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Industrial applications of phase transfer catalysis (PTC): past, present and future

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Abstract - The advantages of PTC for industrial processes are discussed and recent progress in catalysts, methodology and applications is critically reviewed. Various trends and new applications of commercial interest are emphasized.

INTRODUCTION

No new catalytic method in organic synthesis has been so rapidly adopted and applied so extensively as PTC. Since its introduction by the pioneering work of Makosza, of Brandstrom and of Starks in 1965-71, publications in which PTC is the focus (Fig. 1) have increased at a remarkable pace with some slackening in 1985.

Similarly, the number of different applications for PTC has increased to the point where a "compendium" published in 1979 (ref. 1) lists over 65 different types of organic compounds (from acetals to urethanes) which can advantageously be synthesized by PTC techniques. In fact, PTC has become one of the most useful weapons in the arsenal of the organic chemist and, more often than not, is the method of choice for processes in which one of the reactants is an anionic species, either added as an alkali salt or generated *in situ* by a base.

Not only does PTC promote the reaction between reagents which are mutually immiscible (i.e., sodium salts and alkyl halides) but it also, at least for batch processes, offers a number of important process advantages, some of which are listed in Table 1.

These factors contribute to overall process efficiency in terms of process simplification, equipment size, product and solvent purity and ease of recovery, as well as cost saving by the elimination of the need for the expensive solvents, anhydrous strong bases and oxidants needed as the alternative to PTC. The rapidly growing PTC patent literature attests to the industrial interest; even if we assume that only 10-20% of these patents are actually practiced, then its industrial impact is currently significant and its potential even more so.

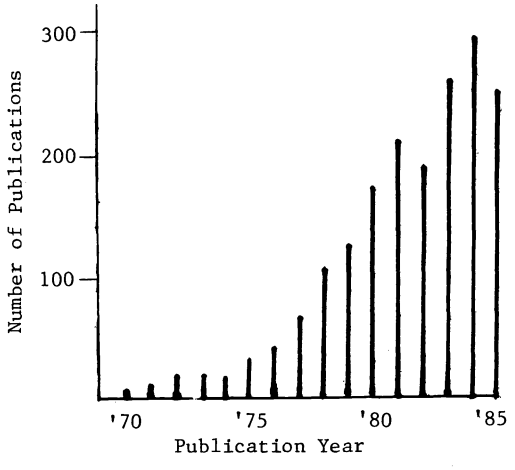
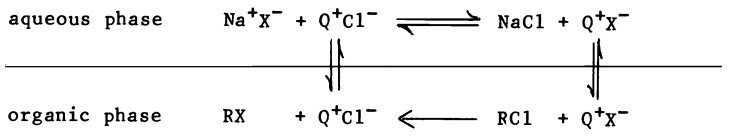


Fig. 1 Growth of PTC Publications, 1970-85

TABLE 1. Advantages of PTC for Industrial Processes

Increased rates of reaction
Increased product specificity
Lower energy requirements
Use of inexpensive, non-toxic, recoverable solvents or use of liquid reactant as solvent
Commercially available, inexpensive catalysts
Use of inexpensive bases for anion generation
Use of inexpensive oxidants

The original Stark's mechanism (ref. 2), generalized for the SN_2 displacement of Cl by a nucleophile X^-, catalyzed by a quaternary ammonium salt (Q^+) is given in (1).



(1)

This has stood the test of time and it is clear that the reaction takes place in the organic phase and that the rate is primarily determined by the extractability of the anionic reactant by the PT catalyst. There remain areas of controversy as to the exact role of the catalyst when the anionic nucleophile is generated in situ by the action of concentrated base on weak acids. However, mechanistic considerations are not our primary interest here; rather, this review will attempt to assess the role of PTC in chemical industry where, for better or worse, primary consideration is given not to mechanism but to utility and economics. The literature has previously been comprehensively reviewed through ca 1979 (refs. 1,3,4) and developments of the past five years will be considered here.

