SELECTIVE MONOETHERIFICATION AND MONOESTERIFICATION OF DIOLS AND DIACIDS UNDER PHASE-TRANSFER CONDITIONS

JAIME DE LA ZERDA, GABRIELA BARAK and YOEL SASSON*

Casali Institute of Applied Chemistry - The Hebrew University of Jerusalem
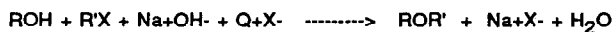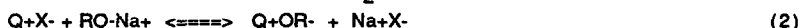Jerusalem 91904 ISRAEL

Abstract - Research on the selectivity of etherification reactions of diols and esterification reactions of diacids by alkyl halides under phase-transfer catalysis has shown that under such conditions, selectivity of monoetherification increases in the order prim < sec < tert diols, though overall yield of monoether decreases from sec to tert diols. Monoesterification of diacids was accomplished with a high degree of selectivity. Optimal extraction of diols and diacids was found to correspond in general to chain lengths of around 5 carbons. This could mean that the complex formed between the catalyst and the anion to react is stabilized for certain carbon lengths by inner solvation in virtue of its spatial conformation.

INTRODUCTION

Selective monoetherification of diols and monoesterification of diacids are of great importance from a synthetic point of view. A study on behaviour of etherification and esterification reactions performed with alkyl halides in the presence of a caustic base under phase-transfer catalysis (ptc) has been undertaken. In these chemical systems, reaction rate, selectivity and yields depend on a number of parameters that simultaneously and interdependently play a role in the system. One obvious such factor is the acidity of the proton in the alcohol's -OH group[1] and the acid's -COOH group[2] in the case of etherifications and esterifications respectively. Another important factor is the extractability of mono- and dianionic species into the organic phase by the phase-transfer catalyst[3]. Since ptc has proven to be an effective method for reaching selectivity in various chemical systems that otherwise would render a mixture of products[4], it was expected that this method would improve yields in such reactions. This work presents the results obtained in an empirical research done on such systems.
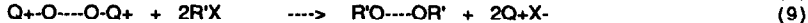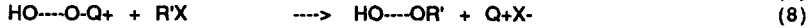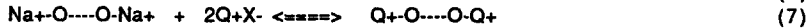
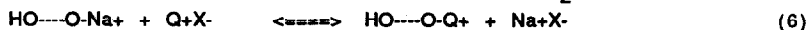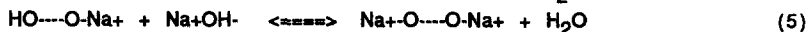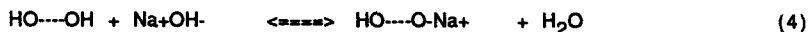### REACTIONS AND EQUILIBRIUM CONDITIONS

The reactions that take place in the more simple case of monoalcohols and monoacids may be summarized as follows (ROH represent both alcohols and acids R"COOH):

$$ROH + Na^+OH^- \quad \Longleftrightarrow \quad RO^-Na^+ + H_2O \qquad (1)$$
$$Q^+X^- + RO^-Na^+ \quad \Longleftrightarrow \quad Q^+OR^- + Na^+X^- \qquad (2)$$
$$Q^+OR^- + R'X \quad \longrightarrow \quad ROR' + Q^+X^- \qquad (3)$$

$$ROH + R'X + Na^+OH^- + Q^+X^- \quad \longrightarrow \quad ROR' + Na^+X^- + H_2O$$

(1) is the step in which the protic H is taken from the alcohol or acid respectively to give the corresponding anion. In (2), the anion formed reacts with Q+X- (a quaternary ammonium salt ["quat"] - the phase-transfer catalyst) to form the ion pair Q+OR-, which further reacts with the alkyl halide in (3) to produce the ether or ester respectively.

In particular, for the case of alcohols the reaction is the well-known Williamson etherification, one of the first to which ptc was succesfully applied[5].

