Phase-Transfer Reactions

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In organic synthesis it is often necessary to bring about the reaction of an inorganic, ionic reagent (base, nucleophile, oxidizing agent, etc.) with a covalent organic compound. For reaction to occur under conventional, homogeneous conditions, both these dissimilar species must have some solubility in the reaction medium, which accordingly may be a mixture of water and a water-miscible solvent such as a lower alcohol, THF or acetone. Faster reactions often occur in the absence of water by the use of dipolar, aprotic solvents, for example DMSO or DMF, which can dissolve both ionic and covalent species, and effectively increase both base strength and nucleophilicity of anions by decreasing ion-pairing and removing the associating effect of a hydroxylic solvent.

With either of these approaches, isolation of the product may entail a fairly lengthy work-up, possibly involving quenching with a larger volume of water, distillative removal of the reaction solvent, followed either by collection of the product by filtration and further washing, or else multiple extractions with a different, water-immiscible solvent, water washes and evaporation of the extraction solvent. Such procedures can be time-consuming, volume-inefficient and often generate large volumes of effluent containing solvent mixtures which may be difficult to recycle.

Phase-transfer methods employ a system consisting of two mutually-insoluble phases, either liquid-liquid or solid-liquid, in which inorganic ions are transported into the organic phase by formation of a complex soluble in organic solvents. Such techniques are particularly useful for base-catalyzed reactions, nucleophilic displacements and oxidations of water-insoluble compounds by inorganic reagents. They have been widely adopted in industrial processes, since they often result in faster, cleaner reactions and greatly simplified work-ups without the need for strictly anhydrous conditions or relatively expensive and difficult to recycle dipolar aprotic solvents.

Quaternary ammonium and phosphonium salts

Quaternary salts have affinity for both polar and non-polar environments. This property has been exploited in the stoichiometric use of reagents containing a quaternary cation in place of the usual metal cation. Of much greater interest, however, is the use of quaternary salts in substoichiometric amounts in biphasic systems containing inorganic ionic species. The technique which has become known as phase-transfer catalysis came to prominence with the early work of Makosza,[1] Brändström[2] and Starks.[3] The principle of the method is shown in Scheme 1,[3] for the nucleophilic displacement reaction of an alkyl chloride RCl with sodium cyanide NaCN, in the presence of a quaternary chloride QCl.

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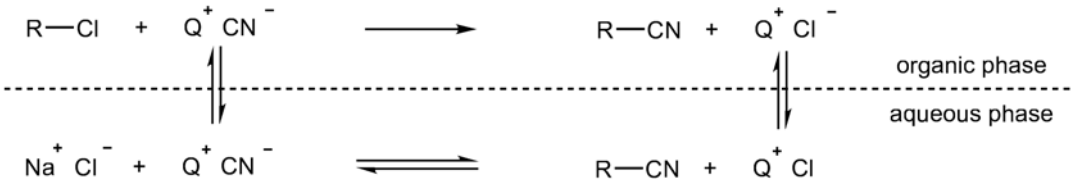
Scheme 1



In order to minimize the effect of hydration of anions in the organic phase, best results are usually obtained with relatively non-polar solvents in which water has very low solubility, most commonly dichloromethane, toluene or benzene. To reach a sufficient degree of solubility in the organic phase, the quaternary cation should normally contain about eight or more carbon atoms, although smaller cations may be useful for specific purposes; for example, tetramethylammonium chloride as a thermally-stable catalyst in halex fluorinations.[4] Chlorides, bromides and hydrogen sulfates are the most widely available and commonly used as catalysts; iodides are usually only effective in near stoichiometric amounts due to the tendency for iodide ion to transfer into the organic phase and form ion pairs with the quaternary salt. Ammonium salts have been used in the majority of reported phase-transfer reactions, but certain phosphonium salts can be equally effective, and may be preferred under conditions of high temperatures or concentrated base where decomposition of the catalyst could occur.[5] Quaternary salts containing a long chain of carbon atoms, such as (1-Hexadecyl)trimethylammonium chloride, have surfactant properties and have been used to catalyze heterogeneous reactions in micelles.[6]

Examples of the use of quaternary salts as phase-transfer catalysts are given throughout the alphabetical section of the Catalogue. Further information can be found in the text entries under specific catalysts and in various reviews and monographs.[7-20]

The following quaternary salts, many of which have found use in phase-transfer type applications, are listed approximately in order of increasing size of the cation i.e. from least to most lipophilic:

