

Alkylation of Pentaerythritol and Trimethylolpropane, Two Very Hydrophilic Polyols, by Phase-Transfer Catalysis

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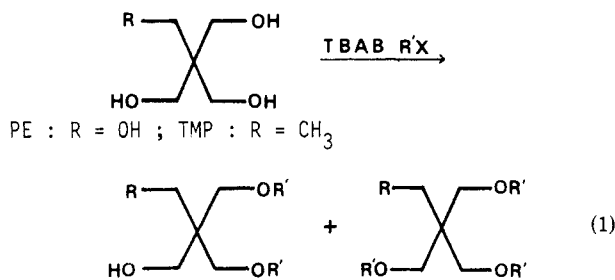
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Two very hydrophilic polyols, pentaerythritol [2,2'-bis(hydroxymethyl)-1,3-propanediol (PE)] and trimethylolpropane [2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP)], can be etherified in good yields by phase-transfer catalysis with allyl chloride or heptyl bromide as alkylating agents. Ion pairs solubilities, lipophilicities of catalysts, and nature of the reaction products which are key factors in achievement of this PTC reaction are discussed.

The phase transfer catalyzed reaction of alkoxide or phenoxide anions and halides has been widely used to prepare a variety of mixed alkyl or aryl alkyl ethers.¹⁻³ However, polyhydroxylic derivatives have, so far, not been alkylated under liquid-liquid PT conditions because "water soluble compounds,... cannot be reacted because their ion pairs are not present in the organic phase".⁴ The only PTC etherifications of carbohydrates described have been carried out via a lipophilic derivative: isopropylidene,⁵ benzylidene acetals,⁶ or tetrahydropyranyl ethers.⁷

Tetraalkylation of pentaerythritol (PE) and trialkylation of trimethylolpropane (TMP) were initially achieved, in good yield (70%), by classical Williamson reaction with NaH in anhydrous dimethylformamide. We have investigated the etherification of pentaerythritol and trimethylolpropane by phase-transfer catalysis.⁸ Surprisingly under these conditions, when an excess of a reactive electrophilic alkylating agent is used, peralkylation occurs in excellent yields (95% for benzyl chloride, 100% for allyl chloride). With less reactive alkyl halides, a mixture of ethers is obtained in good yields (80-86% for *n*-C₇H₁₅Br) (eq 1).



R = OR'	}	R' = allyl	0%	1	R' = allyl	100%
		R' = C ₇ H ₁₅	45%	3	R' = C ₇ H ₁₅	55%
R = CH ₃	}	R' = allyl	0%	4	R' = allyl	100%
		R' = C ₇ H ₁₅	64%	6	R' = C ₇ H ₁₅	36%

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Experimental Section

Gas chromatographic (GLC) analysis were performed on a Delsi IGC 120 instrument with 1.5 m ¹/₈ in. 5% SP 2100, chromosorb G column (70-310 °C, 15 °C/mn). High-pressure LC separations were carried out on a Waters Prep LC/System 500 liquid chromatography by using one Prep PAC-500/Silica cartridge (5.7 × 30 cm) and a hexane-ethyl acetate (7:3) solvent system at a flow rate of 0.1 L/min. ¹H NMR spectra were obtained on a Varian EM 360 instrument in CDCl₃ with Me₄Si as internal standard. Infrared spectra were recorded on a Perkin Elmer grating spectrophotometer. Mass spectra were determined on a Ribermag 10-10 instrument (GC/SM system) by chemical ionization with CH₄.