For dialcohols and diacids the situation is more complex. The concentrations of the monoanion and of the dianion obtained depend on the acidity of each H in the -OH groups. These concentrations, in turn, determine the measure in which they will be transferred by the quat to the bulk of the organic phase in order to react with the alkyl halide to obtain the ether or ester respectively. Reactions that may take place (HO----OH means both diol and diacid) are:

$$HO\text{----}OH + Na+OH\text{-} \quad \text{<====>} \quad HO\text{----}O\text{-}Na+ \quad + H_2O \tag{4}$$

$$HO\text{----}O\text{-}Na+ + Na+OH\text{-} \quad \text{<====>} \quad Na+\text{-}O\text{----}O\text{-}Na+ + H_2O \tag{5}$$

$$HO\text{----}O\text{-}Na+ + Q+X\text{-} \quad \text{<====>} \quad HO\text{----}O\text{-}Q+ + Na+X\text{-} \tag{6}$$

$$Na+\text{-}O\text{----}O\text{-}Na+ + 2Q+X\text{-} \text{<====>} \quad Q+\text{-}O\text{----}O\text{-}Q+ \tag{7}$$

$$HO\text{----}O\text{-}Q+ + R'X \quad \text{---->} \quad HO\text{----}OR' + Q+X\text{-} \tag{8}$$

$$Q+\text{-}O\text{----}O\text{-}Q+ + 2R'X \quad \text{---->} \quad R'O\text{----}OR' + 2Q+X\text{-} \tag{9}$$

ETHERIFICATION - EXPERIMENTS AND RESULTS

Primary, secondary and tertiary diols were reacted with equivalent amounts of benzyl chloride, in the presence of an excess of 50%w KOH. Tetrabutylammonium bisulfate was also present in catalytic amounts (8 mol% in relation to benzyl chloride). Temperature was 50° C and mixtures were mechanically stirred at 500 rpm. Samples were analyzed by gas chromatography, and the products identified by GCMS. Conversion of benzyl chloride after 24 h was always complete. Part of it hydrolyzed and reacted with itself to give dibenzyl ether. Fig. 1 shows schematically the molar percent of main products in the mixtures after 24 h.
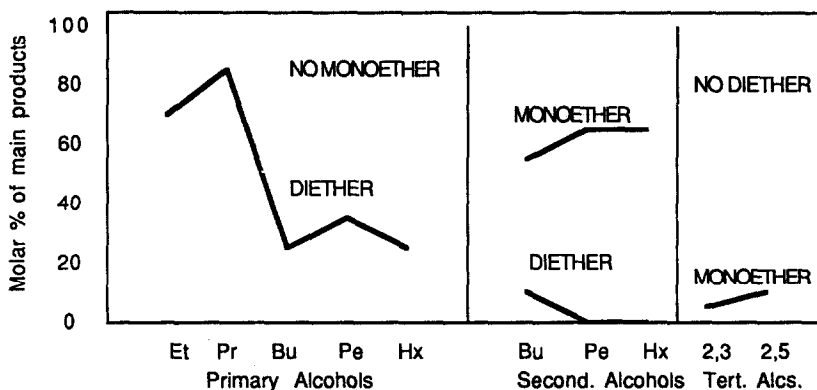

Fig. 1: Molar composition of products obtained in reaction of diols with benzyl chloride (dibenzyl ether formed does not appear in graphs). Prim. alcohols: 1,2-ethanediol to 1,6-hexanediol; sec. alcohols: 2,3-butanediol, 2,4-pentanediol and 2,5-hexanediol; tert. alcohols: 2,3-dimethyl-2,3-butanediol and 2,5-dimethyl-2,5-hexanediol.

Dibenzyl ether is not shown in the graphs (the only substances that may appear in the mixture of products are the monoether and diether, and dibenzyl ether as byproduct). In the case of primary diols, monoether yield was nill, and no monoether was detected at any stage of the reactions, that is, diether was directly obtained from the diols. The general trend was a decrease in the amount of diether obtained as the molecular weight of the alcohol utilized increased. When secondary alcohols were reacted, almost no diether was obtained, and on the other hand, relatively high amounts of monoether were produced. Yields of 60%, 72% and 75% of monoether were obtained in the cases of 2,3-butanediol, 2,4-pentanediol and 2,5-hexanediol respectively. In the case of tertiary alcohols, only monoethers were obtained, and this in small amounts (yields of 4% and 18% for 2,3-dimethyl-2,3-butanediol and 2,5-dimethyl-2,5-hexanediol respectively). Both in the case of sec- and tert- diols, the amount of monoether formed tended to increase as the molecular weight of the molecule increased.

ETHERIFICATION - CONCLUSIONS

1) Primary diols completely react to give diethers. It may be inferred that, since no monoether production was evident throughout the reactions, either the species Q+-O----O-Q+ or the salt Q+-O----O-K+ is formed and carried into the organic phase where it reacts with the alkyl halide. The relatively high acidity of both H in the -OH groups in primary alcohols seems to be enough to permit the formation of the dianion and subsequent simultaneous reaction in the two active sites.