Phase-Transfer Reactions

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Ammonium salts

A13368 Tetramethylammonium bromide
A13288 Tetramethylammonium chloride
A17467 Tetramethylammonium hexafluorophosphate
L09658 Tetramethylammonium hydroxide pentahydrate
A17724 Tetramethylammonium hydroxide, 25% w/w aq. soln.
30833 Tetramethylammonium hydroxide, 25% in methanol
A12811 Tetramethylammonium iodide
41790 Tetramethylammonium nitrate
30834 Tetramethylammonium perchlorate
A17436 Tetramethylammonium tetrafluoroborate
42709 Triethylmethylammonium chloride
A13835 Tetraethylammonium bromide
A15215 Tetraethylammonium chloride monohydrate
L03968 Tetraethylammonium hydroxide, 20% w/w aq. soln.
36560 Tetraethylammonium hydroxide, 35% w/w aq. soln.
16328 Tetraethylammonium hydroxide, 25% w/w in methanol
A11783 Tetraethylammonium iodide
41791 Tetraethylammonium nitrate, 35% w/w aq. soln.
44062 Tetraethylammonium perchlorate
A10211 Tetraethylammonium tetrafluoroborate
A17073 Tetraethylammonium p-toluenesulfonate
L08594 (1-Hexyl)trimethylammonium bromide
B25410 Phenyltrimethylammonium bromide
B22851 Phenyltrimethylammonium chloride
A14402 Phenyltrimethylammonium iodide
A19424 Phenyltrimethylammonium methosulfate
A16840 Benzyltrimethylammonium bromide
A16759 Benzyltrimethylammonium chloride
B20812 Benzyltrimethylammonium hexafluorophosphate
41717 Benzyltrimethylammonium hydroxide, 20% w/w aq. soln.
A14927 Benzyltrimethylammonium hydroxide, 40% w/w in methanol
B23520 Benzyltrimethylammonium iodide
B24128 (1-Butyl)triethylammonium bromide
L08610 (1-Octyl)trimethylammonium bromide
A11522 Tetra-n-propylammonium bromide
19379 Tetra-n-propylammonium chloride
A12002 Tetra-n-propylammonium hydrogen sulfate
17456 Tetra-n-propylammonium hydroxide, 40% w/w aq. soln.
A15961 Tetra-n-propylammonium iodide
L12769 Phenyltriethylammonium iodide
B23828 Methyltri-n-butylammonium bromide
L18019 Methyltri-n-butylammonium chloride, 75% aq. soln. (Aliquat® 175)
L12144 (1-Decyl)trimethylammonium bromide
A14291 Benzyltriethylammonium bromide
A13268 Benzyltriethylammonium chloride
L07850 Benzyltriethylammonium hydroxide, 40% w/w in methanol
B24847 Benzyltriethylammonium tetrafluoroborate
A17924 (1-Dodecyl)trimethylammonium chloride
A10761 (1-Dodecyl)trimethylammonium bromide
L00675 Benzyltri-n-propylammonium chloride
19279 Tetra-n-butylammonium acetate
B24773 Tetra-n-butylammonium acetate, 1.0M aq. soln.
A10249 Tetra-n-butylammonium bromide
A15186 Tetra-n-butylammonium chloride
22754 Tetra-n-butylammonium chloride, 50% w/w aq. soln.
A17196 Tetra-n-butylammonium hexafluoro-phosphate
A14047 Tetra-n-butylammonium hydrogen sulfate
L02809 Tetra-n-butylammonium hydroxide, 40% aq. soln.
16198 Tetra-n-butylammonium hydroxide, 55% w/w aq. soln.
L08164 Tetra-n-butylammonium hydroxide, 1.0M soln. in methanol
A12626 Tetra-n-butylammonium hydroxide, 40% soln. in methanol
A15484 Tetra-n-butylammonium iodide
43342 Tetra-n-butylammonium nitrate
43999 Tetra-n-butylammonium perchlorate, electrochemical grade
30801 Tetra-n-butylammonium perchlorate
19261 Tetra-n-butylammonium phosphate
41723 Tetra-n-butylammonium sulfate, 50% w/w aq. soln.

