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ALKYLATION OF PENTAERYTHRITOL BY PHASE-TRANSFER CATALYSIS
2. Crucial Effect of the Aqueous Sodium Hydroxide Solution.

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Abstract:
The mechanistic aspects of the alkylation of pentaerythritol {2-2'-bis(hydroxymethyl)-1,3-propanediol} (PE) by phase-transfer catalysis have been investigated. The dramatic effect of an excess and renewal of sodium hydroxide solutions on the one hand, and the solubility of the PT catalyst in the organic phase on the other, argue that the selectivity of this reaction appears to be controlled almost completely by the possible protonation of the sodium form of the alkoxide anion of PE (4). This protonation depends on the assumption that water molecules are present in the PT medium, and is based upon the observation that this PT medium is actually a three liquid-layer system. As the unusual layer (catalyst layer) may be readily hydrated, the concentrated sodium hydroxyde solution can be no longer considered as an unquestionable desiccant.

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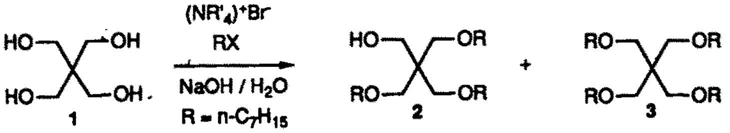
Introduction

In a previous paper,[1] we described the new and facile phase transfer etherification of pentaerythritol (PE), a very hydrophilic polyol. The extension of this technique to water-soluble compounds may lead to further interesting applications.[2] We have discussed the selective extraction of the ion pairs present in this complex medium to explain the lack of formation of mono- or dialkylated products even at low conversion.

The solubility of the ammonium-PE ion pairs in the organic phase was shown to be an important factor in determining the distribution of isolated products. The ratio tetraether 3/triether 2 (eq. 1) obtained in the PT alkylation of PE was then first assumed to depend essentially of the solubility of the catalyst in the organic layer.



(1)

The solubility of catalysts like TBAB ($R'=C_4H_9$) in the organic phase decreases as the tri- and tetraether mixture is gradually formed. This actually involves a phase-transfer reaction where three liquid layers are present one of which is the catalyst[3] (see experimental section : catalyst layer).

Nevertheless, addition of a catalyst like TOAB ($R'=C_8H_{17}$), more soluble in the organic phase, improved the tetraether yield but never drove the reaction to complete conversion of PE to the tetraether 3 (the maximum was 74%).

In this work, we describe a more complete mechanistic interpretation in order to explain the selectivity of this reaction. We have determined that the excess and the nature of the aqueous NaOH layer have a critical effect.

Results

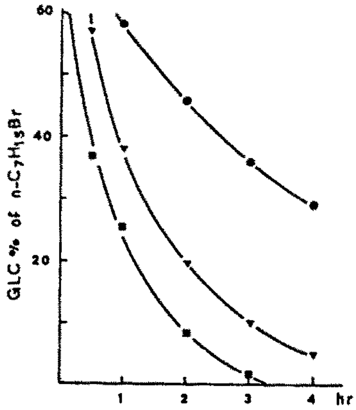
As a rule, the PTC conditions for the formation of ethers are reported to involve of a five-fold excess of 50% aqueous NaOH to alcohol[4]. In our previous paper we used 2 moles of NaOH and

0.1 mole of PE in all experiments.

To facilitate the workup on micro scale experiments while working on the etherification of rare and fine carbohydrates, we used more than a twenty-fold excess of NaOH to hydroxyl groups. The results were so significant for the completion of the etherification that we made the same attempts with PE.

Excess of NaOH. We have increased the excess of the 50% aqueous NaOH solution from 20 to 80 moles of NaOH per one mole of PE. The results are reported in Figure 1.

Figure 1. GC % of n- $C_7H_{15}Br$ in the organic phase for the alkylation of PE (0.1 mol) by n- $C_7H_{15}Br$ (0.4 mol) in the presence of TBAB (0.04 mol) and NaOH (2 mol, ●); (4 mol, ▼); (8 mol, ■).



First we observed that all the halide (4 equiv of n-C_7H_{15}Br for 1 equiv of PE) had been consumed within about 3 h when a NaOH:PE ratio of 80 was used. This result was quite unexpected since, when this ratio was 20 (which is still a very large excess), more than 12 h were required for the disappearance of all the n-heptyl bromide[5].

Moreover, a large excess of NaOH (8 mol) leads to a nearly quantitative conversion of PE (0.1 mol) into ethers **2** and **3**, providing that additional halide (0.4 mol) was added after 4 h, and that the reaction was allowed continue for 16 h. However, despite this noteworthy increase of the tetraether ratio, it only rises to 72%.