General Procedure for the Alkylation of Pentaerythritol. Into a 500-mL round-bottom flask placed in a thermostated oil bath, fitted with an efficient mechanical stirrer (500 rpm) and a reflux condenser, were placed 80 g (2 mol) of NaOH pellets in 80 mL of water. PE (12.6 g, 0.1 mol) were then added, and stirring maintained during 0.5 h at 80 °C until the medium became homogeneous. TBAB (12.9 g, 0.04 mol) and 71.1 g (0.4 mol) of *n*-C₇H₁₅Br were then added and the stirring continued for 7 h at 80 °C. The four layers were separated (solid NaBr, aqueous NaOH, TBAB, organic layer). The organic layer was washed twice with 150-mL portions of water. Two fractions were collected by distillation (300 °C (10⁻³ mbar) after having removed byproducts (1-heptanol, diheptyl ether) at 150 °C (10⁻¹ mbar). The first one contained triether 2 (80%) and tetraether 3 (20%), and the second contained 90% of tetraether. The total separation was achieved by preparative LC, to give pure (>99.6% GLC) 2 (36.72 g) and 3 (44.88 g) as colorless oils (85%). Tetraheptyl ether of PE (3): mass spectra M 528, *m/e* (% base peak) 530 (M + 2 H)⁺ (74), 529 (M + 1 H)⁺ (32.5), 528 (M)⁺ (57.9), 243 (100), 100 (27). Anal. Calcd for C₃₃H₆₈O₄: C, 74.94; H, 12.96. Found: C, 74.96% H, 12.93. Triheptyl ether of PE (2): mass spectra M 430, *m/e* (% base peak) 432 (M + 2 H)⁺ (72), 431 (M + 1 H)⁺ (31.8), 430 (M)⁺ (54.5), 243 (100), 100 (80.7). Anal. Calcd for C₂₆H₅₄O₄: C, 72.50; H, 12.64. Found: C, 72.54; H, 12.63.

Tetraallyl Ether of PE (1). The reaction was similar to that described for heptyl ethers. Allyl chloride (0.5 mol) was added dropwise over 60 min at 40 °C. Toluene (150 mL) was added after reaction to facilitate the workup (29.6 g, 99.6% after purification on silica gel by flash LC hexane-ethyl acetate (5:5)). ¹H NMR δ 3.5 (s, 2 H, CCH₂), 3.9 (d, *J* = 5 Hz, 2 H, OCH₂), 5.0-5.4 (m, 2 H, CH₂=), 5.6-6.2 (m, 1 H, =CH). Anal. Calcd for C₁₇H₂₈O₄: C, 68.92; H, 9.46. Found: C, 68.98; H, 9.51.

Heptyl Ethers of TMP. The experiments were similar to those described above for PE, TMP (0.1 mol), NaOH (1.5 mol), TBAB (0.03 mol), and *n*-C₇H₁₅Br (0.3 mol). After LC, 6 (11.26 g) and 5 (20.03 g) were obtained as colorless oils (87%). Triether of TMP (6): mass spectra M 428, *m/e* (% base peak) 431 (M + 3 H)⁺ (9.1), 430 (M + 2 H)⁺ (69.2), 428 (M)⁺ (30.2), 103 (100). Anal. Calcd for C₂₇H₅₆O₃: C, 75.64; H, 13.17. Found: C, 75.62; H, 13.14. Diether of TMP (5): mass spectra M 330, *m/e* (% base peak) 333 (M + 3 H)⁺ (11.1), 332 (M + 2 H)⁺ (65.5), 330 (M)⁺ (26.7), 117 (100). Anal. Calcd for C₂₀H₄₂O₃: C, 72.67; H, 12.52. Found: C, 72.59; H, 12.58.

Triallyl ether of TMP (4) (25.2 g, 99.2%): ¹H NMR δ 0.8 (t, *J* = 7 Hz, 3 H, CH₃), 1.5 (q, *J* = 7 Hz, 2 H, CH₂), 3.3 (s, 6 H,

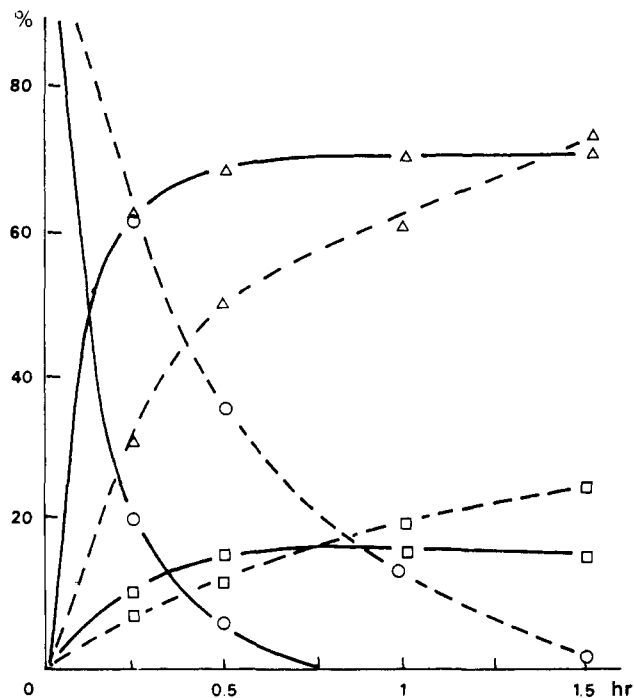


Figure 1. Formation of heptyl ethers of PE (0.1 mol). Relative concentration of (O) $n\text{-C}_7\text{H}_{15}\text{Br}$, (Δ) triheptyl ether (2), and (\square) tetraheptyl ether (3) in two different experiments.

