Liquid-Liquid-Liquid Phase Transfer Catalysis: A Novel and Green Concept for Selective Reduction of Substituted Nitroaromatics

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Abstract: The selective reduction of nitroaromatics to the corresponding amines is an important transformation since many aromatic amines exhibit biological activities and find a multitude of industrial applications, being intermediates for the synthesis of dyes, pharmaceuticals and agrochemicals. A variety of nitroaromatics dissolved in organic solvents was reduced by using aqueous sodium sulfide, and tetrabutylammonium bromide (TBAB) as the phase transfer catalyst by choosing appropriate concentrations which resulted in three immiscible liquid phases. Compared to L-L PTC, the L-L-L PTC offers much higher rates of reaction, better selectivities and repeated use of catalyst. The selectivities for the desired products were 100%.

Keywords: amines; liquid-liquid-liquid PTC; nitroaromatics; phase transfer catalysis; reduction; triphasic catalysis

Introduction

The selective reduction of substituted nitroaromatic compounds has been a major challenge in synthetic organic chemistry.[1] Stoichiometric reagent-based processes are very selective towards reduction of the nitro function but generally not ecofriendly.[2] Catalytic hydrogenation using molecular hydrogen is less chemoselective than the stoichiometric methods; therefore the catalysts have to be poisoned or tailored to achieve the desired selectivity.[3–7] The use of homogeneous iron complexes for the hydrogenation of nitro compounds has been also reported.[8]

Phase-transfer catalysis (PTC) has been applied to over 600 processes in a variety of industries such as intermediates, dyestuffs, agrochemicals, perfumes, flavours, pharmaceuticals and polymers.[9–11] Yadav[12] has discussed recently the advantages of multiple phase *vis-à-vis* the conventional two-liquid PTC and demonstrated how all three-phase PTC reactions are by definition excellent examples for the practice of green chemistry. PTC has been quite successful for *C*-, *N*-, *O*- and *S*-alkylation in fine chemical industries, beside in dehydrohalogenations. The effluent treatment problems associated with soluble L-L PTC requiring a large quantity of water to wash the organic phase has hampered exploitation of PTC in many other bulk industries. The applications of PTC thus are practically confined to the synthesis of low-volume and high-cost, specialty, agro and pharmaceutical chemicals. The main drawback of L-L PTC from the environmental point of view is that the homogeneous catalyst is normally not recovered and reused. The bulk cost of catalyst ranges from US $ 2.00 to 400.00 per kg, crown ethers being the most expensive and hence catalyst recovery or reuse is most desirable. The separation of phase-transfer catalysts from the reaction mixture can be achieved by extraction, distillation and adsorption. Extraction needs an additional solvent that has to be distilled off to recover the catalyst. Distillation becomes feasible only if the catalyst has a lower boiling point than the reactants, products and the solvents. Otherwise, distillation is an energy intensive process to recover catalysts from dilute solutions. In the case of adsorption, the catalyst has to be eluted using a solvent. Since the quantities of the catalyst used are small, they do not contribute much to the expensive product cost. The catalyst is usually not recovered but removed by washing the organic phase with copious quantities of water which are disposed to the effluent treatment plant as an end-of-the-pipe approach for pollution prevention. Although milder reaction conditions and use of cheap solvents in L-L PTC improve the economics, PTC need to be practised from the green chemistry perspective such as solventless synthesis and catalyst reuse, and an overall strategy of waste reduction.

As compared to L-L PTC, in liquid-liquid-solid (L-L-S) PTC, the expensive catalyst is bound to a solid matrix like a polymeric resin or clay and can be recovered. However, there is a substantial reduction in rates of reactions due to associated diffusion limitations. Capsule

