

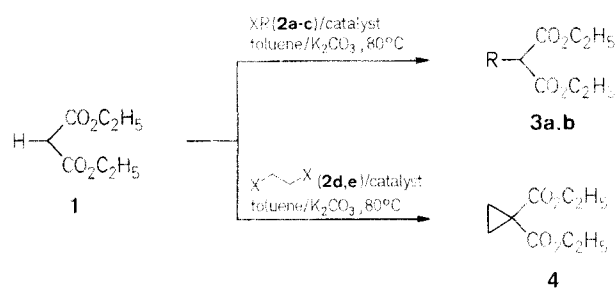
## Co-Catalytic Effects in Phase-Transfer Catalyzed Reactions

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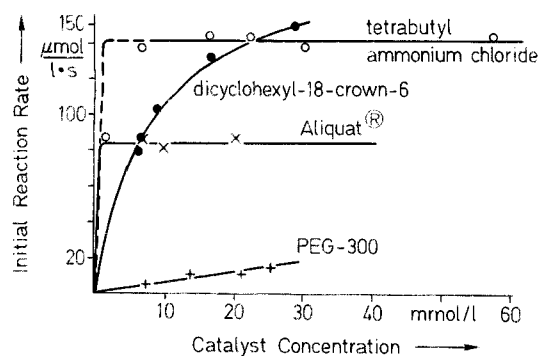
The phase-transfer catalyzed alkylation reaction of diethyl malonate with butyl bromide using solid potassium carbonate as base could not be accelerated above a limiting reaction rate by increasing the concentration of the onium salt catalyst. The rate limit could be exceeded by using crown ether in addition to an onium salt. Polyethylene glycols exhibit a similar effect. These results were used to improve the yields in a series of related alkylation reactions.

The combination of the base potassium carbonate with a lipophilic cation was introduced into phase-transfer catalytic techniques by Makosza et al.<sup>1</sup> Subsequently, many alkylations of weak CH and NH acids have been performed successfully in this way.<sup>2,3</sup> The lipophilic cationic catalysts used were onium salts (e.g., tetrabutylammonium chloride, Aliquat®). We have investigated the catalytic effect of some onium salts, crown ethers, and polyethylene glycols in this type of reaction. In particular, we have studied the alkylation and cyclodialkylation of diethyl malonate (**1**) with monofunctional and bifunctional alkylating agents (**2**), respectively.



2	R	X
a	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Br
b	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Br
c	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Cl
d	—	Br
e	—	Cl

We found that the reaction rate of the alkylation of diethyl malonate (**1**) with 1-bromobutane (**2a**) using onium salt catalysis could not be increased above distinct limits by the addition of further onium salt (Figure).



**Figure.** Dependence of initial alkylation rate on catalyst concentration for the reaction of diethyl malonate (**1**; 10 mmol) with 1-bromobutane (**2a**; 10 mmol) and potassium carbonate (12 mmol) in toluene (10 ml) at 80°C; stirring rate: 800 rpm.

**Table 1.** Initial Reaction Rates at Reflux Temperature as shown in the Figure

Catalyst (Concentration <i>c</i> = 4 mmol/1000 ml)	Initial Reaction Rate <sup>a</sup> of the Alkylation of Diethyl malonate ( <b>1</b> ) with 1-Bromobutane ( <b>2a</b> ) [ $\mu\text{mol} \cdot \text{dm}^{-3} \cdot \text{s}^{-1}$ ]
Aliquat <sup>®</sup>	80
Benzo-15-crown-5	20
Aliquat <sup>®</sup> + Benzo-15-crown-5	120

<sup>a</sup> Determined by GLC analysis (conditions: see Table 3, footnote a) of the alkylation product formed after 30, 60 and 90 minutes.

In the case of tetrabutylammonium chloride, the reaction could not be accelerated above the plateau by adding the onium salt Aliquat<sup>®</sup>. However, the initial reaction rate exceeded this limit when onium salt and a crown ether were used together. Crown ethers themselves catalyse the alkylation. The dependence of the initial reaction rate on crown ether concentration for the alkylation of **1** by **2a** is different from that obtained for the onium salts, showing instead a continuous increase (Figure). Crown ethers used together with onium salts exhibit an additive effect and, in some cases, a synergic effect (Table 1).

The kinetic data thus obtained were utilised for preparative purposes: the alkylations (Scheme) were accelerated and the yields were improved (Table 2). In some cases, there even was a

**Table 2.** Yield of Alkylation Reactions (Scheme)

Alkylating Agent	Catalyst	Reaction Time (h)	Conversion (%) (GLC)	Yield (%) of Isolated Product <b>3</b> or <b>4</b>
<b>2a</b>	a	5	62	
	b	5	58	
	c	5	59	
	d	5	73	
	e	5	15	
	b + d	5	90	92
<b>2b</b>	b + e	5	85	
	b	5	76	
	d	1	93	
	e	5	4	
	b + d	1	94	
	b + e	1	93	
<b>2c</b>	b	5	54	
	d	5	40	
	e	5	3	
	b + d	5	75	81
	b + e	5	75	
<b>2d</b>	b	5	44	
	d	5	54	
	e	5	5	
	b + d	5	73	70
	b + e	5	46	
<b>2e</b>	b	5	32	
	d	5	5	
	e	5	4	
	b + d	5	72	75
	b + e	5	38	

<sup>a</sup> 0.013 g Aliquat<sup>®</sup>.

