Ring-closure Reactions. Part 15.[1] Solvent Effects on Cyclic Aralkyl Ether Formation by Intramolecular Williamson Synthesis

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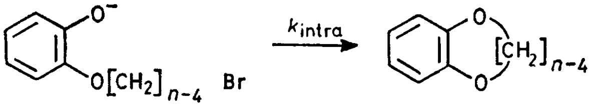
Product analysis, rate data, and effective molarity (e.m.) values have been obtained for the formation of catechol polymethylene ethers by the intramolecular alkylation of *o*-ω-bromoalkoxyphenoxides in Me$_2$SO–water (99 : 1, v/v). Twelve ring sizes were investigated in the range 6—32. Comparison with similar data for the reaction in EtOH–water (75 : 25, v/v) (except for *n* 32) showed that the e.m. values are largely independent of solvent despite the large solvent effect observed in both the cyclization reaction and the related intermolecular model reaction. Small effects only were observed in the medium ring region. The main possible factors playing a role in solvent effects on intramolecular cyclization have been critically analysed in the light of the data.

A THOROUGH understanding of the reactivity of intramolecular reactions requires structural and solvation effects to be assessed on a firm experimental basis. The large rate accelerations of intra- over inter-molecular reactions (the so-called intramolecular effect)[2] have stimulated a great deal of experimental as well as theoretical study, which are of interest not only *per se*, but also in connection with the elucidation of the mechanism of enzyme action.[2-4] Whereas structure effects have been the subject of several investigations, less attention has been devoted to solvent effects in spite of the fact that solvation has been suggested to have a role in the intramolecular effect.[3,4] A suitable approach to fill this gap is to carry out a solvent-sensitive reaction in two solvents of basically different nature and to test ring-closure tendencies over a wide spectrum of ring sizes. A simple reaction is desirable in order to avoid complications arising from complex reaction mechanisms and/or possible changes in the rate-limiting step due to solvent change. The formation of catechol polymethylene ethers (2) by intramolecular S_N2-type alkylations of *o*-ω-bromoalkoxyphenoxides (1) seems to meet these conditions. In particular, the reaction of the 2-methoxyphenoxide ion with butyl bromide, which is an intermolecular counterpart of reaction (1) has been found to proceed in Me$_2$SO–water[5] (99 : 1 v/v, referred to as 99% Me$_2$SO) 10^4 faster than in EtOH–water[6] (75 : 25 v/v, referred to as 75% EtOH). The formation of the sixteen-membered ring (2; $n = 16$) is similarly affected by these solvents.[5,7]



(1) (2) (1)

Since we have obtained rate data for cyclization reaction (1) in 75% EtOH[7] for a number of ring sizes in the range 6—24, we now report similar data for 99% Me$_2$SO solution which permit a comparison of the effect of the solvent on the effective molarity of reaction (1) over several ring sizes including 6—14, 16, and 24. The present study also includes the formation of the 32-membered ring, which is the largest polymethylene ring compound considered so far in rate studies.

RESULTS

Rate measurements were carried out at 25.0 °C in 99% Me$_2$SO solution by monitoring the disappearance of the phenoxide absorption at 314 nm. The anions (1) were generated *in situ* by adding to the parent phenols a calculated amount of KOH solution.[5] Initial concentrations were in the range 6×10^{-5}—3×10^{-4}M, *i.e.* low enough to ensure that the cyclization reactions are free from any appreciable contribution of second-order polymerization. First-order plots showed good linearity to at least 80% conversion and, whenever tested, the first-order rate constants (k_{obs}) were independent of initial concentrations in the given range. The formation of the six- and seven-membered rings was too fast to be followed by conventional spectrophotometry. A stopped-flow technique was required in these cases. Cyclization to the six-membered ring, which is the fastest reaction studied, is also very rapid on an absolute scale, the half-life (0.7 ms) being of the same order of magnitude as the mixing time of the instrument. As previously noted[6,8] the infinity spectra showed a residual phenoxide absorption which disappeared on adding a drop of concentrated hydrochloric acid. This phenomenon is partly due to a competing intramolecularly assisted elimination of the $E2$ type.[6,8] Since the side-reaction uses up another equivalent of base, the amount of KOH stock solution added at zero time was adjusted accordingly. The yields of cyclic products were calculated as $100\ (1 - \mathrm{OD}/\mathrm{OD}_0)$, where OD is the amount of absorption which disappeared upon acidification at infinity time, and OD$_0$ refers to zero time. Table 1 reports the results of the rate measurements and shows that, apart from the eight- and nine-membered rings, the extent of the side-reactions does not exceed 10% of the total reaction, so that only a minor correction is required in most cases to convert the k_{obs} values into the corresponding k_{intra} values. In the case of the 24- and 32-membered rings the correction was somewhat more uncertain, because of a minor disturbance probably due to some precipitation of the products, which was still appreciable at the lowest possible concentration, *ca.* 5×10^{-6}M. Analysis of the kinetic solution at the end of the reaction showed that the eight-membered ring was formed in 78 ± 2% yield, in fairly good agreement with the value (83%)