CATALYSTS

The choice of which PTC catalyst to use - quaternary ammonium (Q^+), phosphonium (QP^+), crown ether, such as 18-crown-6 (18-C-6) or a polyethylene glycol (PEG), will depend on a number of process factors. These include reaction type, solvent, temperature, base strength and ease of catalyst recovery and removal. If these factors are not decisive, then catalyst cost will determine the choice. Table 2 lists most of the common, commercially available in bulk PT catalysts and estimates the cost for 5 mol % of each.

TABLE 2. Commercially Available PT Catalysts

Catalyst	Source	Approx. M.W.	Cost/lb	Cost of 5 mol %
PEG-600[a]	Union Carbide	600	$ 0.60	$0.04
TBMAC[b]	Ethyl Corp.	236	2.15	0.07
BTEAC[c]	RSA Corp.	228	3.50	0.09
Aliquot-336[d]	Henkel Corp.	400	2.00	0.09
Adogen-464[d]	Sherex Chem. Corp.	400	2.00	0.09
TBAB[e]	Hexel Corp.	340	5.50	0.21
TBPC[f]	RSA Corp.	340	35.00	1.30
18-C-6	Parish Chem. Corp.	264	225.00	6.50

[a] Polyethyleneglycol
[b] Tributylmethylammonium chloride (75% soln.)
[c] Benzyltriethylammonium chloride
[d] Tricaprylmethylammonium chloride
[e] Tetrabutylammonium bisulphate
[f] Tetrabutylphosphonium chloride (tech., 85%)

Both the least and most expensive catalysts in Table 2 are polyethers which presumably function similarly as cation complexers. Where the OH groups of the PEG are detrimental (i.e., for oxidations) their mono- and di-alkylated derivatives are available and can be substituted. Recent work suggests that the PEG's can replace the expensive 18-C-6. Examples where the former equalled or outperformed the latter include synthesis of 1-cyanooctane (ref. 5), esterification (ref. 6), phenol alkylation (ref. 7), matrix immobilization (ref. 8) and alkaline hydrolysis of poly(methyl methacrylate)(ref. 9). PEG's have been termed "the poor chemist's crown" (ref. 9a) and the applications listed in Table 3 testify to their increasing importance as PT catalysts.

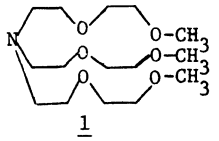
With two exceptions, the Q^+s remain as the PT catalyst of choice; Q^+'s are inherently thermally unstable and decompose at temperatures over 90° and are also decomposed by bases stronger than 60% sodium hydroxide. Under these conditions the catalysts of choice are the QP^+'s or polyethers, both of which have greater stability. However, if the reaction is reasonably fast, Q^+ may still be preferred, even if replenishment is necessary.

TABLE 3. Use of PEG's as PT Catalysts

Reaction or Product	Catalyst	Approx. # of exs.	Average yield (%)	Reference
Triarylphosphates	PEG-400	6	90-96	10
Ester hydrolysis	PEG-400-4000	1	100	11
Phenol alkylation	PEG-400-4000	3	80	11
Oxidation of C-acids	various PEG's	6	50	12
Horner-Emmons rxn	various PEG's	-	-	13
N-alkylation	PEG/dialk PEG	5	"excellent"	14
Ethers	dialk. PEG's	5	90	15
Alkoxylation of halobenzenes	PEG-6000	8	65	16
Phenytoin synth	PEG-600	1	90	17
Reduction of C=O	PEG/dialk.PEG	10	80	18
Dehydrohalog.	various PEG's	8	80	19
Nitration with nitrite	PEG-600	1	—	20
Williamson ether synth.	DiBu-PEG-600	5	90	21
Aldol rxn	PEG-600	-	50	22
N-protection of Amino Acids	PEG-600	4	-	23
Esterification	PEG-400 (on Al_2O_3/SiO_2)	2	50	24
Oxidation with NaOCl	PEG-350	2	30	24