expt	$n\text{-C}_7\text{H}_{15}\text{Br}$	TBAB	NaOH (mol)
1 (-)	0.1	0.01	0.5
2 (-)	0.2	0.02	1

CCH_2O), 3.9 (d, $J = 5$ Hz, 6 H, OCH_2C), 5.0–5.4 (m, 6 H, $\text{CH}_2=$), 5.6–6.2 (m, 3 H, $=\text{CH}$). Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_3$: C, 70.87; H, 10.24. Found: C, 71.01; H, 10.36. The progress of all these reactions was monitored by GLC. Aliquots of 1 mL were dissolved in 1 mL of diethyl ether, 1 mL of water was added, and 0.5 mL of the ethereal layer was dried on 3 Å molecular sieve and analyzed by GLC.

Results and Discussion

Under the conditions described in the Experimental Section, the formation of heptyl ethers of PE (Figure 1) and TMP (Figure 2) was fast. When using less than a stoichiometric amount of $n\text{-C}_7\text{H}_{15}\text{Br}$ the reaction was complete in less than 45 min. For 1 equiv of PE and 1 equiv of $n\text{-C}_7\text{H}_{15}\text{Br}$, the yield of isolated ethers was 23% (theoretical 25%), for 3 equiv the yield was 70%, and for 4 equiv (stoichiometry) the yield was 83% (reaction time 7 h).

After optimization it appeared that the amount of sodium hydroxide and catalyst was an important factor in this reaction. In a final choice, 5 equiv of sodium hydroxide and 0.1 equiv of TBAB were used for 1 equiv of alkyl halide.

The formation of byproducts, diheptyl ether (5–10%), 1-heptene (1–5%), 1-heptanol (3–5%), and tributylamine (<1%), was expected in phase-transfer Williamson ether synthesis. The catalyst (TBAB) was recovered in high yield, 98% after purification.

Attempts to improve the amount of tetraether in the alkylation of PE, with a large excess of $n\text{-C}_7\text{H}_{15}\text{Br}$, gave only a few percent increase. Further alkylation, under the same conditions, of the isolated tri- and tetraethers mixture leads to only a minor change in the tri/tetra ratio (from 58/42 to 47/53). PTC alkylation of pure isolated triether, also leads to a mixture of unreacted triether (37%) and tetraether (63%). Facile tetraalkylation by $n\text{-C}_7\text{H}_{15}\text{Br}$ in homogeneous dimethylformamide solution indicates that

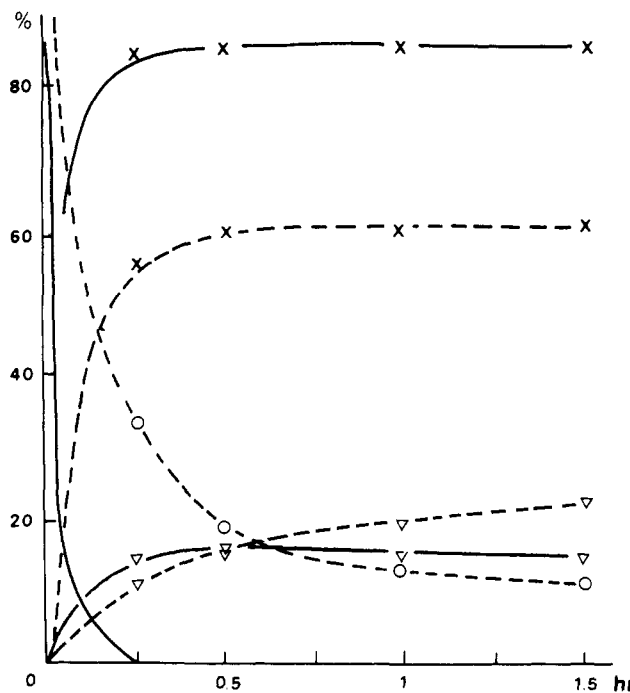
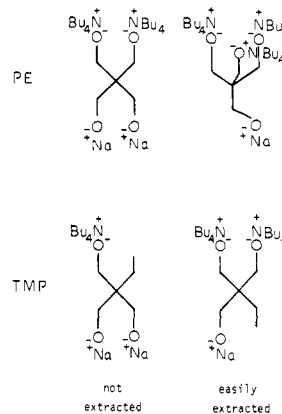