estimated spectrophotometrically. Furthermore, cyclisations leading to ring compounds (2; n = 11—14 and 16) have been carried out on a preparative scale under conditions close to those of the kinetic experiments,[9] with isolated yields in the range of 58—73%.

TABLE 1

Kinetic data for the ring-closure reactions of o-$^{-}OC_6H_4O[CH_2]_{n-4}Br$ in 99% Me_2SO at 25 °C

n [a]	k_{obs}/s^{-1} [b]	Yield (%) [c]	k_{intra}/s^{-1} [d]	k_{intra} (99% Me_2SO) / k_{intra} (75% EtOH) [e]
6	$1.02 \pm 0.01 \times 10^3$	92	9.4×10^2	9 700
7	4.07 ± 0.07	90	3.7	4 900
8	$2.66 \pm 0.18 \times 10^{-1}$	83	2.2×10^{-1}	7 300
9	$3.91 \pm 0.02 \times 10^{-2}$	67	2.6×10^{-2}	4 600
10	$9.20 \pm 0.20 \times 10^{-3}$	91	8.4×10^{-3}	2 400
11	$9.34 \pm 0.01 \times 10^{-2}$	92	8.6×10^{-3}	8 900
12	$1.11 \pm 0.01 \times 10^{-2}$	93	1.0×10^{-2}	
13	$9.94 \pm 0.03 \times 10^{-3}$	92	9.1×10^{-3}	
14	$8.43 \pm 0.30 \times 10^{-3}$	90	7.6×10^{-3}	15 200
16	$8.79 \pm 0.13 \times 10^{-3}$ [f]	91	8.0×10^{-3}	13 100
24	$1.22 \pm 0.08 \times 10^{-2}$	*ca.* 95	1.2×10^{-2}	5 100
32	$1.25 \pm 0.05 \times 10^{-2}$	*ca.* 95	1.2×10^{-2}	
Inter [g]			2.95×10^{-1}	9 700

[a] Size of the ring to be formed. [b] Average from 2—4 independent runs. [c] As based on spectrophotometric analysis. [d] Calculated as k_{obs} (yield %/100). [e] At 25 °C. Rate constants in 75% EtOH were evaluated from data at different temperatures.[7] [f] The present value compares well with that ($9.04 \pm 0.11 \times 10^{-3}$ s^{-1}) previously reported.[5] [g] The intermolecular model reaction is the alkylation of 2-methoxyphenoxide ion with butyl bromide. The rate constant (k_{inter}) is given in l mol^{-1} s^{-1} (from ref. 5).

DISCUSSION

The rate data reported in Table 1 show that in 99% Me_2SO the dependence of the reactivity on the chain length displays essentially the same features as those previously recorded in 75% EtOH,[7] namely, (i) a steep drop on increasing the chain length for the lower members of the series, (ii) the lack of a reactivity minimum in the medium ring region, and (iii) a remarkable insensitivity of the reaction rate to chain length in the large ring region. The last point is further stressed by the 32-membered ring, whose ease of formation is comparable to those of other large rings.