membrane phase-transfer catalysis (CMPTC) involves a catalyst anchored to a capsule membrane which is recovered and reused. CMPTC has been exploited in our laboratory in a number of reactions of industrial importance.[13,14] Furthermore, a third, catalyst-rich, phase can be created between the aqueous and organic phases containing the reactants whereby the reaction occurs in the middle phase through a proper balance of liphophilicity, hydrophilicity, interfacial tension, solubilities, phase equilibria and density; and this constitutes the so-called liquid-liquid-liquid (L-L-L) PTC. It was observed that when the amount of catalyst exceeds a critical value the rate of reaction increases sharply. Indeed, we have found in a number of reactions that not only the rates of reaction but also the selectivity can be enhanced dramatically thereby reducing reaction time and separation costs.[15] The third liquid phase is the main reaction phase for the phase-transfer catalyst to catalyse the reaction and the recovery and reuse of the catalyst is easier since it forms an immiscible third liquid phase. The advantages of L-L-L PTC over L-L PTC are: (i) enhanced reaction rates and milder reaction conditions such as lower temperature, (ii) easier catalyst recovery and reuse, (iii) suppression of by-products and increased yields and selectivity with respect to the desired product, and (iv) the catalyst need not be bound to a solid support. Hence the attendant difficulties of reduced activity and mechanical strength associated with L-L-S PTC can be avoided. This is the major advantage of L-L-L PTC over L-L-S PTC. The L-L-L PTC requires more catalyst (PTC) but since it is recovered and reusable, it is an excellent way of reducing waste. The rates are very high and thus reduce the reaction times and reactor volumes, leading to economic advantages.

The reduction of nitroaromatics to the corresponding amines can be affected by aqueous inorganic sulphides and polysulphides and the rates of these biphasic reductions are amenable to intensification under PTC. There are quite a few reports on phase-transfer-catalysed sulphide reductions in the literature. The reduction of p-nitrotoluene[16] with sodium sulphide and bisulphide to selectively obtain p-toludine is also reported. Reductions of o-chloronitrobenzene[17] and p-chloronitrobenzene[18] with sodium sulphide/disulphide have been carried out by using polar solvents such as dimethylformamide and N-methylpyrrolidone (NMP) with good yields of the corresponding products. Uncatalysed[19] and PTC[20] reductions of nitroaromatics such as m-nitrochlorobenzene, m-dinitrobenzene and p-nitroaniline by aqueous solutions of sodium monosulphide and disulphide have been reported. The phase-transfer-catalysed[21] reduction of aromatic nitro compounds such as nitrobenzene, m-dinitrobenzene, o-chloronitrobenzene, p-chloronitrobenzene to the corresponding monoamino compounds with sodium sulphide, with tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst has also been investigated. Yadav et al.[22] reported

the selective reduction of p-nitroanisole to p-methoxyaniline with sodium sulphide under L-L PTC.

So here we have developed an efficient methodology for selective reduction of different nitroaromatics with sodium sulphide using L-L-L PTC leading to 100% selectivity for the amine (Scheme1).

Results and Discussion

Several experiments were done to understand the critical parameters for maintaining three immiscible phases at 80 °C under agitation. The L-L-L system depends on the nature of the substrate and solvent, type and amount of the catalyst, composition of the aqueous phase and the temperature. Thus, there is a range over which three immiscible liquid phases are created. For each system this was verified at the operating conditions. The composition was such that the fidelity of the three separate phases was maintained at all temperatures between 50 and 80 °C both during intense agitation and without agitation. When the agitation was stopped, the reaction mass had droplets of organic phase covered by a thin dark film in a pool of aqueous phase, which was a continuous phase (Figure 2), and which would slowly disintegrate and the three phases would emerge out as shown in Figure 1. Even after cooling the mixture to room temperature, the phases would retain their identity.

The rate of reaction depends on the speed of agitation up to a certain value since it affects the rates of mass transfer from the aqueous and the organic phases to the middle catalyst-rich phase. We studied the effect of speed over a range of 1000–1800 rpm for each system. There was an increase in the rate of reaction when the speed was increased from 1000 to 1500 rpm. However, there was no further increase in the rate beyond 1500 rpm. Thus, a speed of agitation of 1500 rpm was chosen.