Renewal and excess of NaOH. The reaction is then run as describe above (PE, 0.1 mol ; NaOH, 2, 4 or 8 mol), but, after 4 h the aqueous NaOH layer is replaced by a fresh 50% NaOH solution. The reaction is then resumed after additional n-heptyl bromide is added. When 20 equiv of fresh NaOH are used, the conversion of PE into tetraether is 65%. However, the above scenario, carried out with 80 equivalents of NaOH (in two steps like above) drove the reaction to an almost complete conversion of PE to the tetraether (90%) (Figure 2).

This effect is not a simple salt-effect. Addition of NaBr in the second NaOH solution had no significant effect on the formation of the tetraether[7]. In the PTC synthesis of methyl or benzyl ethers of partially protected carbohydrates, it has been observed (but without any comments on this observation)[10] that the replacement of the aqueous layer by a fresh sodium hydroxide solution is sometimes required to obtain complete etherification when benzyltriethylammonium chloride is used. However, this effect was not observed with TBAB as the catalyst.

Renewal of NaOH and catalyst. We have previously observed[1] that an increase of the solubility of the catalyst in the organic phase may increase the amount of the tetraether. We have tried to combine this effect and the effect observed upon renewal of the NaOH solution. The reaction is then carried out with 40 equiv of NaOH, 1 equiv of PE, 4 equiv of n-$C_7H_{15}Br$ and 0.4 equiv of TBAB. After 4 h, the aqueous NaOH solution is replaced by a fresh solution, 0.4 equiv of TBAB (expt 1) or 0.4 equiv of TOAB (expt 2) are added as 4 equiv of additional halide. As indicated in Figure 3, the conversion of PE to the tetraether proceeds to completion when TOAB is added in the second step instead of TBAB.

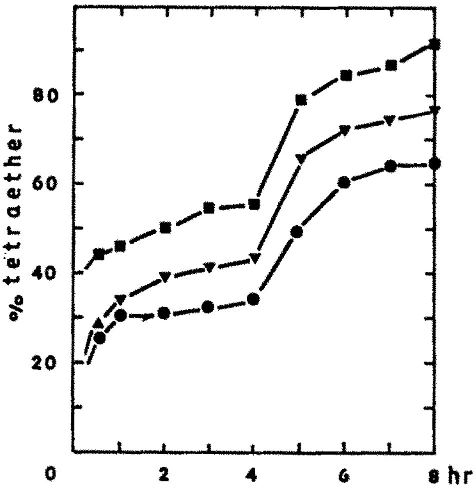


Figure 2. Formation of the tetraether (in %) for the alkylation of PE (0.1 mol) by n-$C_7H_{15}Br$ (0.4 mol) in the presence of TBAB (0.04 mol) and NaOH (2 mol, expt 1, ●) or (4 mol, expt 2, ▼) or (8 mol, expt 3, ■).
After 4 h the NaOH - NaBr layer were removed and 50% aqueous NaOH (2 mol, expt 1) ; (4mol, expt 2) ; (8 mol, expt 3) and n-$C_7H_{15}Br$ (0.4 mol) were added.

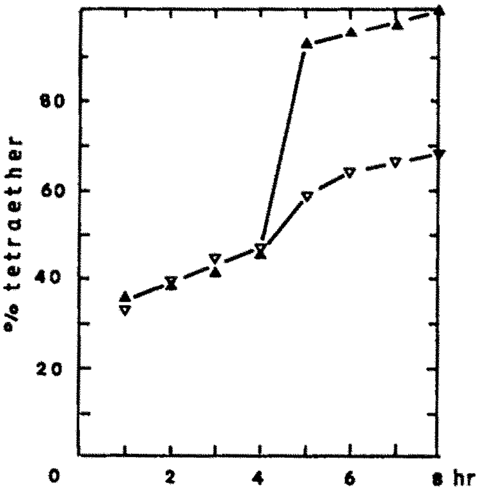


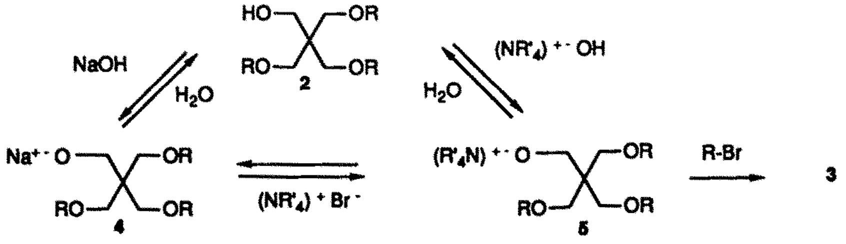
Figure 3. Formation of the tetraether (in %) for the alkylation of PE (0.1 mol) by n- $C_7H_{15}Br$ (0.4 mol) in the presence of TBAB (0.04 mol) and NaOH (4 mol).
After 4 h, the NaOH - NaBr layer were removed and 50% aqueous NaOH (4 mol) and TBAB (0.04mol), expt 1, ▽ , or TOAB (0.04 mol), expt 2, ▲ , were added.