Where catalyst cost is not critical, TBAB, first introduced by Brandstrom, remains the most popular. A recent economic evaluation of Q^+'s in industrial applications (ref. 25) concludes that at a price of $4,500/ton, TBABr is practical even for higher priced commodities. A final decision will depend on the cost of catalyst recovery, usually by aqueous extraction of the organic layer and re-extraction of the Q^+ with an appropriate solvent. For TBABr (and perhaps other Q^+'s as well) a novel process using aqueous extraction and pH adjustment yielded an organic layer containing 92% Q^+ which was recycled at least 10 times with no yield loss (ref. 26). Removing the last traces of Q^+, usually by ion-exchange, can be difficult and expensive but is often required for drugs and Q^+-sensitive products. Most of this technology is propietary and little literature is available.

New PT catalysts continue to be reported (1-4) which are claimed to have superior thermal stability.



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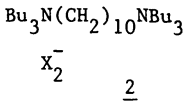

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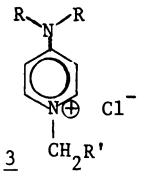

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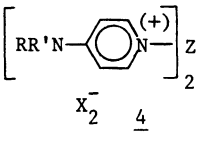
R,R'=various alkyl's



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R,R'=alkyls
Z=alkylene,PEG

TDA-1 (1), recently introduced on a limited commercial basis by Rhone-Poulenc, is an open chain cryptate analog which, according to its discover, is effective for aromatic substitutions at 130° and also exerts a synergistic effect in the Ullman reaction (ref. 27). The General Electric Co. has patented two di-Q^+'s (2 & 4), both of which are claimed to be useful for the synthesis of the precursor compounds for polyether imides (refs, 28, 29), production of one of which (Ultem®) is expected to reach 12 million pounds in the near future (ref. 30). The dimethylaminopyridinium Q's (3), of which 4 is a variant, have been described in detail by Brunelle (ref. 31) who states that these are effective PT catalysts for aromatic nucleophilic displacements, are up to 100 times more stable than TBABr to phenoxide and can function at 200°. This is certainly a notable advance.

METHODOLOGY

Techniques

The original premise that the solid-liquid PTC technique is limited to catalysis by crown ethers has long been shown to be incorrect and that Q^+ catalysis is equally applicable. A recent example reports the esterification of the dry sodium salt of 14 different aromatic carboxylates with alkyl bromides catalyzed by TBABr in 80-100% yield (ref. 32). Similarly, solid-liquid PTC is preferred for SNAr reaction of activated aryl halides with phenoxide (ref. 33). Tundo has developed still another technique, - gas-liquid PTC, in which a gaseous alkyl halide is continuously reacted at temperatures up to 170° with various nucleophiles catalyzed by a QP^+ salt deposited on a solid matrix. This method was used to prepare alkylated malonates (refs. 34, 35), carboxylate esters (ref. 36), transesterification products (ref. 37) and alkenes by the Wittig reaction (ref. 38). Using QP^+ catalyst at 200°, a melt synthesis of diaryl sulfides was accomplished (ref. 39). Finally, using solid-liquid PTC with TBABr at high dilution, ω-bromocarboxylates were converted to macrolides (n=7-17) in excellent yields (ref. 40).

Supported catalysts

When originally introduced as "triphase catalysis" (ref. 41) polymer-supported PTC showed promise for solving two important PTC deficiencies: lowering catalyst cost by recycling and eliminating residual catalyst in the product. This promise has not been realized and we are not aware of any industrial applications of supported PTC. The reasons for this can be inferred from the extensive investigations of Ford (ref. 42,43) which have recently been reviewed. As a catalyst, Q^+ immobilization on a polystyrene matrix currently suffers from diffusion limitations, gradual loss of activity and mechanical unstability. Recent work has focused on polymer supported PEG's. Applications and supports include phenate alkylation at 250° (ref. 44), block copolymers (ref. 45), immobilization on metal surfaces (ref. 46) and on alumina or silica (ref. 47).

