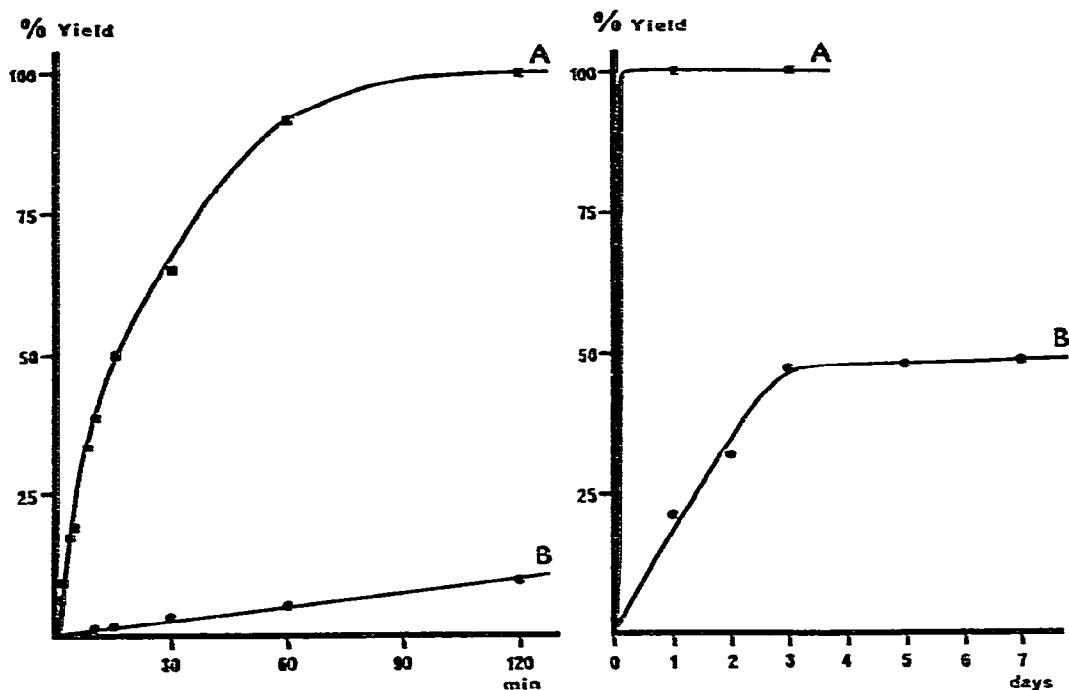


Fig. 1. Influence of TBA concentration on the butylation of benzoic acid. Organic solvent: methylene chloride. Alkylating agent: butyl iodide (1.0 mol/l). Benzoic acid concentration: $1.00 \cdot 10^{-2}$ mol/l. TBA concentration: A, $5.00 \cdot 10^{-3}$ mol/l; B, $0.50 \cdot 10^{-3}$ mol/l.

pared with carboxylic acid is necessary for complete alkylation to be achieved. This observation again demonstrates that protolysis of the acid (step II in the proposed reaction sequence¹⁶) is essential for the reaction to proceed.

Influence of the alkylating agent

It was shown in Part I¹⁶ that the butylation of benzoic acid in methylene chloride was first order with respect to butyl iodide. The same relationship between k' and butyl bromide concentration was valid in methyl ethyl ketone, as shown in Fig. 2. Another way to control the reaction rate is to use alkyl halides of different natures, e.g., a change in the length of the carbon chain and the halogen atom. Table V gives the reactivities of some alkylating agents in methylene chloride. The reactivity increased in the order chloride, bromide, iodide. Benzyl iodide was considerably more reactive than the others. In methyl ethyl ketone, butyl iodide (0.1 mol/l) had a k' of 0.54 (Table III), whereas butyl bromide was only one tenth as reactive (Fig. 2) at the same concentration. Butyl chloride was even less reactive.