2) Secondary and tertiary diols give almost or only monoethers. This is probably due to the fact that acidities of protic hydrogens decrease in alcohols in the order prim>sec>tert[1]. Thus, it is much more difficult for the dianionic species to be formed in these cases. Only monoanion will be obtained, and from it, the corresponding monoether.

3) The rise in activity in primary diol molecules in which the -OH groups are separated by about 5 or 6 C

atoms suggests a stabilization of the extracted complex for those sizes of molecules. Inner solvation of the alkoxide molecule by itself through a H bridge, which would add such stability to the complex, could be an explanation to this fact. Fig. 2 gives a possible representation of such arrangement.
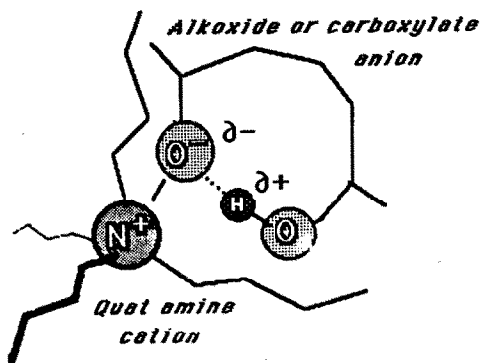

Fig. 2: Complex between quaternary amine cation and alkoxide or carboxilate monoanion – H bond stabilizes complex

ESTERIFICATION - EXPERIMENTS AND RESULTS

The extractability of the monoanionic and the dianionic species of normal aliphatic acids C_2 (oxalic acid) to C_{12} (dodecanoic diacid) - except C_7 and C_8 - into organic media by the quaternary ammonium salt Aliquat 336 (tricaprylmethylammonium chloride) was studied. Heterogeneous mixtures of 5 volumes of CH_2Cl_2 per volume NaOH 10%w were made, adding to them the organic acid and the quat in a molar ratio of 1:1; The molar ratio of NaOH to acid was 1:1 in one set of experiments (thus producing the monoanion) and 2:1 in other (thus producing the dianion). Mixtures were vigorously shaken, and phases subsequently separated. The amount of acid in each phase was determined by titration. Results are summarized in Fig. 3, which presents graphically the molar relationship of monoanion to dianion in the organic phase for the different diacids studied. There seems to be an optimum length of chain (C_5 - glutaric acid) for which monoanion/dianion ratio is highest in the organic phase.

Esterification reactions were subsequently performed with benzyl chloride and butyl bromide as alkylators. The molar ratio substrate:reactant:NaOH was 1:2:1. Aliquat was added in stoichiometric amounts. Despite the differences in extraction preferences between monoanion and dianion as described above, no particular trend was observed in the reaction yields. Monoester was always obtained in an amount that varied between 90 and 99 % of the total amount of products, being the total conversion of the reaction around 65 % after 24 h, at reflux temperature.

ESTERIFICATION - CONCLUSIONS

The fact that an optimum is obtained in the length of the carbon chain for selective extraction of the monoanion against the dianion suggests that, again, an internally solvated complex of the kind presented in Fig. 2 may be formed. Among the diacids studied, C_5 would form a ring most convenient to obtain the structure described.

On the other hand, there seems to be no correlation between the difference in extraction preference of monoanions against dianions and the ratio of monoester vs diester obtained when working with equal number of moles of acid and of NaOH. This would mean that, more than anything else, the factor that determines that ratio is the relatively high acidity of the diacids, which is such that the mole per mole relationship between acid and base leads to an almost complete conversion of the acid into monoanion, which subsequently is carried into the organic phase by the quat and reacts with the alkyl halide; at the same time, the difference in acidity of the two acidic H+ seems to be large enough so that the monoanion is preferentially created, and almost no dianion is formed. This would explain the fact that even the lower values of ratio of extraction of COO-/(COO-)$_2$ are relatively high.