GENERAL APPLICATIONS

Polymers

The polymer chemists have enthusiastically adopted PTC and continue to utilize it for various polymer applications including monomer synthesis, polymerization, polymer modification and, in a recent development, free radical catalyst activation. The literature is voluminous and has been reviewed for polymer synthesis (ref. 48), and modification (ref. 49), and for polymerization, including condensation (ref. 50), anionic (ref. 51) and free radical (ref. 52). Here we can only touch on recent significant developments.

PTC is particularly well adapted for condensation polymerization and, in fact, was being used for the production of polycarbonates from bis-phenate salts and phosgene even before it was recognized as a PTC example. It is probable that this is the major PTC polymer application today even though the recent literature ignores polycarbonates in favor of other polymers prepared by condensation polymerization of bisphenol-A in aqueous base with organic solutions of various dihalo compounds. These include the production of polyethers by reaction with 1,4-dichloro-2-butene (ref. 53), dibromomethane (ref. 54) and p-xylylene dichloride (ref. 55) and of polyesters from isophthaloyl chloride (ref. 56). Percek has reached paper #14 in his studies on aromatic polyethers and derived block copolymers and is currently exploring their thermotropic properties (ref. 57).

PTC continues to be productive for the chemical modification of polymers, an area summarized by Frechet (ref. 58). Chloromethylated polystyrene continues to be the most studied substrate (ref. 59). Among the many modifications currently reported are etherifications (ref. 60), Wittig-type reactions (ref. 61), reactions with phthalimide (ref. 62) and with malononitrile (ref. 63). Other polymer reactions include poly(methylmethacrylate) hydrolysis (ref. 64), dehydrohalogenation of poly(vinylchloride) and its copolymers (ref. 65), cycloproponation of butadiene-based rubber (ref. 66), nucleophilic substitution on poly(1-chloro-2-epoxypropane)(ref. 67), poly(vinylfluoride) dehydrohalogenation (ref. 68) and grafting on poly(vinyl-chloride)(ref. 69). This list is by no means complete but is indicative of the activity in this area.

The most significant recent application of PTC to polymer science is in free radical polymerization catalysis as discovered and developed by Rasmussen (ref. 70). The use of 18-C-6 or a Q^+ solubilizes potassium peroxydisulfate, or similar radical-forming

salts, in organic solvents and greatly increases their ability to initiate free radical polymerizations of various acrylic monomers. The patented process (ref. 71) has been scaled up to at least 2000 gal. batches in the pilot plant (ref. 72). Though mechanistic problems remain (ref. 73) PTC-promoted free radical initiation is an important contribution.

Aromatic substitution

Recent work has greatly extended the use of PTC for substitution of aromatic halides, usually activated chloride. Table 4 lists some representative examples. In many of these reactions a temperature above the normal decomposition point of the Q^+ catalyst is employed. An exception to this is the use of a QP^+ catalyst (ref. 77a) and the thermally stable catalyst, TDA (ref. 79).

TABLE 4. Aromatic Substitution Reactions

Reaction	# of Exs.	Approx. Yield (%)	Reference
2,6-dihalopyridines ⟶ 2-hydroxy-6-halopyridines	9	95	74
m-dinitrobenzene ⟶ m-nitroanisole	1	83	75
2,5-dichloro-nitrobenzene ⟶ 2-hydroxy-5-chloro-nitrobenzene	1	92	76
poly-chlorobenzenes ⟶ alkyl aryl sulfides	~8	80	77, 77a
dinitrochlorobenzenes ⟶ nitrochlorobenzonitriles	-	-	78
4-chloronitrobenzene ⟶ 4-subst. nitrobenzene	4	85	79

