Simplify gas–liquid phase transfer catalysis

This technique is adaptable to continuous-flow operation. An important industrial example is the use of dimethylcarbonate as an environmentally preferable methylating agent.

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Reactions between activated anions in a liquid phase and a gaseous organic substrate can be carried out under continuous-flow (CF) conditions using gas–liquid phase transfer catalysis (GL-PTC) (*1*, *2*). The process uses a phase transfer (PT) catalyst immobilized on a solid bed. The solid support may also be a reagent in the reaction. Reaction occurs in the immobilized liquid phase with continuous transfer of products and reactants between the gas and liquid phases (Figure 1).

Phosphonium salts (*3*), polyethylene glycols (PEGs), crown ethers (*4*), and cryptands (*5*) are used as PT catalysts because they promote the transfer of anions into the organic phase and then activation (Figure 2, p. 32). Although PEGs are less efficient than other PT catalysts, they are relevant in GL-PTC (*6–8*) because they are nontoxic and inexpensive. They complex alkaline metal cations and therefore can solubilize the related solid reagents into the supported liquid phase, making them more readily available for reaction. PEGs' behavior as PT catalysts has been reviewed by Harris et al. (*9*) and Totten and colleagues (*10, 11*).

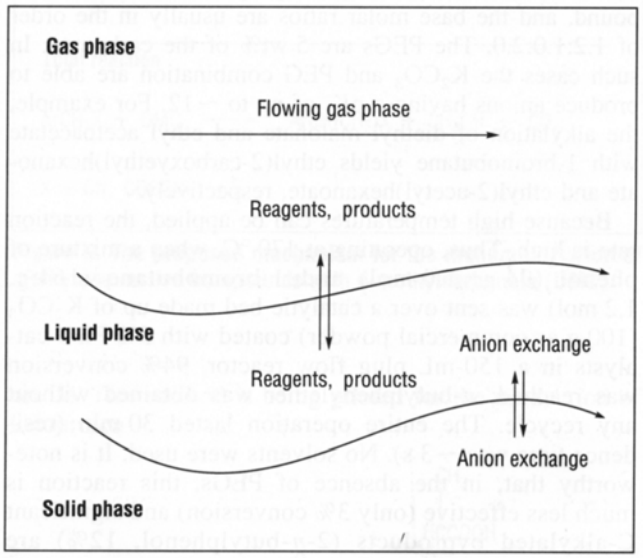

Figure 1. **In gas–liquid phase transfer catalysis (GL-PTC), the catalysts are located between a solid support and the flowing gas phase.** The desired reaction takes place in the liquid phase.

Types of GL-PTC catalysis

Anion activation is involved in four types of GL-PTC catalysis. The first two types use reactive beds. A gaseous reagent reacts with a solid salt, and gaseous products leave the reactor. The reagent solid salt (MY) is transformed into a new solid salt (MX).

$$RX_{gas} + M^+Y^-_{solid} \xrightarrow{\text{PT catalyst}} RY_{gas} + M^+X^-_{solid}$$

The second two types involve conventional catalysis, that is, the solid phase functions strictly as a catalyst in the reaction.

Stoichiometric reactions with alkaline metal salts. This reaction occurs via the transfer of reactive anions from the solid phase. Small amounts of molten PT catalysts (usually 0.5–5% molar equivalents) are able to promote the reaction of the solid salts as a whole; during the reaction they move from the original surface to the inner core of the crystals. PT catalysts such as quaternary phosphonium salts are required for these reactions. Examples are the synthesis of alkyl halides (*12*) and esters (*13*). For example, when 1-bromobutane flows through ground potassium iodide, practically no 1-iodobutane is obtained. However, 96% conversion to iodobutane is reached in the presence of 5% $Bu_4P^+I^-$. Similarly, when ethyl bromide is sent at 150 °C into a column filled with sodium acetate (1.6 molar equiv), a reaction does not take place, whereas 96% conversion into ethyl acetate is observed by coating the solid salt with 2% molar equiv of $Bu_4P^+Br^-$.

Stoichiometric reactions with strong bases. The base on the solid bed acts as a mediator in producing the actual nucleophile. The resulting nucleophile undergoes nucleophilic displacement. Active catalysts for these types of reactions are polyethylene glycols (PEGs); such reactions mainly involved soft anions as intermediates.