Although the catalyst is soluble in both phases under normal PTC, depending on the type of catalyst, its distribution coefficient is affected by the presence of salts and the type of solvent. The aqueous phase is saturated by sodium sulphide thereby partitioning the catalyst preferentially in the middle phase and the solubility of the catalyst phase in the organic phase is very low due to the use

R^1 = H, CH$_3$, OCH$_3$, OC$_2$H$_5$, OC$_6$H$_5$
R^2 = H, CH$_3$, OCH$_3$
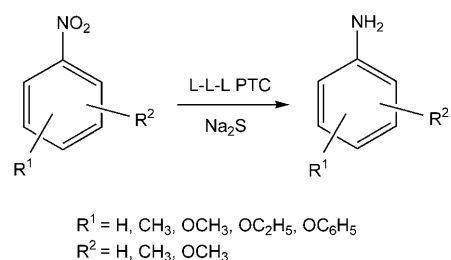
Scheme 1.

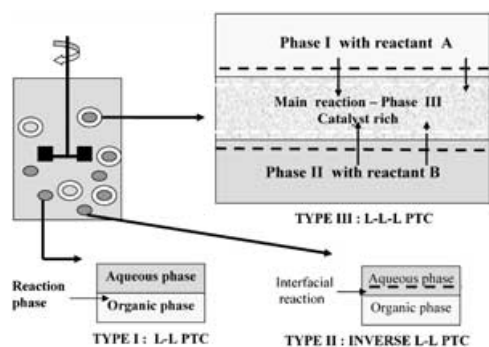**Figure 1.** Top phase: organic phase, middle phase: catalyst-rich phase, bottom phase: aqueous phase.

Figure 2. L-L-L PTC: Locale of reaction phases. Type III is the main contributor to the overall rate of reaction. The normal L-L PTC is type II. The rate enhancement in type III is compared with that in type II.

of toluene as a solvent. Because of this more of catalyst is available in the middle phase and is subsequently reused for further reaction. This can be seen in Figure 1. Waste minimization is a theme of green chemistry. Thus, there is reduction in waste, due to reuse of catalyst, enhancement of rates by an order of magnitude and a decrease in reaction times and thus an increase in profitability.

Overall Stoichiometry

The reduction reaction of nitroarenes by negative divalent sulphur (sulphide, sulphahydrate, and polysulphide) is called the Zinin reduction. The overall stoichiometry of this reaction using sulphide as reducing agents is as follows:

$$4\ C_6H_5NO_2 + 6\ S^{2-} + 7\ H_2O$$

$$\longrightarrow 4\ C_6H_5NH_2 + 3\ S_2O_3^{2-} + 6\ OH^-$$
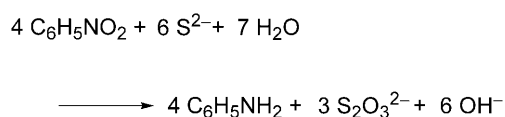
Obviously this reaction involves a complex mechanism and the rate-determining step has to be evaluated.

Mechanism of L-L-L PTC

Since the stoichiometry of the overall reaction suggests a complex mechanism, the following steps were envisaged. S is a multivalent species and thus different monovalent anions, such as HS^-, HSO^-, HSO_2^-, and HSO_3^-, can be formed sequentially which are capable of producing ion-pairs with single quaternary cations more readily than those multivalent anions which require ion-pairing with multiple quaternary cations. In the aqueous phase S^{2-} reacts with OH^- to form HS^-. Thus Q^+HS^- which is readily formed in the aqueous phase is transferred to the middle (third) phase where several consecutive and parallel reactions occur as shown in Figure 3. The contribution to the overall rate of the reaction can be shown by three mechanisms. Since it is known that the creation of a third catalyst-rich phase enhances the rate of the reaction, it should be the main reaction phase into which the substrate from the organic phase and the nucleophile from the aqueous phase are transferred. However, the aqueous phase reagent in the form of the ion-pair can also transfer across the third phase-organic phase interface and there is a possibility of some reaction occurring in the organic phase. Similarly, the reaction can occur near the interface between the third and the aqueous phase on the aqueous phase side due to the very limited solubility of the substrate in the aqueous phase. It should be pointed out, however, that the substrate would have already reacted in the third phase. Thus the contribution of the reaction in the aqueous phase is negligible.