Figure 2. Formation of heptyl ethers of TMP (0.1 mol). Relative concentration of (O) $n\text{-C}_7\text{H}_{15}\text{Br}$, (X) diheptyl ether (5), and (∇) triheptyl ether (6) in two different experiments.

expt	$n\text{-C}_7\text{H}_{15}\text{Br}$	TBAB	NaOH (mol)
1 (-)	0.1	0.01	0.5
2 (-)	0.3	0.03	1.5

Chart I



steric effects cannot be taken into account. In such bi-phasic media, ion pairs solubility is very likely a key factor in determining the ratio of tri- or tetraethers.

Mono- or diethers of PE were never observed, neither in the first samplings, at the beginning of the experiment, nor in the isolated mixture of ethers. The lack of formation of mono- or dialkylated products even at low conversion can be rationalized by the fact that the mono- and bis-(tetrabutylammonio)-PE salts are not transported into the organic phase. This requires transport of the tris(tetrabutylammonio)-PE salt into the organic phase to be fast; the result is facile triether formation. An alternative explanation of these results (given by Gallucci for biphenols)⁹ is that the diether is considerably more soluble in the organic phase than the monoether and forms triether at a much faster rate. According to this explanation, the triether, more soluble in the organic phase than the diether,

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Table I. Influence of the Nature of Catalyst on the Alkylation of PE (with and without Solvent)

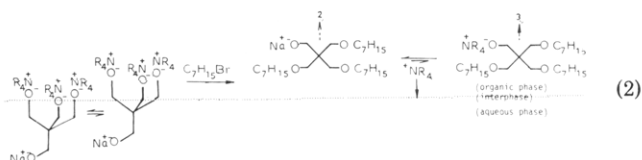
catalyst	solvent	yield, %	t/T, %
TBAB ^a	none	83	53/47
TBAB ^a	toluene	52	73/27
TBAB ^a	dioxane	47	88/12
TBAB ^a	octane	68	88/12
TOAB ^b	none	67	27/73
TOAB ^b	toluene	50	76/24
HTBPP ^c	none	50	26/74

^aTetrabutylammonium bromide. ^bTetraoctylammonium bromide. ^cHexadecyltributylphosphonium bromide.

would form tetraether at a much faster rate.

The first explanation seems then more plausible than the second, tetraether formation being in fact very slow. The nature of ion pairs involved appears in Chart I for PE and TMP.

The slow formation of tetraethers implies that the conversion of the alkoxide anion from the sodium to ammonium form in the organic phase (eq 2) is difficult. The



presence in the organic phase of the alkoxide anion of triheptyl ether in the sodium form is effectively possible, when sodium (1.2 mmol) is added to a 50/50 mixture of tri- and tetraether (1 g); the solution becomes homogeneous after 2 h at 60 °C in a sonic bath. Moreover this mixture is clearly soluble in toluene (2 mL).

When the reaction was nearly complete, the organic phase contained mainly tri- and tetraethers, which have a high paraffinic character; in this medium TBAB is sparingly soluble, and its solubility decreases with gradual formation of the tetraether (3).

If, however, a larger, more lipophilic cation is used, like tetraoctylammonium bromide or hexadecyltributylphosphonium bromide, this effect is to some extent counteracted. The effect of the nature of the catalyst is summarized in Table I for the alkylation of PE.

As indicated in Figure 3, when TBAB is used as catalyst, after 7 h, the ratio tetraether/triether (T%/t%) is about 0.9 and additional *n*-C₇H₁₅Br and TBAB are then added; after an additional 7 h this ratio is 1.1 showing a slow evolution of reaction products.

However, when TOAB is added instead of TBAB and the mixture stirred over a period of 7 h, the ratio is then 1.9. The very lipophilic N⁺(C₈H₁₇)₄ cation is present in the organic phase and ensures a highest rate for tetraether formation.