When phenols, thiols, or weak CH-acidic compounds (such as malonate esters) and an alkylating agent (such as alkyl halide) pass through a bed containing K_2CO_3 and PEGs, the intermediate anions (ArO^-, RS^-) are formed, and the corresponding alkylated products leave the reactor,

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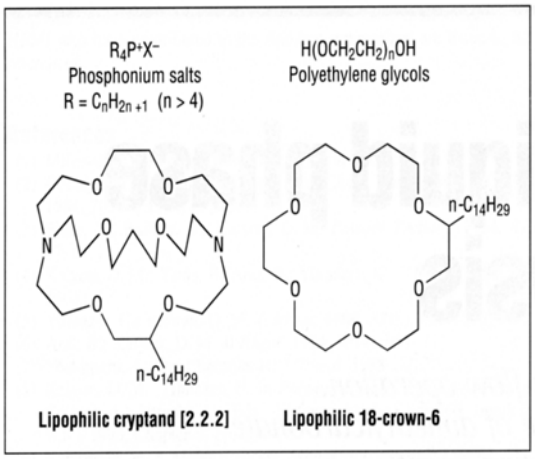


Figure 2. **Phase transfer catalysts used in GL-PTC.**

and the inorganic potassium salts are formed on the reaction bed (*14–16*). The alkylating agent, the acidic compound, and the base molar ratios are usually in the order of 1.2:1.0:2.0. The PEGs are 5 wt% of the carbonate. In such cases the K_2CO_3 and PEG combination are able to produce anions having a pK_a of up to ~12. For example, the alkylation of diethyl malonate and ethyl acetoacetate with 1-bromobutane yields ethyl(2-carboxyethyl)hexanoate and ethyl(2-acetyl)hexanoate, respectively.

Because high temperatures can be applied, the reaction rate is high. Thus, operating at 170 °C, when a mixture of phenol (94 g, 1.0 mol) and 1-bromobutane (164 g, 1.2 mol) was sent over a catalytic bed made up of K_2CO_3 (100 g as commercial powder) coated with 5% PEG catalysts in a 150-mL plug flow reactor, 94% conversion was reached; *n*-butylphenylether was obtained without any recycle. The entire operation lasted 30 min (residence time was ~3 s). No solvents were used. It is noteworthy that, in the absence of PEGs, this reaction is much less effective (only 3% conversion) and significant C-alkylated byproducts (2-*n*-butylphenol, 12%) are formed, thus showing that the reaction proceeds in a more polar environment (*14*).

Reactions with neutral and acidic media. Activated halide anions react with alkyl halides (*17*) or protonated alcohols (*18*) to yield an alkyl halide. For instance, when a mixture of *n*-BuOH·HCL 35% (in a 1:1.3 M ratio) was allowed to pass over a catalytic bed composed of silica gel coated with 5% $Bu_4P^+Br^-$, conversion into *n*-BuCl was 78%. The reaction was carried out at 170 °C and at a weight hourly space velocity of 0.095 $g_{mixture}/h\text{-}g_{bed}$. Phosphonium salts, coated on macroporous solid supports, are the catalysts. In the case of alkyl halides, the reaction is equilibrium type (thermodynamic equilibrium is reached); in the case of protonated alcohols, the reaction is entirely shifted toward the products.

Reaction with bases as co-catalysts. PEGs are effective catalysts in this type of reaction. For example, the transesterification reaction (*19*), which is an equilibrium reaction, is readily accomplished in the presence of K_2CO_3 as a co-catalyst:

$$ROH + R'COOR'' \underset{}{\overset{K_2CO_3,\ PEGs}{\rightleftharpoons}} R''OH + R'COOR$$

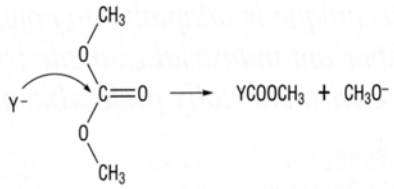
Reactions with dimethylcarbonate (DMC) belong to this class.

Reactions with DMC. Among the reactions carried out under GL-PTC conditions, those of DMC are of great relevance (*20, 21*). DMC can be considered an environmentally safe reagent; although its traditional synthesis involved phosgene, it can now be produced by the oxidative carbonylation of methanol

$$2CH_3OH + {}^1/_2O_2 + CO \longrightarrow H_3C{-}O{-}CO{-}O{-}CH_3 + H_2O$$

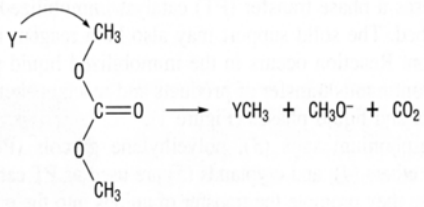
as practiced by Enichem (Italy) (*22*).