Since the third phase is generated beyond the critical concentration of the catalyst, the locale of the PTC reaction occurring in the organic phase in the biphasic condition is shifted to the third phase. Depending on the amount of catalyst beyond the critical value, the contribution to the overall rate of reaction would be either totally by the reaction in the third phase or in the organic phase. The thickness of the third phase also matters since the reactive species have to diffuse from the organic phase to third phase as an ion-pair.

Just below the critical concentration for third phase formation, the biphasic reaction has the maximum conversion. In the absence of any mass transfer limitation, the reaction is kinetically controlled and occurs in the organic phase. However, after the formation of the third phase, there is a likelihood of mass transfer resistance setting in due to the higher rates of reaction in the third phase which deplete the concentration of the reactants in the third phase.

The model of the reaction shows that the quaternary cation of the catalyst, Q^+, pairs up with different anions for its reaction with the substrate but most of it remains in the form of Q^+HS^- in the reaction medium and makes possible a cycle of the catalyst in that form among the phases.
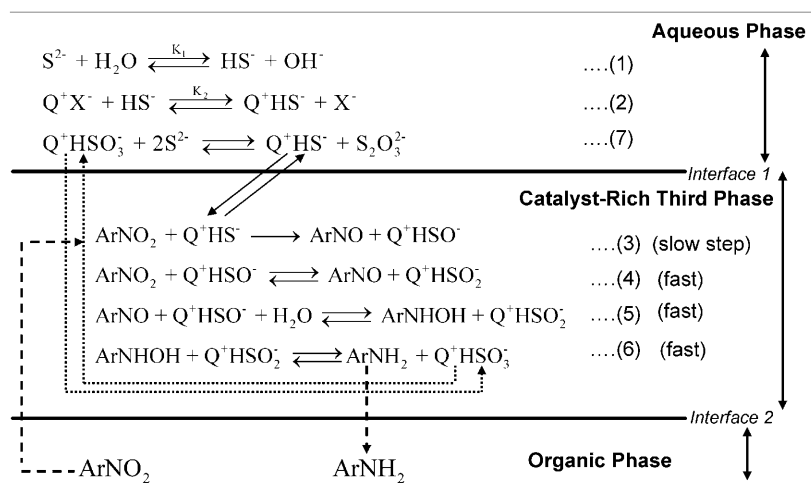
Figure 3. Mechanism of reduction of nitro- to aminoaromatic compounds under L-L-L PTC.

Reusability of Catalyst

The novelty of our work is the reusability of the catalyst. After completion of the experiment, the reaction mixture was allowed to settle and which formed clearly three distinct phases. The upper organic phase containing the product was removed. The catalyst reusability studies could be done in two ways, either by using the catalyst-rich phase alone or by using the catalyst-rich and the aqueous phases together.

Reuse of Third Catalyst-Rich Phase Only

The third phase was separated from the previous experiment and then reused by adding fresh aqueous and organic phase reactants. In this method the third phase was used three times starting with the fresh use. As explained earlier, there is a distribution of catalyst in the catalyst-rich third phase and the organic phase and aqueous phase. Since both the aqueous and organic phases were freshly used, there was a loss of the catalyst with the discarded organic and aqueous phases. Therefore, there is once again a distribution of catalyst available from the third phase to the organic phase which reduces the volume of the third phase and hence the rates of the reaction.

Reuse of Catalyst and Aqueous Phase

Thus, the second method was adopted wherein the aqueous phase and the catalyst phase were reused five times and the organic phase along with the aqueous reactants was replenished every time. The reusability was found to be good up to 4 uses.