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Ammonium salts con't

A11013 Tetra-n-butylammoniumtrifluoromethane-sulfonate
L10294 (1-Tetradecyl)trimethylammonium bromide
L12484 (1-Tetradecyl)trimethylammonium chloride
A15235 (1-Hexadecyl)trimethylammonium bromide
B23991 Ethyl(1-hexadecyl)dimethylammonium bromide
L14088 Tetra-n-pentylammonium iodide
B23941 Benzyltri-n-butylammonium bromide
A10345 Benzyltri-n-butylammonium chloride
B22837 Benzyltri-n-butylammonium iodide
A14825 (1-Hexadecyl)pyridinium bromide monohydrate
A13499 (1-Hexadecyl)pyridinium chloride monohydrate
B24832 Di-n-decyldimethylammonium bromide, 80% aq. gel
A11372 Tetra-n-hexylammonium bromide
43882 Tetra-n-hexylammonium hydrogen sulfate
A17589 Tetra-n-hexylammonium iodide
30830 Tetra-n-hexylammonium perchlorate
B22839 Di-n-dodecyldimethylammonium bromide
B21584 Adogen® 464
A17247 Aliquat® 336
A15218 Tetra-n-heptylammonium bromide
A16642 Tetra-n-heptylammonium iodide
A14929 Tetra-n-octylammonium bromide
B23788 Dimethyldistearylammonium chloride
L08153 Tetra-n-dodecylammonium iodide
20582 Tetraoctadecylammonium bromide

Phosphonium salts

L14339 Bis(triphenylphosphoranilydene)-ammonium chloride
L01335 (1-Hexadecyl)tri-n-butylphosphonium bromide
A10868 Tetra-n-butylphosphonium bromide
A15860 Tetraphenylphosphonium bromide
A10575 Tetraphenylphosphonium chloride
B24758 Tetraphenylphosphonium hexafluoro-antimonate
A11539 Tetraphenylphosphonium iodide
A15141 Tetraphenylphosphonium tetrafluoroborate
B22319 (Triphenylmethyl)triphenylphosphonium chloride

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Crown ethers

Crown ethers, first reported by Pederson,[21] are macrocyclic molecules containing oxygen atoms suitably positioned to permit selective complexing with metal cations. They can assist the transport of inorganic ions into organic solution from the solid phase. In the organic medium, which may be a relatively non-polar solvent like benzene, toluene or dichloromethane, or a polar aprotic solvent such as acetonitrile, the anions remain unsolvated and these "naked" anions are often highly reactive. The availability of crown ethers with various ring sizes permits selective complexation with cations of matching size; in particular 12-Crown-4 [1,4,7,10-Tetraoxacyclododecane], 15-Crown-5 [1,4,7,10,13-Pentaoxacyclopentadecane], and 18-Crown-6 [1,4,7,10,13,16-Hexaoxacyclo-octadecane] are selective for Li^+, Na^+, and K^+, respectively. Many examples of the use of crown ethers in organic synthesis are given under individual products in the main section of the Catalogue. Cyclic molecules containing heteroatoms apart from oxygen are also of value in particular applications. Similarly, certain acyclic polyethers and amines may also show crown-ether like complexing properties. Further information on crown ether chemistry can be found in reviews and monographs.[22-30]

Crown ethers

A16011 Benzo-15-crown-5
A16223 Benzo-18-crown-6
A11972 12-Crown-4
A12265 15-Crown-5
A11249 18-Crown-6
L16964 Cyclohexano-15-crown-5
A13133 Dibenzo-18-crown-6
L14559 4',4''(5'')-Di-tert-butyldibenzo-18-crown-6
A15344 Dicyclohexano-18-crown-6
44509 2-Hydroxymethyl-12-crown-4
44500 2-Hydroxymethyl-15-crown-5
44477 2-Hydroxymethyl-18-crown-6
A16225 4-Nitrobenzo-15-crown-5
A16138 4-Nitrobenzo-18-crown-6

Crown compounds containing other heteroatoms

B22268 1,4,7,10-Tetraazacyclododecane tetrahydrochloride [Cyclen tetrahydrochloride]
A11516 1,4,8,11-Tetraazacyclotetradecane [Cyclam]
30854 1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane
B21454 1,7,10,16-Tetraoxa-4,13-diazacyclooctadecane
L08148 1,4,10,13-Tetrathia-7,16-diazacyclooctadecane

Acyclic molecules analogous to crown ethers

L02161 Hexaethylene glycol
A10133 Pentaethylene glycol
B21918 Polyethylene glycol 200
B21992 Polyethylene glycol 400
B21798 Polyethylene glycol 600
B22134 Polyethylene glycol 1000
L13544 Tris(3,6-dioxaheptyl)amine ("TDA-1")