Dehydrohalogenation

With few exceptions, PTC has not been particularly successful for base catalyzed dehydrohalogenation, particularly with respect to selectivity in the production of geometrical and/or positional isomers. At least part of the problem can be attributed to the low extractability of hydroxide. This can lead to a rate determining, diffusion controlled process with unexpected complications involving catalyst, agitation and solvent (ref. 80). This is documented by the work of Rostomyan, et. al., who has reached paper #12 in the series "Dehydrohalogenation of Organic Compounds using Phase Transfer Catalysis" (ref. 81), and reports that vinyl chloride is obtained from dichloroethane by KOH/Q^+ dehydrochlorination in 99% yield in benzene or toluene, but only in 50% yield in ethylbenzene. Lack of selectivity is evident in the formation of a mixture of cis- and trans-, 1- and 2-chloropropene from KOH/ polyether dehydrohalogenation of 1,2-dichloropropane (ref. 83) as well as the carefully defined conditions needed for the optimal preparation of 2-chloro-1,3-butadiene (ref. 82). Other recent examples include the synthesis of phenylacetylenes (ref. 84), 1-phenyl-2-chloroacetylene (ref. 85), α,β-unsaturated acids (ref. 86) and ketones (ref. 87), p-chloromethyl styrene (ref. 88), methyl α-(bromomethyl)acrylate (ref. 89) and the dehydrohalogenation of poly(vinylchloride) (ref. 90).

Oxidations

Inorganic oxidants in organic media under PT conditions has been and continues to be an important synthetic tool. The most commonly used oxidant has been potassium permanganate whose properties and utility have been reviewed (ref. 91). For pharmaceuticals this expensive reagent may be the oxidant of choice as, for example, in the synthesis of fusaric acid (ref. 92). However, 10% aqueous hypochlorite, generally supplied as "swimming pool bleach" can, in many cases, act as an effective, inexpensive substitute. A number of new applications using hypochlorite have been reported since its introduction by Lee and Freedman (ref. 93). These include oxidation of hydroquinone and catechols (ref. 94), 4-naphthoquinone (ref. 95), glycolic to glyoxylic esters (ref. 96), acids from aldehydes (ref. 97) and thioether oxidation (ref. 98). The hypochlorite oxidation of benzyl alcohol (ref. 93) continues to be investigated, both as to the effect of conditions on product selectivity (ref. 99) and the use of solid phase catalysts (ref. 100).

Epoxidation by oxidation with H_2O_2 is a fertile new PTC area. This new catalytic 2-phase system requires both tungstate and phosphate (or arsenate) as the epoxidizing catalyst and a Q^+ or QP^+ for solubilizing the latter in the organic solvent. when all three components are present, epoxidation using dilute (< 10%) H_2O_2 becomes extremely efficient and both terminal and internal olefins are epoxidized with 80-90% selectivity on both olefin and H_2O_2 (ref. 101). this process requires the unsually low pH of <2 for maximum efficiency but apparently is useful even for acid sensitive epoxides. The question of whether or not at this low pH this process is compatible with the Starks mechanism remains to be answered, but there can be no doubt that epoxide production using dilute peroxide has economic potential.

Organometallic

This has been reviewed in 1981 (ref. 101) and in 1984 (ref. 102) by Alper, one of the major contributors to the use of PTC for carbonylation of halides, hydroformylations and reduction of olefins, nucleophilic substitution and isomerizations. Recent PTC work with potential for industrial application include iron pentacarbonyl catalyzed formations of carboxylic acid derivatives (ref. 103), alkoxycarbonylation of conjugated dienes (ref. 104) and dehydrohalogenation of organic halides (ref. 105). Lastly, solid phase PT catalysis, consisting of PEG's covalently bonded to a metal oxide surface, has been used for the carboxymethylation of benzyl bromide to methyl phenylacetate and propylene oxide to methyl 3-hydroxybutyrate (ref. 106).