DMC can be used as a carboxylating agent:



Transesterification

In this reaction Y^- refers to anions such as ArO^-, ArS^-. DMC can also be used as a methylating agent at higher temperatures:



Methylation

The leaving group (methoxycarbonate anion, CH_3OCOO^-) is not stable—it rapidly decomposes into methanol and CO_2. The methanol produced in both reactions can be recycled to DMC production.

Both carboxylation with phosgene and methylation with dimethylsulfate reactions generate stoichiometric quantities of inorganic salts because a base must be used as a reagent to capture the HCl^- or H_2SO_4.

$$2\ PhOH + COCl_2 + 2\ NaOH \longrightarrow PhOCOOPh + 2\ NaCl + 2\ H_2O$$

$$PhOH + (CH_3O)_2SO_2 + NaOH \longrightarrow PhOCH_3 + CH_3OSO_2O^-Na^+ + H_2O$$

$$PhOH + CH_3Cl + NaOH \longrightarrow PhOCH_3 + NaCl + H_2O$$

Under continuous GL-PTC conditions, methylation reactions of DMC are readily achieved in the presence of weak bases (e.g., K_2CO_3) when operating at high temperatures (160–180 °C) (Table 1). Under batchwise conditions at the reflux temperature of DMC (90 °C), only carboxymethylations occur through an equilibrium-type reaction; stronger bases (sodium methylate) are used. Actually, at high temperatures, the methylation reaction prevails over carboxymethylation because the former is not an equilibrium reaction. Thus, when a mixture of phenol (94 g, 1.0 mol) and DMC (2.0 mol) is allowed to flow once over a 100-g catalytic bed composed of 5% PEG 6000 and 95% K_2CO_3 at 180 °C, anisole is obtained

Table 1. **Reactions of dimethylcarbonate (DMC) with different nucleophiles under batch and continuous-flow conditions (GL-PTC)**

Reagent	Product	
	Batch[a]	Continuous flow
ArOH	$ArOCOOCH_3$	$ArOCH_3$
ArSH	$ArSCH_3$	$ArSCH_3$
$ArNH_2$	$ArNHCOOCH_3$	$ArNHCH_3$
ROH	$ROCOOCH_3 + (RO)_2CO$	$ROCOOCH_3 + (RO)_2CO$
$ArCH_2CN$	$ArCH(COOCH_3)CN$	$ArCH(CH_3)CN$

[a] Batchwise reactions occur at the reflux temperature of DMC (90 °C) in the presence of strong bases (sodium methylate or hydride) (*43–46*). Methylation reactions expressly require high temperatures (160–180 °C). Weak bases (alkaline carbonates) are used.

(100% conversion). The run takes place in 1 h (residence time ~10 s) (*23–25*).

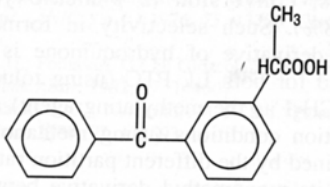
$$PhOH + DMC \xrightarrow{PEGs;\ K_2CO_3} PhOCH_3 + CH_3OH + CO_2$$

When performed with GL-PTC, DMC reacts with primary aromatic amines (*26*, *27*) and with methylene-active compounds to produce monomethylated derivatives with a selectivity not previously observed. In fact, monomethylation reactions of methylene-active compounds are not a one-step process in industrial production because of the amounts of dimethyl derivatives obtained with the usual methylating agents. For example, under classical liquid–liquid phase transfer catalysis (LL-PTC) conditions, the reaction of phenylacetonitrile with CH_3I gave a mixture of the starting reagent, monomethylated and dimethylated derivatives (6, 66, and 28%, respectively) from which the monomethylated product cannot be separated (*28*).

Intermediates for nonsteroidal analgesics

The monomethylation of arylacetonitriles and arylacetoesters is noteworthy because arylacetonitriles and arylacetoesters can produce 2-arylpropionic acids (anti-inflammatory drugs) from readily available intermediates. With the use of DMC, under either GL-PTC (*29*, *30*) or batch conditions (*31*, *32*), it is possible to synthesize 2-arylpropionic acid derivatives with >99% purity in monomethyl derivatives, at complete conversion, using a 10–30 M excess of DMC (Table 2). The proposed reaction is shown in Figure 3.

In methylene-active compounds, DMC acts first as a carboxymethylating agent that allows the protection of the methylene-active derivatives and permits nucleophilic displacement to occur with another molecule of DMC (Figure 3). This method is being piloted for the production of ketoprofen



at Tessenderloo Chemie (Belgium).

