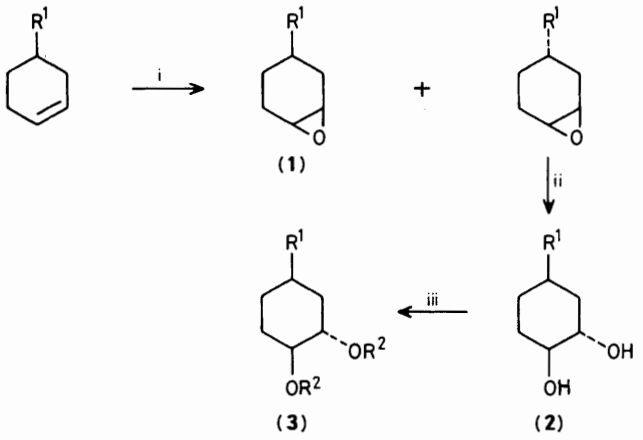
'Flipped-out' Ionophores. *trans*-Cyclohexano Pentaethylene Glycol Diethyl Ethers

Morton Raban,* Edwin Hortelano, John Quin, III, Nancy King, and Jill Koch
Department of Chemistry, Wayne State University, Detroit, MI 48202, U.S.A.

The equilibrium constants for alkali metal complexation of polyethylene glycol ethers can be measured by low temperature n.m.r. spectroscopy using a method which makes use of conformational biasing.

While polyethylene glycol dimethyl ethers (polyglymes) exhibit ionophoric properties, these are much less pronounced than in their cyclic counterparts, the crown ethers.[1] This has been referred to as the macrocyclic effect which appears in the latter but is absent in the former. While a detailed explanation of the macrocyclic effect is lacking, it is thought that it is due to the restriction in non-ionophoric conformations (with *anti*-ethylene glycol fragments) in the crown ethers. In order to probe the effect of conformational restriction on complexation ability (with respect to alkali metal cations), and to use our previously described stereochemical method[2,3] for measuring complexation ability, we have constructed conformationally biased pentaethylene glycol diethyl ethers and examined their complexing ability using low temperature ^{1}H n.m.r. spectroscopy.

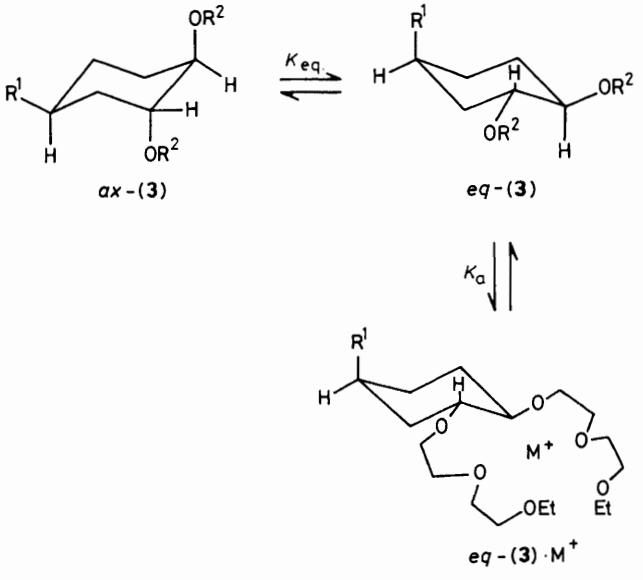
We chose the *trans*-cyclohexano group to provide a conformational bias since ring reversal could be slowed on the n.m.r. time scale and since the degree of bias could be controlled by changing ring substituents. Two examples with small (methyl) and large (formyl ethylene glycol acetal) substitutents were prepared as illustrated in Scheme 1. This synthesis is noteworthy in that the epoxidation reaction is not appreciably



a; R^1 = Me, R^2 = $CH_2CH_2OCH_2CH_2OEt$

b; R^1 = $\overline{C(H)OCH_2CH_2O}$, R^2 = $CH_2CH_2OCH_2CH_2OEt$

Scheme 1. *Reagents:* i, H_2O_2–CCl_3CN/K_2HPO_4 buffer, CH_2Cl_2, pH 6.8—7.0; ii, NaOH, H_2O, reflux; iii, NaH, $Et(OCH_2CH_2)_2OSO_2C_6H_4Me$-*p*, dry THF.