<sup>b</sup> 0.025 g Aliquat<sup>®</sup>.

<sup>c</sup> 0.05 g Aliquat<sup>®</sup>.

<sup>d</sup> 0.013 g Dicyclohexyl-18-crown-6.

<sup>e</sup> 0.025 g Polyethylene glycol 300.

**Table 3.** Physical and Spectral Data of the Diethyl Alkylmalonates **3** and Diethyl Cyclopropane-1,1-dicarboxylates **4** Prepared

Product	GLC Retention Time <sup>a</sup> (s)	b.p. (°C)/torr		IR (capillary film) <sup>b</sup> $\nu$ (cm <sup>-1</sup> )	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ) <sup>c</sup> $\delta$ (ppm)
		found	reported		
<b>3a</b>	180 (t = 150°C)	125–133/18	130–135/20	1730, 1740, 1025, 855	0.91 [t, 3H, (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ]; 1.1–1.6 (m, 4H); 1.9 (m, 2H) [(CH <sub>2</sub> ) <sub>3</sub> ]; 1.25 (t, 6H, 2OCH <sub>2</sub> CH <sub>3</sub> ); 3.29 (t, 1H, CH); 4.18 (q, 4H, 2OCH <sub>2</sub> CH <sub>3</sub> )
<b>3b = 3c</b>	100 (t = 200°C)	173–178/18	158/8	3045, 1710, 1720, 1025, 850, 745, 695	1.14 (t, 6H, 2OCH <sub>2</sub> CH <sub>3</sub> ); 3.0–3.45 (m, 2H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ); 3.55 (dd, 1H, CH); 4.10 (q, 4H, 2OCH <sub>2</sub> CH <sub>3</sub> ); 7.16 (m, 5H <sub>arom</sub> )
<b>4d = 4e</b>	100 (t = 150°C)	110–115/18	214–216/748	1720, 1730, 1200, 1015, 845	1.25 (t, 6H, 2OCH <sub>2</sub> CH <sub>3</sub> ); 1.38 (s, 4H <sub>cyclopropane</sub> ); 4.17 (q, 4H, 2OCH <sub>2</sub> CH <sub>3</sub> )

<sup>a</sup> Chromatron GCHF 18; 120 cm long, i.d. 3 mm column; 3% QF<sub>1</sub> silicon oil on Chromosorb G 60/80 Mesh; carrier gas: N<sub>2</sub>; 0.4 atm inlet pressure.

<sup>b</sup> Specord 75 IR spectrophotometer.

<sup>c</sup> 60 MHz Perkin-Elmer R12 spectrometer.

<sup>d</sup> For preparation of authentic samples see: **3a** (Lit.<sup>4</sup>), **3b** (Lit.<sup>5,6</sup>), **4** (Lit.<sup>7</sup>).

significant increase in yield. We next tested other, more easily available agents as co-catalysts.<sup>9a,6</sup> Since polyethylene glycols are known to show catalytic activity in phase-transfer reactions<sup>8,9</sup> we tried their use in our alkylation reaction (Scheme) and we found that they also exert a positive effect, but the yields are still only poor to moderate. However, when used as co-catalysts with onium salts the polyethylene glycols led to improved yields (Table 2).

The results listed in Table 2 show that the yield of phase-transfer catalyzed alkylation reactions in which solid potassium carbonate is used as base (Scheme) can be improved by using lipophilic cationic (onium salts) catalysts and complexing (crown ether or polyethylene glycol) catalysts together. The mechanism of co-catalysis is unclear. The different curve shapes obtained for onium salts and complexing catalysts (Figure) might suggest two different mechanisms. An interfacial process similar to a liquid-liquid base-catalysed reaction mechanism, as proposed could be assumed for onium salts. In crown ether-catalysed cases, a process including the dissolution of carbonate ions into the organic phase, i.e., a Starks type<sup>11,12</sup> reaction, could be envisaged. The latter mechanism is, however, inconsistent with the low lipophilicity of carbonate ion (CO<sub>3</sub><sup>2-</sup>). It has been reported<sup>13</sup> that dissolution of alkali carbonates in solutions containing crown ethers could not be detected. Therefore, interfacial processes are probably operative in both cases.

It is worthy of note from the alkylation reactions according to the following general procedure practically no dialkylated products could be observed when 1-bromobutane (**2a**), benzyl bromide (**2b**), or benzyl chloride (**2c**) were used and that the formation of monoalkylated products was not observed in the cyclopropane-forming reaction with 1,2-dibromoethane (**2d**) or 1,2-dichloroethane (**2e**).

Catalysts and starting materials were of commercial origin.

#### Alkylation and Cyclodialkylation of Diethyl Malonate (**1**); General Procedure:

Dry toluene (5 ml), dry potassium carbonate (1.7 g, 12 mmol), diethyl malonate (0.801 g, 5 mmol), the alkylating agent **2** (5 mmol), and the catalyst (0.03–0.15 mmol) are placed in a conical flask (25 ml volume, 35 mm Ø at the base) fitted with a reflux condenser and a magnetic stirrer (15 mm length). The mixture is stirred (800 rpm) at 80°C, and the conversion is monitored by GLC. After the reaction is complete the mixture is filtered, the precipitate is washed with toluene, and the product is isolated by distilling off the organic solvent at reduced pressure (For further purification, the product **3** or **4** may be distilled at reduced pressure).

Received: 30 July 1986  
(Revised form: 7 January 1987)

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