TABLE 2

Comparison of e.m. data in 75% EtOH and 99% Me_2SO for the ring-closure reactions of o-$^{-}OC_6H_4O[CH_2]_{n-4}Br$

n	E.m./M [a] (99% Me_2SO, 25°)	E.m./M [b] (75% EtOH, 50°)	E.m./M [b] (75% EtOH, 25°)	E.m. (75% EtOH; 50 °C) / E.m. (99% Me_2SO; 25 °C)	E.m. (75% EtOH; 25 °C) / E.m. (99% Me_2SO; 25 °C)
6	3 200	3 900	3 200	1.2	1.0
7	12.5	36	25	2.9	2.0
8	0.75	1.8	0.99	2.3	1.3
9	0.088	0.31	0.19	3.5	2.2
10	0.028	0.15	0.11	5.4	3.9
11	0.029	0.046	0.032	1.6	1.1
12	0.034	0.057		1.7	
13	0.031	0.038		1.2	
14	0.026	0.022	0.016	0.85	0.62
16	0.027	0.023	0.020	0.85	0.74
24	0.041	0.064	0.070	1.6	1.7
32	0.041				

[a] This work. [b] From ref. 7.

A closer comparison of reactivity data in the two solvents is rendered possible by inspection of the last column of Table 1 and of the effective molarity (e.m.)* data reported in Table 2. A complete set of e.m. values in 75% EtOH at 50 °C has been reported,[7] except for ring size 32 whose study was made impracticable in this medium by very low solubility. Whenever possible, extrapolation to 25 °C from data at different temperatures has been carried out on the basis of the known temperature coefficients of the rate constants.[7] It is worth noting that in spite of the fact that cyclisation rates are significantly faster in 99% Me_2SO than in 75% EtOH, rate ratios and e.m. values exhibit relatively small or, in some cases, no changes at all. In the case of the six-membered ring, the rate of formation is affected by the solvent change in exactly the same way as in the intermolecular model reaction. In some compounds with larger than six-membered rings, appreciable solvent effects are observed beyond the experimental error, allowance being made for the different temperature used.

To discuss solvent effects on intramolecular reactions we may wonder to what extent the inherent reactivity of the end-groups of $\alpha\omega$-bifunctional chain molecules is affected by possible changes in the solvation shells around the end-groups as a function of the length of the chain. The simplest conceivable model is to consider the structure of the solvation shells as independent of chain length for a given cyclisation series. Examination of the entropies of activation for the present reaction in 75% EtOH,[6] as well as for other cyclisation reactions,[10] led to the suggestion that the above model is reasonably good, with the possible exclusion of the very short chains. Thus, the free energy change due to solvent reorganization when the two solvation shells surrounding the functional groups are replaced by a common solvation shell in the transition state ($\Delta G^{\ddagger}_{solv.}$) may be assumed to be essentially constant along the cyclisation series and, except for special cases,[1] similar to the corresponding quantity for the intermolecular model reaction. The observed insensitivity of the e.m. values to solvent change indicates that in both solvents the quantities $(\Delta G^{\ddagger}_{solv.})_{intra} - (\Delta G^{\ddagger}_{solv.})_{inter}$ are vanishingly

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* Calculated as k_{intra}/k_{inter}, where k_{inter} refers to an intermolecular model reaction (see footnote *g* in Table 1). A full definition of e.m. may be found in ref. 7.

small in most cases. This is a striking result since the $\Delta G^{\ddagger}_{\text{solv.}}$ term in an S_N2 reaction involving an anionic nucleophile is known to be quite large and should differ appreciably in the two solvents investigated. For instance, we have estimated [6] that $\Delta S^{\ddagger}_{\text{solv.}}$ for the present reaction in 75% EtOH is a large positive quantity, *i.e.* + 17 cal mol^{-1} K^{-1}, which is believed to arise mainly from extensive desolvation of the nucleophile in the transition state.

The above evidence definitely demonstrates that solvation does not provide an explanation for the intramolecular effect and that the major factor determining e.m. values is structure. Similar conclusions, although in a less straightforward manner, were drawn by Dafforn and Koshland [11] in a study of lactone and thiolactone formation in water and sulpholan, as possible models of solvation effects in enzymatic reactions, as well as by Bruice and Turner [12] in an analogous comparison of anhydride formation in water and in Me_2SO plus 1M-water.