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References

(1) M. Makosza, B. Serafinowa, *Rocz. Chem.*, **39**, 1223 (1965); M. Makosza, W. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).
(2) A. Brändström, K. Gustavii, *Acta Chem. Scand.,* **23**, 1215 (1969).
(3) C. M. Starks, *J. Am. Chem. Soc.,* **93**, 195 (1971).
(4) M. Maggini, M. Passudetti, G. Gonzales-Trueba, M. Prato, U. Quintily, G. Scorrano, *J. Org. Chem.*, **56**, 6406 (1991); Y. Sasson, S. Negussie, M. Royz, *Chem. Commun.,* 297 (1996).
(5) D. Landini, F. Montanari, F. Rolla, Synthesis, 428 (1974); Tetrahedron Lett, 349 (1979); N. Yazawa, H. Zuzuki, Y. Yoshida, O. Furusawa, Y. Kimura, *Chem. Lett.,* 2213 (1989).
(6) B. Jursic, *Tetrahedron*, **44**, 6677 (1988); *Can. J. Chem.*, **67**, 1381 (1989).
(7) 'Quaternary ammonium salts in organic synthesis', J. Dockx, *Synthesis*, 441 (1973).
(8) 'Phase-transfer-catalysed two-phase reactions in preparative organic chemistry', E. V. Dehmlow, *Angew. Chem. Int. Ed.*, **13**, 170 (1974).
(9) 'Advances in phase-transfer catalysis', E. V. Dehmlow, *Angew. Chem. Int. Ed.*, **16**, 493 (1977).
(10) 'Applications of phase-transfer catalysis in heterocyclic chemistry', *Adv. Heterocycl. Chem.*, **36**, 175 (1984).
(11) 'Hydroxide ion initiated reactions under phase transfer catalysis conditions: mechanism and implications', M. Rabinovitz, Y. Cohen, M. Halpern, *Angew. Chem. Int. Ed.*, **25**, 960 (1986).
(12) 'Catalysis in two-phase systems: Phase-transfer and related phenomena, M. Makosza, M. Fedorynski,' *Adv. Catal.*, **35**, 375 (1987).
(13) 'Improvement brought by solid-liquid phase-transfer catalysis without solvent', G. Brain et al, *Bull. Soc. Chim. Fr.*, **247** (1989).
(14) 'Thirty years of phase transfer catalysis: M. Makosza, M. Fedorynski', *Pol. J. Chem.*, **70**, 1093 (1996).
(15) 'Recent highlights in phase-transfer catalysis', S. Tyler, J. Clark, *Chem. Ind. (London)*, 22 (1997).
(16) Y. Goldberg, *Selected Problems of Phase-Transfer Catalysis*, Gordon and Breach, N.Y. (1992).
(17) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman and Hall, N.Y. (1994).
(18) E. V. Dehmlow, S. S. Dehmlow, *Phase-Transfer Catalysts*, 3rd ed., VCH, N.Y. (1993).
(19) *Phase-Transfer Catalysis: Mechanisms, and Syntheses*, M. E. Halpern, Ed., ACS, Washington, DC (1997).
(20) *Handbook of Phase Transfer Catalysis*, Y. Sasson, R. Neumann, Eds., Blackie, London (1997).
(21) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 2495 (1967).
(22) 'Macrocyclic polyethers and their complexes', C. J. Pedersen, H. K. Frensdorff, *Angew. Chem. Int. Ed.*, **11**, 16 (1972).
(23) 'The synthesis and ion-binding of synthetic multidentate macrocyclic compounds', J. J. Christensen, D. J. Eatough, R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974).
(24) 'Principles and synthetic applications in crown ether chemistry', G. W. Gokel, H. D. Durst, *Synthesis*, 168 (1976).
(25) 'Synthetic aliphatic aza-crown ethers', G. W. Gokel et al, *Synthesis*, 997 (1982).
(26) 'Complexes of crown ethers with molecular guests', I. Goldberg in *Inclusion Compounds* Vol. 2, J. L. Atwood et al, Eds., Academic Press, London (1984), p261.
(27) *Synthetic Multidentate Macrocyclic Compounds*, R. M. Izatt, J. J. Christensen, Eds., Academic Press, N.Y. (1978).
(28) M. Hiraoka, *Crown Compounds: Their Characteristics and Applications*, Kodansha, Tokyo/ Elsevier, Amsterdam (1982).
(29) G. W. Gokel, *Crown Ethers and Cryptands*, RSC, Cambridge (1991). *Crown Compounds; Towards Future Applications,* S. R. Cooper, Ed., VCH, N.Y. (1992).
(30) J. S. Bradshaw et al, *Aza-Crown Macrocycles*, Wiley, N.Y. (1993).