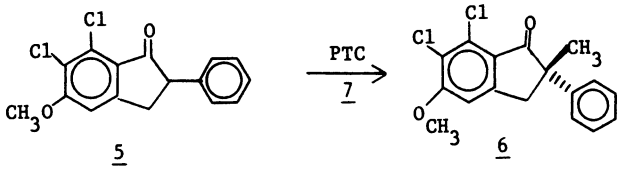
Polyhydroxy compounds

Alkylation of sugars and carbohydrates has been an active area. PTC technique has been successfully used for the esterification of hexitols (ref. 107), derivatization of D-arabinofuranose (ref. 108), stereoselective α-glucosylation (ref. 109), synthesis of tetra-O-acetyl—β—D-glucopyranosyl and galactopyranosyl sulfides (ref. 110), acetylated aryl—β—D-gluco and galactolpyranosides (ref. 111) and O-alkylation of carboxymethylcellulose (ref. 112). The industrially important alkylation of cellulose has been accomplished with benzyl and ethyl chloride as well as chloroacetic acid and acrylonitrile in the presence of $Me_4N^+Cl^-$ (ref. 113), a Q^+ not normally known for its efficiency in PT processes. We can speculate that stability rather than lipophilicity is important here.

Chiral PTC

The use of optically resolved catalysts for the direct synthesis of enantiomerically pure compounds remains one of the major "holy grails" of the organic chemist. It would seem that PTC is particularly well adapted to this problem and that catalytic quantities of optically pure Q^+, QP^+ or crown ethers, if present in a chirally discriminating tight ion pair in the transition state, would yield pure enantiomeric products either from prochiral substrates or by kinetic resolution of racemic substrates. The realization of this goal has proven to be difficult and the bulk of the early attempts, using mainly Q^+'s derived from natural product alkaloids, gave dissappointingly small ee's.

A recent breakthrough has demonstrated the need for carefully controlling the many reaction variables. Dolling and his co-workers (ref. 114) have successfully demonstrated the first efficient chiral PTC alkylation, the conversion of 5 to 6 in 95% yield and 92% ee using as catalyst 8-R,9-S,N-(p-trifluoromethylbenzyl) cinchonium bromide, 7. Besides the catalyst, the reaction variables which affected the ee and required optimization include the solvent, substrate, base and alkyl halide concentration, agitation rate and temperature.



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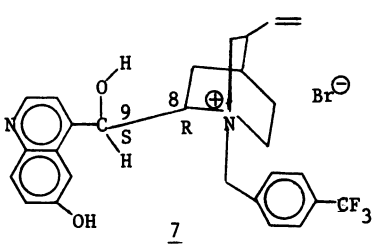

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An interesting example of kinetic resolution by PTC has recently appeared (ref. 115). Using resolved $Et_3N^+CH_2CH(Me)EtBr^-$ as catalyst, α-methylbenzyl alcohol was methylated in 50% NaOH/pentane to yield 84% of the R(+) methyl ether with 48% ee, while the recovered alcohol had 40% ee.

A new type of chiral catalyst has been prepared by quaternization of resolved 2,2'-bisbromomethyl-1,1-binaphthyl with (-)ephedrine and gave 37% ee in a PTC epoxidation (ref. 116). Considering that even minor changes in the catalyst strongly influences optical purity (ref. 117), it is difficult to assess the potential of new catalysts which afford products with only moderate ee.

It is even more difficult to understand the enthusiastic acceptance of polymer-supported PTC for chiral reactions. Considering that these supported catalysts have been markedly inferior as PT catalysts in general, it is remarkable that a 1984 review (ref. 118) lists over 60 references for supported chiral PTC. Though little of promise has appeared, the optimism remains and recent work covers the use of chiral functional polymers. This includes esterification using poly(L-isopropylethylene-imine)(ref. 119), copolymers of (-)methylmethacrylate with vinyl compounds for ketone reduction (ref. 120) and polystyrene resins with protected galactose functions (ref. 121). In no case was a practical optical yield obtained.

GENERAL INDUSTRIAL APPLICATIONS

Pharmaceutical

From its inception, PTC has been adopted by the pharmaceutical industry. This is certainly not unexpected considering the importance of improved synthetic methodology for the production of their high value products. This topic has been reviewed (ref. 122) with emphasis on Beecham's and Astra's processes for synthetic penicillins and for drugs derived by O- and N-alkylation of various heterocycles. These remain as important commercial processes while additional PTC applications to drug production continue to be introduced. Table 5 lists some of these processes, most of which are related to well established PTC reactions.