The most significant solvent effects, though small, are observed with the medium rings and presumably are related to the strain of the ring to be formed. It is worth noting that the e.m. values are generally higher in 75% EtOH than in 99% Me_2SO. A tentative explanation may be found in terms of changing bond-breaking and bond-making contributions at the transition state in the two solvents by applying Thornton's reaction bond rules [13] to the reaction at hand. Transfer from 75% EtOH to 99% Me_2SO will increase the nucleophilicity of the nucleophile and decrease the leaving-group ability of the leaving group. The two factors oppose each other, with the net result that motion along the reaction co-ordinate (parallel effect) will be little affected. However, the indicated solvent change would favour a simultaneous decrease of both nucleophile–carbon and carbon–leaving-group distances (perpendicular effect) and cause the transition state to be tighter and, specifically, the oxygen–carbon distance to be shorter in 99% Me_2SO than in 75% EtOH. In consequence, the cyclic transition states leading to the medium-sized rings in 99% Me_2SO should be affected to a greater extent by the steric strain typical of medium rings, *i.e.*, transannular interactions and bond opposition forces,[14] which are due to steric crowding.

A final comment may be devoted briefly to the problem of solvent-induced conformational changes of chain molecules and of the possible effects of these changes on the ease of cyclisation, as pointed out by Winnik.[15] Although the present comparison is confined to two solvents only, which makes it difficult to assess subtle effects of this sort,[15] the observed behaviour, notably the virtual constancy of the e.m. values for the large rings, seems to indicate the absence of a significant influence of any possible modification of the chain conformation upon transfer from 75% EtOH to 99% Me_2SO.

As a concluding remark, we note that in spite of minor effects detected in the medium ring region, for the remaining ring sizes the essential cancellation of the solvent contributions to the $k_{\text{intra}}/k_{\text{inter}}$ ratio occurs in two solvents which belong to neatly different categories.[16] Thus, the most important factor upon transfer from the protic 75% EtOH to the essentially aprotic 99% Me_2SO is the change of the inherent reactivities of the end-groups. Also, this work further emphasizes the important role of the e.m. parameter in a general discussion of reactivity in intramolecular reactions. The finding that e.m. is, to a good approximation, independent of solvent, provides another illustration of its definition as a genuine, absolute measure of the ring-closure tendency of bifunctional chain molecules.

EXPERIMENTAL

The mixed solvent (99% Me_2SO) and the KOH stock solution (2×10^{-2}N in 93% Me_2SO) were prepared, stored, and handled as before.[5] The apparatus was largely as previously reported.[5] Stopped-flow kinetics were carried out on a Durrum–Gibson stopped-flow spectrophotometer model D-110, matched with a Hewlett–Packard storage oscilloscope model 1207 B.

Materials.—1,28-Dibromo-octacosane was prepared in 33% yield by a modification [17] of the Woolford procedure,[18] m.p. 78—79 °C (from EtOAc) (lit.,[18] 78—79 °C). 28-Bromo-octacosyl *o*-hydroxyphenyl ether was synthesized from 1,28-dibromo-octacosane and catechol in a way similar to that reported [9] for the preparation of 20-bromoicosyl *o*-hydroxyphenyl ether. Elution on silica gel of the crude reaction product with CCl_4 gave a 29% recovery of unchanged dibromoalkane. Further elution with $CHCl_3$ gave the pure title compound in 37% yield, m.p. 65—67 °C. The spectral properties were similar to those of the lower homologues [9] and confirmed the expected structure. Bromine content was within 0.5% of theory. Other materials were available from previous investigations.[8,9]

Product analysis was carried out for the cyclisation of (1; $n = 8$) on a scaled-up kinetic experiment. After the standard work-up, the yield of cyclic product was determined by g.l.c. analysis (internal standard) on a 1 m column, packed with 2% SE 30 plus 0.5% FFAP on Chromosorb W 60—80, operated at 120°.

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