Conclusions

Total waste-free process, although ideal, are not realisable in practice and thus waste minimisation, by any and all means, fits into the theme of green chemistry. An end-of-pipe solution as a regulatory approach has been adopted by several industries assuming that the technology is perfect, economical and only the effluent should be treated. Phase-transfer catalysis is a popular technique having around 600 industrial applications but with very few attempts to improve the process from environmental perspectives. The L-L PTC reactions are conducted under milder conditions, using cheaper solvents at much faster reaction rates and improved selectivities to the desired products and are thus by definition waste reduction processes. However, the phase-transfer catalyst is not recovered but treated as a waste since the quantities are very small and do not contribute much to the expensive product. L-L PTC can be elegantly modified to convert it into L-L-L PTC, to recover and reuse the catalyst and also to enhance selectivity.

Experimental Section

Reaction Procedure

All reactions were studied in a 5.0 cm i.d. fully baffled mechanically agitated contactor of 100 cm^3 total capacity, which was equipped with a 6-blade-turbine impeller. The reactor was kept in a constant-temperature water bath. Typical runs were conducted by taking sodium sulphide 0.15 mole in water and made up to 25 cm^3. To this 0.0075 mol of TBAB catalyst was added. The organic phase comprised 0.0075 mole of nitroaromatics, made up to 15 cm^3 with toluene. All the typical reactions were carried out at 80 °C and 1500 rpm under variable times. This the composition of the reaction mixture created three distinct and stable phases at the operating conditions. The said composition of the reaction mixture created three dis-

Table 1. Reduction of substituted nitroaromatics with sodium sulphide under L-L and L-L-L PTC.

No.	Reactant	Product	Enhancement factor[a] $\phi = \dfrac{r_{i-3L}}{r_{i-2L}}$	Time t [min]	Yield [%] after time t	
					L-L PTC[b]	L-L-L PTC[c]
1	nitrobenzene	nitrobenzene	4.8	20	34.2	98.6
2	2-nitrotoluene	2-methylaniline	4.0	45	32.5	98.6
3	3-nitrotoluene	3-methylaniline	7.1	60	38.6	98.4
4	4-nitrotoluene	4-methylaniline	3.4	45	43.5	98.7
5	2,3-dimethylnitrobenzene	2,3-dimethylaniline	3.1	45	35.6	96.8
6	3,4-dimethylnitrobenzene	3,4-dimethylaniline	4.3	30	37.5	97.5
7	2-methoxynitrobenzene	2-methoxyaniline	3.2	45	42.5	96.7
8	3-methoxynitrobenzene	3-methoxyaniline	7.0	60	35.4	95.7
9	4-methoxynitrobenzene	4-methoxyaniline	3.8	45	41.7	97.8
10	4-ethoxynitrobenzene	4-ethoxyaniline	3.7	45	44.3	98.4

Table 1 (cont.)

No.	Reactant	Product	Enhancement factor[a] $\phi = \dfrac{r_{i-3L}}{r_{i-2L}}$	Time t [min]	Yield [%] after time t	
					L-L PTC[b]	L-L-L PTC[c]
11			6.0	60	28.6	96.7
12			4.6	60	33.5	95.4

The yield is the amount of product formed relative to the amount of substrate reacted. The yield is equal to selectivity here.
[a] Enhancement factor is defined as the ratio of the initial rate of reaction under L-L-L PTC to that under L-L PTC (before the third phase is created).
[b] L-L PTC: nitroaromatics 0.0075 mol, sodium sulphide 0.1125 mol, TBAB 0.0025 mol, toluene 15 cm³, water 25 cm³, speed of agitation 1500 rpm, temperature 80 °C.
[c] L-L-L PTC: All same as for L-L PTC except TBAB 0.0075 (reusability of catalyst).

tinct and stable phases at the operating conditions (Figure 1). The analysis of all reactions was done by GC (Chemito 8610) using a stainless steel column (3.25 mm × 2 m) packed with a liquid stationary phase of 10% SE-30, with a flame ionisation detector.

Isolation of the Product

The isolation of product is very simple. At the end of the reaction, the organic phase, which contained the corresponding amine and toluene, was washed with copious quantities of water to remove any traces of catalyst and the solvent was distilled under vacuum to get a pure product. All the products were also confirmed by GC-MS. All the compounds reported are shown in Table.1.

Acknowledgements

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