When TOAB is used in the presence of a solvent like toluene, the medium becomes less lipophilic, TOAB is not soluble in this organic phase, and the tetraether is again the minor product.

These results indicate that catalyst solubility in the mixture gradually formed of tri- and tetraether of PE is also a key in converting the last alkoxide group from the sodium to ammonium form and then to forming tetraether in high yields.

Conclusions

The phase-transfer catalyzed reaction of very hydrophilic compounds like PE and TMP, with reactive electrophilic alkylating agent, leads to total etherification with

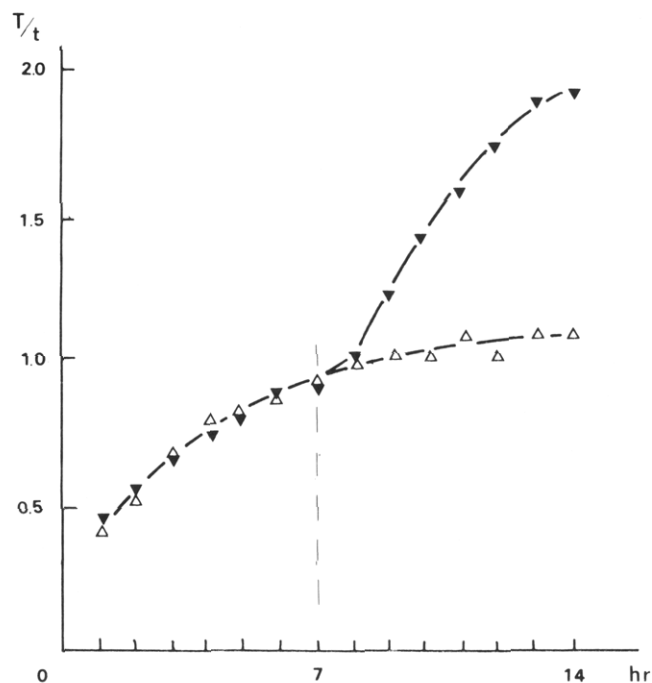


Figure 3. Evolution of the ratio of tetraether (3) and triether (2) (T/t) for the alkylation of 0.1 mol of PE by 0.4 mol of *n*-C₇H₁₅Br in the presence of TBAB (0.04 mol). After 7 h 0.01 mol of TBAB (expt 1, Δ) or TOAB (expt 2, ▼) is added.

excellent yields. Sodium alkoxide anion of these polyols are only present in the aqueous phase and TBAB only present in the organic phase. However the formation of ion pairs between alkoxide and ammonium occurs and takes place at the interphase (as a phase boundary process). The selective extraction of the ion pairs depends on their solubility in the organic phase; the structure of the trialkoxide anion may also be important in determining the reaction products. The mono- and bis(tetraalkylammonio)-PE salts and the mono(tetraalkylammonio)-TMP salt are not transported into the organic phase; this explains the failure to obtain mono- or diethers of PE and a monoether of TMP even at low conversions.

Transport of the tris(tetraalkylammonio)-PE salt and the bis(tetraalkylammonio)-TMP salt is a very fast process; consequently, the triether of PE and the diether of TMP are assumed to be formed very rapidly and are soluble in the organic phase as sodium salts. The last etherification of the fourth alkoxide anion of PE and the third one of TMP occurs in the organic phase, after conversion of the alkoxide group from the sodium to the ammonium form. The rate of this conversion depends of the concentration of N⁺R₄ in the organic phase. When the reaction products are low lipophilic ethers (allyl, benzyl ethers), TBAB is present in the organic phase and the last displacement reaction easily occurs. When the reaction products are more lipophilic (heptylethers), TBAB becomes sparingly soluble in the organic phase and the concentration of the ammonium form of the alkoxide anion is very low; the rate of the last etherification is then very slow. If more lipophilic cations are used, they are present in the organic phase even when the reactions products are heptyl ethers; the exchange Na⁺/N⁺R₄ is then possible and leads to much higher yields of fully etherified products.

Registry No. 1, 1471-18-7; 2, 97431-23-7; 3, 97431-24-8; 4, 682-08-6; 5, 97431-26-0; 6, 97431-25-9; TMP, 77-99-6; *n*-C₇H₁₅Br, 629-04-9; pentaerythritol, 115-77-5; 1-heptanol, 111-70-6; diheptyl ether, 629-64-1; allyl chloride, 107-05-1; 1-heptene, 592-76-7.