Also, the methylation of aroxyacetonitriles and methyl 2-aroxyacetates proceeds with a selectivity up to 99% in the monomethyl derivatives: 2-aroxypropionitriles and methyl 2-aroxypropionates are the corresponding products (Bomben, A.; Marques, C. A.; Selva, M.; Tundo, P., unpublished results). These products are widely used as biologically active compounds (*33*, *34*) and plant growth regulators (*35*, *36*).

$$ArCH_2X + B \rightleftharpoons ArC(-)HX + BH^+$$

$$ArC^-HX + DMC \rightleftharpoons ArCH(COOCH_3)X + CH_3O^-$$

$$BH^+ + CH_3O^- \rightleftharpoons B + CH_3OH$$

$$ArCH(COOCH_3)X + B \rightleftharpoons ArC^-(COOCH_3)X + BH^+$$

$$ArC^-(COOCH_3)X + DMC \longrightarrow Ar{-}\overset{\overset{COOCH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}X + CO_2 + CH_3O^-$$

$$Ar{-}\overset{\overset{COOCH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}X + CH_3O^- \rightleftharpoons ArC^-(CH_3)X + DMC$$

$$ArC^-(CH_3)X + BH^+ \rightleftharpoons ArCH(CH_3)X + B$$

Total reaction

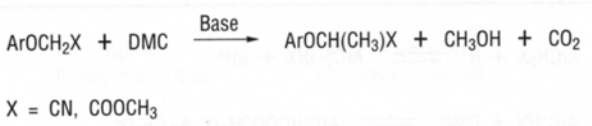
$$ArCH_2X + DMC \longrightarrow ArCH(CH_3)X + CH_3OH + CO_2$$

X = CN, $COOCH_3$

Figure 3. **The proposed mechanism for the monomethylation of methylene-active compounds with dimethylcarbonate (DMC).**

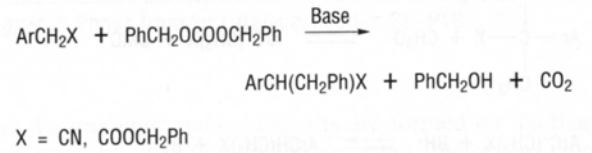
Table 2. **Monomethylation of arylacetonitriles and methyl arylacetates by DMC**

X	Ar	Conversion, %	Selectivity in monomethylation, %	Intermediate for
CN	4-isobutylphenyl	99	99	Ibuprofen
CN	3-carboxymethylphenyl	100	>99	Ketoprofen
$COOCH_3$	2-(6-methoxynaphthyl)	100	>99	Naproxen



Reactions with other dialkylcarbonates

At operating temperatures of 180–220 °C, other dialkylcarbonates produce both O-alkylation of phenols and C-alkylation of methylene-active compounds in high yields. For example, the reaction of phenols with dibenzylcarbonate affords benzyl aryl ethers while arylacetonitriles and benzyl arylacetates are selectively mono-C-benzylated to the corresponding 2-aryl-3-phenyl propionitriles and benzyl 2-aryl-3-phenylpropionates (*37*):



The selectivity in the monoalkylated products is >99%.

Changing processes changes products

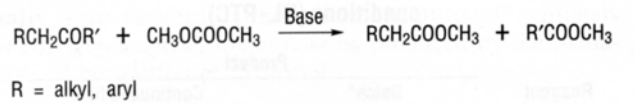
Under continuous GL-PTC conditions, partition phenomena between the liquid phase of the catalyst and the flowing gas phase result in different products from those occurring under liquid–liquid (LL)-PTC conditions (Figure 4).

Consider, for example, the reaction of hydroquinone with DMC in a pilot plant reactor (Ligorati, F.; Tundo, P., unpublished results) operating at 280 °C over a bed composed of 10 wt% of KOH on α-alumina. Working at a molar ratio of DMC to hydroquinone of 3.0, formation of *p*-dimethoxybenzene was 90% at a contact time of 21 s. Working with a lower molar ratio (1.5) and at a contact time of 13 s, conversion to *p*-methoxyphenol was observed (78%). Such selectivity in formation of the monomethyl derivative of hydroquinone is higher than those reported for both LL-PTC (using toluene, aqueous NaOH, and CH_3I as the methylating agent) and homogeneous alkylation conditions (using methanol and CH_3I). This is explained by the different partition ratios of hydroquinone and its monomethyl derivative between the two liquid phases (in the case of LL-PTC) and between a liquid and a gaseous phase (in the case of GL-PTC). In LL-PTC, hydroquinone is less soluble in the organic phase than its monomethyl derivative, so the latter can react far more efficiently to yield the dimethyl derivative. In GL-PTC, products and reagents divide as follows between the liquid and gas phase according to their relative volatilities: hydroquinone, bp = 285–288 °C; *p*-hydroxyphenol, bp = 224 °C. The more volatile *p*-hydroxyphenol is preferentially stripped from the liquid phase, thus increasing its selectivity.