TABLE 5. Pharmaceutical-Related PTC Processes

Product	Reaction	Reference
Vincamines	Alkylation	123
Morphine	Ring-annelation	124
Azapins	N-alkylation	125
Amrinone	Cyclocondensation	126
Chloropromazine	N-alkylation	127
2-H-Chromene	O-alkylation	128
Phenoxyalkanoic Acids	Dichlorocarbene addition	129
Erythromycin A	Transesterification	130
Prostatrienoic Acids	Condensation	131
Penicillins	Esterification	132
Pyrimidine diones	Alkylation	133
Deazadeoxyinosine	Glycosylation	134
Alkoxypyridazinones	Alkoxylation	135
Benzodiazapin-2-ones	N-arylation	136

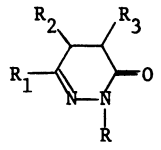
Unnatural amino acids have potential bioactivity and O'Donnell's (ref. 136) method via PTC alkylation of the Schiff's base (Eq. 2) presents a novel route to these compounds. His recent work includes the synthesis of 1-aminocyclopropane-1-carboxylic

$$\phi_2C{=}O + H_2NCH_2COOEt \longrightarrow \phi_2C{=}NCH_2COOEt \xrightarrow[PTC]{RX} \phi_2{=}N\underset{R}{C}HCOOEt \longrightarrow NH_2\underset{R}{C}HCOOH \qquad (2)$$

acid, cycloleucine and 2,6-diaminopimelic acid (ref. 137) as well as the use of potassium carbonate in refluxing acetonitrile with a Q^+ as an alternative to his previous use of hydroxide-methylene chloride/Q^+ (ref. 138). This method has been adapted and modified to include a PT catalyzed Michael addition for the production of glutamic acid (ref. 139) and for the α-hydroxylation of amines by reaction of the Schiff's base with an aldehyde (ref. 140).

Maximizing pharmacological activity calls for extensive derivatization, often by N, O, S and C-alkylation for which PT catalysis is particularly well suited. Three

examples, of the many newly available, are given here. Thirty-five derivatives of the pyridazinone (8) were prepared in good yields by TBABr catalyzed N-alkylation



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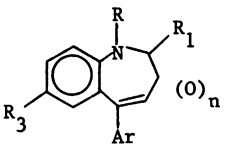

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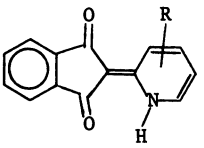

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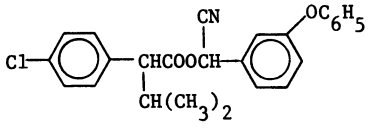
(ref. 141) while the benzodiazapin 9 was similarly N-alkylated in yields 90% using BTEAC (ref. 142). The N-alkylation of the pyridyl-indon-1,3-dione 10 is a particularly dramatic case; whereas mixtures of N- and C-alkylated products were obtained in DMF with sodium hydride, only regioselective N-alkylated products were obtained using PTC in aqueous hydroxide-methylene chloride. (ref. 143).

Pesticides

The production of synthetic organic pesticides is a multi-billion dollar industry in which PTC continues to make significant contributions. The synthetic pyrethroids, including fenvalerate (11), cypermethrin (12) and their various analogs are



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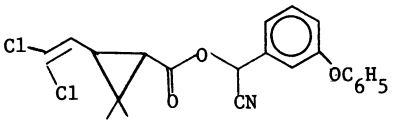

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commercially produced utilizing PTC methods for the C-alkylation of the former type and esterification of the latter. Details are available in the voluminous patent literature issued to Sumimoto, Shell, ICI, etc., of which we cite only two (ref. 144). Other recent applications include stereospecific S-alkylation of phenylphosphonothiolates (ref. 145), herbicidal 2-halo-acetamides (ref. 146), insecticidal 1,5-bis-aryl-1,4-pentadiene-3-ones (ref. 147) and substitutions of aromatic or heterocyclic 2-acetonitriles as pesticide intermediates (ref. 148).