Discussion

This last result suggests that catalyst solubility, in the gradually formed tri/tetraether mixture, is one of the key factors in converting the last alkoxide group of PE from the sodium to the ammonium form, however, this effect is masked to some extent by the dramatic importance of the quantity and the nature of the bulk aqueous NaOH solution.

The rate acceleration upon changing from 20 to 80 NaOH equivalents, and the increase in the tetraether ratio upon renewal of the sodium hydroxide solution, indicate that, in the organic phase, the equilibrium between the alkoxide form **4** and the protonated form **2** exist and is shifted to **4** (eq. 2).

Then, the role of the excess and renewal of NaOH solution would be to maintain a high concentration of **4** in the medium. In these conditions, an increase of the catalyst concentration in the organic phase would have then a greater effect on the equilibrium between **4** and **5**. The ammonium form of the triether **5** predominates in the organic phase, and the tetraether **3** is readily obtained.



(2)

The above observations may suggest that the protonation of the ion pair **4**, may take place in the catalyst layer or at the interface of the catalyst layer and organic layer. This third liquid, very polar layer, containing mainly the catalyst and water[13,19] seems to have a great importance on the selectivity of this PT reaction.

Conclusion

We conclude that our findings provide a reasonable explanation of the mechanism of the PT alkylation of pentaerythritol.

The selectivity of the reaction is controlled by the following reaction rates : a) the possible protonation in the organic phase of ion pairs **4** and in a lesser extent **5** , b) the formation of **5** from **4**, and c) the alkylation of **5** into the tetraether **3** (see eq 2).

When the halide is a reactive electrophilic agent, like allyl or benzyl chloride, the fourth alkylation is faster than protonation of the alkoxide **5**, and the reaction products (allyl or benzyl ethers) are low lipophilic ethers. The catalyst is present in the organic phase untill the alkylation is complete[16], and the cation exchange is faster than protonation of **4**.

When the halide is the heptyl bromide, the last etherification of the fourth alkoxide anion of PE occurs in the beginning of the reaction. Due to the high paraffinic character of the ethers formed, the catalyst becomes sparingly soluble in the organic phase. From this moment, a PT system with three liquid layers is involved, one of the layers being the catalyst.

In this very polar layer, water molecules may be present[17], NaOH solution serves as an effective but not absolute desiccant. Protonation of alkoxide ion pairs can then readily occur as a phase boundary process.

These effects can be counteracted by increasing NaOH quantities[18] or by replacement of the NaOH solution during the course of the reaction to keep a sufficient desiccant effect for the bulk aqueous NaOH layer.

In the same way the use of a more hydrophobic catalyst as a co-catalyst more soluble in the organic phase, accelerates the cation exchange but also may avoids the presence of water molecules near to the organic phase[13,14].

Experimental section

GLC analysis, separation techniques, and identification of the by products (1-heptene, n-diheptyl ether) and PE ethers (triether + tetraether) were performed in the same way as previously described.[1] All reactions were carried out under dry nitrogen, PE was dried at 140°C and stored in a drying oven, TBAB at 60°C under reduced pressure (10^{-3} hPa).

Change in the excess of NaOH

40 equiv - 4 h : PE (13.6 g, 0.1 mol) was dissolved in a mechanically stirred solution of NaOH (160 g, 4 mol) and water (160 mL) for 1 h at 80°C. TBAB (12.9 g, 0.04 mol) and n-heptyl bromide (71.1 g, 0.4 mol) were then added and the stirring continued for 4 h. The NaOH layer was separated, the organic layer was cooled, 100 mL of diethyl ether were added, and the solid TBAB layer was filtered of. The organic layer was washed with 2x150 mL of water. After drying (Na_2SO_4) and distillation of diethyl ether, careful fractional distillation afforded : 1-heptene, 0.9g ; n-heptyl bromide, 7.0 g ; n-diheptyl ether, 5.5 g ; tri+tetraether mixture, 32.0 g (tri 52,9%, tetra 47.1%) ; yield 68.0%.

40 equiv - 16 h : The reaction was carried out in the same way as above, but after 4 h, additional n-heptyl bromide (0.4 mol) was added and the stirring was continued for 12 h at 80°C : 1-heptene, 10.0 g ; n-heptyl bromide, 28.1 g ; n-diheptyl ether, 13.0 g ; tri+tetraether mixture, 47.9 g (tri 47%, tetra 53%) ; yield 99.96%.