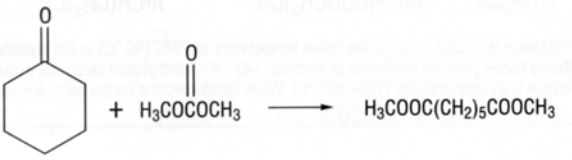
In the alkylation of hydroquinone, the catalyst worked for ~200 h, after which time activity decreased. This is due to formation of tar on the catalyst bed. The bed can be regenerated without KOH loss by treatment with air at 500 °C. The regenerated bed showed the same catalytic activity as the original bed.

Other applications

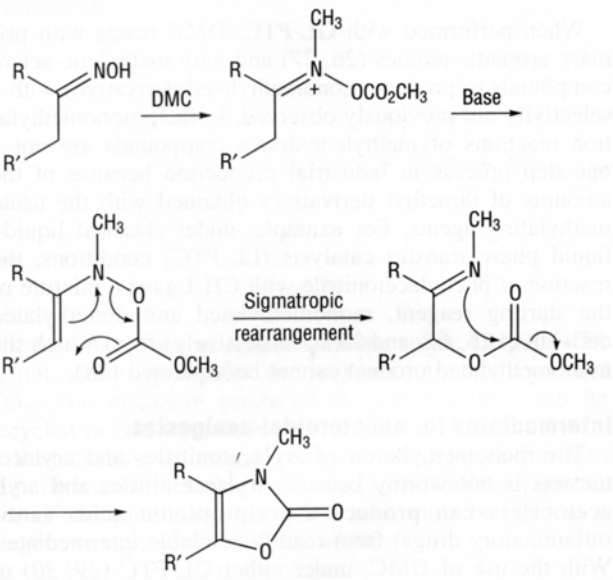
DMC has been treated batchwise with ketones (*38*) and ketoximes (*39*). In the case of ketones, DMC adds to both benzylic and aliphatic ketones, which then split into two methyl esters:



Accordingly, without involving the usual oxidant conditions using HNO_3 (*40*), alicyclic ketones afford esters of α,ω-dicarboxylic acids; for instance, cyclohexanone gives dimethyl pimelate.



In the case of ketoximes, DMC allows both *O*-carboxymethylation and *N*-methylation of the ketoximes, and then a [3,3]sigmatropic rearrangement occurs, yielding 3-methyl-4,5-disubstituted-4-oxazolin-2-ones:



These products can be used as precursors of β-aminoalcohols, which can be used in the synthesis of ephedrines (*41*).

Conclusion

The continuous-flow GL-PTC process using DMC has the following noteworthy features:

- The reagents (DMC) and catalysts (PEGs) are nontoxic.
- No byproducts are produced.
- High selectivity in monomethylation of methylene-active compounds is achieved.

This process contributes to pollution prevention (*42*). Its development is an example of how environmental needs can influence basic research and lead to improved industrial processes.

Acknowledgments

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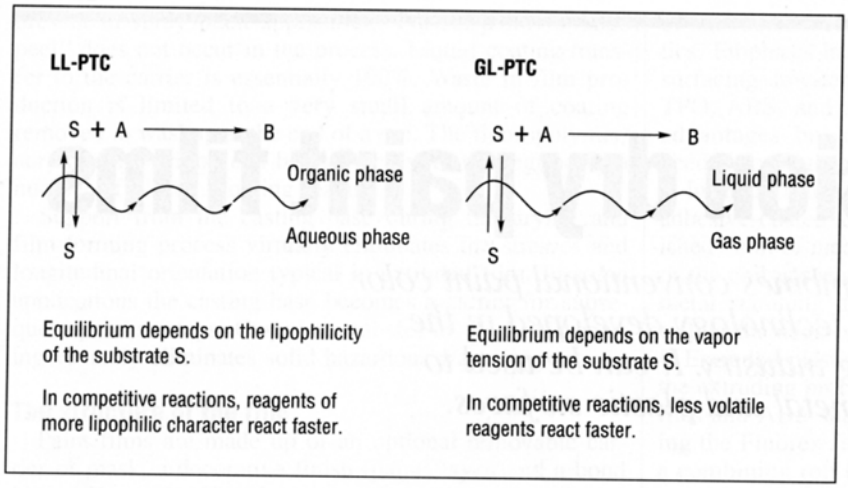

Figure 4. **A comparison of product selectivity resulting from partition phenomena in liquid–liquid and gas–liquid phase transfer catalysis.**

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