Temperature effects

Variation of the temperature is another possible means of influencing the reaction rate. In the butylation of benzoic acid the pseudo-first-order rate constants varied greatly with temperature (Table VI); for example, an increase in temperature from 20.0 to 50.0°C produced about a 10 times more rapid alkylation in methyl

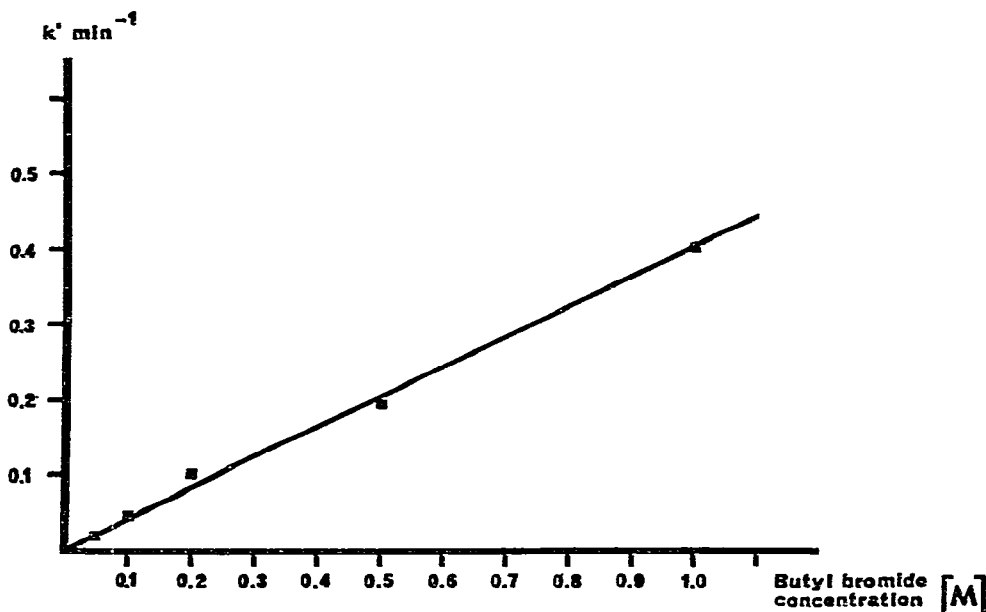


Fig. 2. Relationship between observed rate constant and butyl bromide concentration in the butylation of benzoic acid. Organic solvent: methyl ethyl ketone.

TABLE V

ALKYLATION OF BENZOIC ACID WITH DIFFERENT ALKYLATING AGENTS

Organic solvent: methylene chloride. Concentration of alkylating agent: 1.0 mol/l.

Alkylating agent	$k' \cdot 10^2$ (min^{-1})	Calculated time for 99% alkylation (min)
Methyl iodide	77	6
Ethyl iodide	8.1	57
Propyl iodide	4.4	105
Butyl iodide	3.9	118
Butyl bromide	1.1	419
Butyl chloride	0.010*	46050
Benzyl iodide	—	1**
Benzyl chloride	1.3	354

* In this instance the reaction was not followed to completion but k' was calculated by assuming $C_\infty = 1.00 \cdot 10^{-3}$ mol/l.

** It was not possible to make a kinetic measurement in this instance because the reaction was complete within 1 min.

TABLE VI

BUTYLATION OF BENZOIC ACID AT DIFFERENT TEMPERATURES

Organic solvent: methyl ethyl ketone. Alkylating agent: butyl bromide (0.1 mol/l).

Temperature ($^{\circ}\text{C}$)	$k' \cdot 10^2$ (min^{-1})	Calculated time for 99% alkylation (min)
10.0	0.70	658
20.0	4.7	98
30.0	17	27
40.0	37	12
50.0	54	9

ethyl ketone. This solvent could be suitable for work at higher temperatures as TBA bicarbonate did not decompose as it did in the halogenated solvents (*cf.*, *stability of TBA bicarbonate*).

The advantage of using the ketones is considerable, as they are readily available, stable and can be evaporated fairly easily. The last property contrasts with those of other dipolar aprotic solvents such as dimethylformamide, dimethyl sulphoxide and dimethylacetamide.

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