80 equiv - 4 h : PE (0,05 mol) ; n-heptyl bromide (0.2mol) ; TBAB (0.02 mol) : 1 heptene, 1.1 g ; n-heptyl bromide, 0.2 g ; n-diheptyl ether, 4.1 g ; tri+tetra mixture, 16.95 g (tri 47.5%, tetra 52.5%); yield 71.2%.

80 equiv - 16 h : similar conditions but additional n-heptyl bromide (0.2 mol) after 4 h : 1-heptene, 2.9 g ; n-heptyl bromide, 10.5 g ; n-diheptyl ether 9.5g ; tri+tetra mixture, 13.4g (tri 28.4%, tetra 71.6%) ; yield 94.5%.

Reactions with renewal of NaOH solution

The progress of these reactions as indicated by the tri:tetraether ratio was monitored by GLC with samplings at 0.25, 0.5, 1,2,..,8 h. The reaction mixture was not treated after reaction.

80 equiv : PE (5.3 g) ; NaOH (124 g) ; H_2O (124 mL); TBAB (5 g) ; and n-heptyl bromide (28.1 g) were stirred 4 h at 80°C as usual. Just after the sampling (4 h), NaOH layer was thoroughly removed without elimination of TBAB. A new solution (NaOH, 124 g ; H_2O, 124 mL) was then added, the mixture was stirred for 15 min, and n-heptyl bromide (28.1 g) was added the stirring was continued for 4 h with samples being taken out.

40 equiv : PE (10.6 g) ; NaOH (124 g) ;H_2O (124 mL); TBAB (10 g) ; n-heptyl bromide (56.2 g) ; second step : NaOH (124 g) ; H_2O (124 mL) ; n-heptyl bromide (56.2g).

20 equiv : PE (18 g) ; NaOH (88 g) ; H_2O (88 mL) ; TBAB (14.2 g) ; n-heptyl bromide (79.4 g) ; second step : NaOH (88 g) ; H_2O (88 mL) ; n-heptyl bromide (79.4 g).

Reactions with renewal of the NaOH solution and addition of catalyst

- Addition of TBAB. The reaction was carried out as above (40 equiv - first step). The second step was identical, but with addition of TBAB (10 g).
- Addition of TOAB. The same experiment but TBAB was replaced by TOAB (16,4 g) in the second step.

Reactions with renewal of the NaOH solutions and addition of NaBr

Two similar experiments were carried out with 80 equiv NaOH in two steps. In the first one, for the second step, after renewal of NaOH solution, a fresh NaOH solution was added and the mixture was stirred additional 12h. In the second experiment, NaBr was added into the fresh NaOH solution for the second step. After overall 16h the reaction mixture was worked up and the products were isolated.

Fresh NaOH : PE (0.05 mol) ; NaOH (4 mol) n-heptyl bromide (0.2 mol) ; TBAB (0.02 mol) ; second step NaOH (4 mol) ; n-heptyl bromide (0.2 mol) : 1-heptene, 7 g ; n-heptyl bromide, 2.8 g ; n-diheptyl ether 16.1 g ; tri+tetraether mixture, 18.35 g (tri 9.7%, tetra 90.3%) ; yield 71%.

Fresh NaOH + NaBr : The same first step, second step: NaOH (4 mol) ; NaBr (0.2 mol) ; n-heptyl bromide (0.2 mol) : 1-heptene, 3.8 g ; n-heptyl bromide, 16.4 g ; n-diheptyl ether, 10.85 g ; tri+tetra ether mixture, 18.45 g ; (tri 13.2%, tetra 86.8%) ; yield 72%.

Catalyst layer

It is interesting to note the physical appearance of the catalyst layer after cooling at the end of the reactions as a function of the quantity of NaOH solution. With 20 equivalents of NaOH, the catalyst layer is a pale yellow liquid even at room temperature.

With 80 equivalents NaOH the catalyst layer, which is a liquid during the reaction (80°C) becomes a white crystalline solid on cooling (60°C). This is an indication that the extent of hydration is different[19]. An experiment can be carried out to verify the facile hydration of the TBAB layer : to 5 g (0.015 mol) of dry TBAB, fractions of water (0.1 g) are added and the stirred mixture is warmed at 55°C ; after addition of only 0.3 g (0.016 mol) of water the mixture is a clear liquid (0.6 g of water are required at 25°C).

In all experiments the catalyst (TBAB or TOAB) is recovered in 90-95% yield.

References and notes

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