General

The maturation of PTC has led to an increase in industrially oriented applications in diverse areas, some quite unexpected. In this section we document a number of these.

One of the problems associated with the PT process is that a mole of salt is generated for each mole of product. This often leads to a costly waste disposal problem inasmuch as the resulting salt stream is invariably contaminated with trace amounts of organics. Renga has developed (ref. 149) a novel salt-free process for the production of aryl ethers by using methyl trichloroacetate as a proton sponge in the presence of catalytic amounts of potassium carbonate and 18-C-6 (Eq. 3). Over 15 aryl ethers

$$ArOH + RX \xrightarrow[K_2CO_3,\ 18\text{-}C\text{-}6,\ 150^{\circ}]{CCl_3COOCH_3} ArOR + CHCl_3 + CH_3X + CO_2 \qquad (3)$$

have been prepared in yields of 72-91% and an analogous process for the methylation of carboxylic acids is available (ref. 150). In both processes the relatively high temperature needed makes the use of a Q^+ impractical, but it is likely that PEG's can substitute for the 18-C-6.

Epichlorohydrin (epi), a commodity chemical, has inspired a number of PTC applications leading to the reactive intermediates, glycidyl ethers and esters. A sampling of recent work includes the reaction of epi with bisphenol-A (ref. 151), aminophenols (ref. 152), alcohols (ref. 152a) and sodium stearate (ref. 153).

Finally, we have chosen some unusual PTC processes with commercial implications. Benzotrichlorides are obtained from benzal or benzylchlorides by reactions with perchloroalkanes; i.e., 3-methylbenzal chloride in refluxing carbon tetrachloride with 50% sodium hydroxide and a Q^+ affords 93% of 3-methylbenzotrichloride (ref. 154). Scrap rubber can be converted to an improved product by cleaving polysulfide cross-links by treating the hydrocarbon swollen rubber particles with hydroxide/Q^+ (ref. 155). PCB's can be removed from transformer oils by reaction with alkyl mercaptans in a toluene/potassium hydroxide/Q^+ system (ref. 156). Similarly PCB's can be reacted with PEG's/hydroxide at 75-120°; presumably the PEG functions both as reactant and catalyst (ref. 157).

Phenolic products can be removed from aqueous alkali waste streams by contacting the stream in a continuous reactor-settler with a toluene solution of benzyl chloride and a PT catalyst. The O-benzylated phenol can be recovered and the phenol content lowered to 45 ppm (ref. 158). Heating 4-chlorobenzonitrile with sodium sulfide/QP^+ without a solvent at 150° yields $(4\text{-}CNC_6H_4)_2S$ (ref. 159) and by now it should come as no surprise that even coal can be O-alkylated to form ethers and esters by standard PTC methods (ref. 160).

THE FUTURE FOR PTC

In the past, each successful PTC application stimulated research which in turn led to additional applications and improved processes. There is every reason to believe that this trend will continue, at least for the near future. This growth is being further accelerated by the chemical industry's shift away from commodities, in which PTC has historically played a minor role, to the "specialties" for which PTC is particularly well adopted. Further, the inherent convenience of the PTC method has been made even more so; all the common and many of the more esoteric catalysts are commercially available, the former in drum or carload quantities. The PTC literature has been organized, digested and alphabetically arranged in the numerous journal reviews, chapters and books. It remains only for the chemist to adapt it toward the application of interest.

Rather than try to predict where future progress in PTC lies, we list those areas which are currently of potential commercial importance but are not yet economically viable. It is reasonable to expect future PTC research to concentrate on:

- -matrix supported catalysts with minimal diffusion limitations and maximal recyclability
- -PTC reactions not limited to batch but adaptable to continuous processes
- -high temperature and strong base stable catalysts
- -efficient processes for catalyst recovery and trace removal
- -new stereospecific reactions with high ee.
- -processes using organometallic catalysts.

It will be of interest to reassess the progress in PTC five years from now.

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