GENERAL CONCLUSIONS

It may be concluded in general terms that, from a synthetic point of view, phase-transfer catalysis
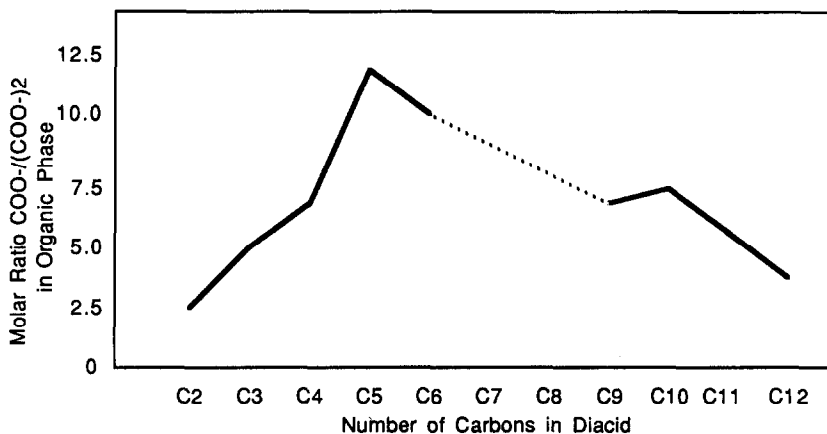
Fig. 3: Molar ratio of carboxylic monoanion to dianion as found
in the organic phase for the homologous series of normal diacids
from oxalic acid to dodecanoic diacid, except C7 and C8.

proves to be a useful method to achieve high selectivity in the preparation of monoesters from diacids
and alkyl halides. High selectivity is also achieved in the preparation of monoethers from tertiary and
secondary alcohols. The relative low conversion in the case of tertiary alcohols could probably be
improved by changing experimental conditions, as increasing the amount of catalyst. More research is to
be done on finding convenient conditions for monoetherification of diols.

The fact that optimum chain lengths of diols and diacids for the formation of monoethers and monoesters
respectively were found in some cases suggest that the geometry of both the quat and the reactant could
determine the final yield of the desired mono- product. Thus it could be that certain quat could perform
better that another one in catalysing a given etherification or esterification reaction because of steric
factors.This important point is to be further investigated.

EXPERIMENTAL

a) __Etherifications__: Reactions were performed at 50°C on a three-necked 250-ml flask. Stirring was
mechanical (500 rpm), and a Heidolph stirrer was utilized for this purpose. A typical reaction to study
mono/dietherification selectivity was as follows: .1 mol of diol was stirred with 100 ml toluene; 37 ml
of a 50 %w KOH aqueous solution (.5 mol of pure KOH) and .542 g (.0016 mol) tetrabutylammonium
bisulfate were subsequently added to the system, and stirring was continued for 15 min to allow for
equilibration. Then 23 ml (.2 mole) benzyl chloride were added and the mixture was stirred for 24 hrs.
Samples were taken and analysed with a Packard 427 flame detector gas chromatograph with a 2 m x
.25 in column packed with 15% OV-17 on acid-washed Chromosorb W, oven temperature programmed
according to diol utilized in the reaction (usually between 90 and 180°C), N_2 as carrier gas, flow rate
30 ml min^{-1}. Different main reaction products were identified by analysis with a Helwett-Packard
5790A-5970A GCMS system, comparing them to known compounds. The system was equipped with a 25
m capillary column packed with 15% OV-101 on acid-washed Chromosorb W, being He the carrier gas.
Oven temperatures as above; flow rate was 10 ml min^{-1}.

b) __Esterifications__: The following procedure describes the preparation of a given monoester: .02 mol
seboceic acid is reacted with a KOH (.02 mol) solution in water (10 ml) stirring for 1 hr at room
temperature. Enough toluene is added and the azeotrope is evaporated to dryness. 4.8 g (.02 mol) of
potassium seboceate are obtained. 60 ml toluene are added and mixed with .6 g (.002 mol) TBAB and 4.6
ml (.o2 mol) benzyl chloride. The mixture is stirred at reflux temperature for 4 1/2 hrs. 65.6%
conversion is obtained with selectivity to monoester = 97.9% and selectivity to diester = 2.1%.

Analyses were done for all esterifications by gas chromatography after methylation of the sample with
diazomethane. Conditions were as above.

BIBLIOGRAPHY

1. J. Murto, in "The Chemistry of the Hydroxil Groups", Vol. 2, p. 1077, in "The Chemistry of Functional
   Groups" Series, Saul Patai, Ed., Interscience Publishers, London 1971.
2. R. T. Morrison and R. N. Boyd, "Organic Chemistry", p. 579, Allys and Bacon Inc., Boston 1973.
3. E. W. Dehmlow and S. S. Dehmlow, "Phase-Transfer Catalysis", Verlag Chemie, Weinheim 1980.
4. As in 3 and references therein.
5. H. H. Freedman and R. A. Dubois, Tetr. Lett. 38, 3251-4, 1975