Scheme 2

stereoselective, yielding a mixture of diastereoisomers of (**1**), but the epoxide opening is stereoconvergent, resulting in a single diastereoisomer of the diol (**2**).

Compounds (**3a**) and (**3b**) exist as mixtures of conformers *ax*-(**3**) and *eq*-(**3**) which interconvert by ring reversal of the cyclohexane ring (Scheme 2). At low temperatures (*ca.* −90 °C) ring reversal is slowed and a measure of the equilibrium constant can be obtained by integration of corresponding signals in the 300 MHz ^{1}H n.m.r. spectrum. In both cases the predominant isomer was *ax*-(**3**) since the *A*-value for R^1 is substantially greater than twice that for the much smaller alkoxy group. The equilibrium constant for (**3a**) ($K_{eq.}$ 0.1) could be related to the *A*-values[4] of methyl (1.7 kcal/mol, 7.1 kJ/mol) and alkoxy (0.60 kcal/mol, 2.5 kJ/mol) if one takes into account the additional destabilization in *eq*-(**3**) resulting from the *gauche* interaction of the alkoxy groups.[5] This *gauche* destabilization was estimated as 0.60 ± 0.40 kcal/mol, 2.5 ± 1.7 kJ/mol, by Zefirov for the interaction of alkoxy and acetoxy groups.[5] In the present case the measured equilibrium constant and the reported *A*-values for methyl and alkoxy yield a value of 0.30 kcal/mol, 1.3 kJ/mol, for two vicinal diequatorial alkoxy groups, well within the range of the Zefirov determination. Only an upper limit for the equilibrium constant for (**3b**) (K_a <0.02) could be obtained since the signal of the minor isomer, *eq*-(**3b**), was too weak to be measured.

Since *eq*-(**3**) [but not *ax*-(**3**)] can achieve a conformation similar to the corresponding crown ether, 18-crown-6, we expect it to be much more effective at complexation than *ax*-(**3**). Indeed, addition of KSCN to (**3a**) and (**3b**) was occasioned by an increase in the signal assigned to *eq*-(**3a**) [now due to *eq*-(**3a**) *and eq*-(**3a**)·K^+] in the spectrum of (**3a**) and the appearance of a new signal in the spectrum of (**3b**) ascribed to *eq*-(**3b**)·K^+. The equilibria are governed by equation (1) or equation (2) if the concentration of *eq*-(**3**) can be neglected. Application of equation (1) to data for (**3a**) and equation (2) to data for (**3b**) afforded the following equilibrium constants: (**3a**), $K_{eq.}$ 0.1, K_a 1600, $K_aK_{eq.}$ = 160 mol^{-1}; (**3b**) $K_aK_{eq.}$ = 23 mol^{-1}.

$$K_a = \frac{(R - K_{eq.})(1 + R)}{K_{eq.}[M(R+1) - I(R - K_{eq.})]} \quad (1)$$

$$K_a = \frac{R}{K_{eq.}[M - (RI)/(1+R)]} \quad (2)$$

where R = [*eq*-(**3**) + *eq*-(**3**) · K^+]/*ax*-(**3**);

$K_{eq.}$ = *eq*-(**3**)/*ax*-(**3**);

I = total polyether conc.; M = total metal salt conc.

The value of $K_aK_{eq.}$ is a measure of how well the exothermicity of complexation can overcome the difficulty of converting *ax*-(**3**) into a conformation suitable for complexation, *viz. eq*-(**3**). This value is substantially larger for (**3a**) than for (**3b**) as expected from the difference in size of the two R^1 substituents. We expect this difference to lie in $K_{eq.}$ rather than K_a since complexation of *eq*-(**3**) should be insensitive to the steric bulk of the R^1 moiety. If we assume $K_{eq.}$ is about the same for (**3a**) and (**3b**) we can estimate the value of $K_{eq.}$ for (**3b**) as 0.01 which corresponds to a reasonable *A*-value of 2.6 kcal/mol, 10.9 kJ/mol,† for the acetal moiety.

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† Although we do not consider this estimate as an accurate determination of the *A*-value for the acetal moiety, its similarity to the best value (2.2 kcal/mol, 9.0 kJ/mol) given for the isopropyl group[4] provides support for our treatment.