Kinetic medium effects of cationic cosolutes in aqueous solution: the effects of alkylammonium bromides on the neutral hydrolysis of 1-benzoyl-1,2,4-triazole

Peter Hol,[a] Lisette Streefland,[a] Michael J. Blandamer[b] and Jan B. F. N. Engberts*,[a]

[a] *Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands*
[b] *Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH*

We have investigated the kinetic effects of alkylammonium, alkyldimethylammonium, alkyltrimethylammonium and tetraalkylammonium bromides on the water-catalysed hydrolysis of 1-benzoyl-1,2,4-triazole at pH 4 and 25 °C. All cosolutes retard the reaction. The retardation is attributed to a dominant stabilisation of the initial state through hydrophobic interactions with the cosolute. The results are analysed in terms of pairwise Gibbs energy interaction parameters. These G(C) values show that alkyl groups shorter than propyl have no significant influence on the medium effect. The extensively hydrated ammonium groups prevent the formation of a well developed hydrophobic hydration shell by methylene moieties in its vicinity. We observe additivity of kinetic effects of methylene groups outside the ionic hydration sphere on the hydrolysis reaction. Pairwise group interaction parameters were obtained for the CH_2-group of the different cosolutes; the contribution of the CH_2-group to the overall cosolute effect is -94 J kg mol^{-2} for both alkylammonium bromides and alkyldimethylammonium bromides, and -110 J kg mol^{-2} for alkyltrimethylammonium bromides. Ammonium bromide, which is primarily hydrophilic, also retards the reaction. We suggest that competition between ammonium bromide and the transition state for water molecules results in the strict orientational requirements for the water molecules in the activated complex not being met. Hence the hydrolysis is retarded.

Introduction

Rate constants for chemical reactions in water often change dramatically when organic cosolvents or cosolutes are added.[1,2] Chemical reactivity in aqueous solutions is influenced by specific, noncovalent interactions between cosolutes and the reactants. Noncovalent interactions between apolar alkyl moieties, the so-called hydrophobic interactions, are responsible for, *inter alia*, the stabilisation of proteins,[3] the assembly of lipids in biomembranes,[4] surfactant aggregation[5] and enzyme–substrate interactions. However, the molecular mechanism of these interactions is still under extensive investigation.[6]

Kinetic medium effects of low concentrations of chemically inert cosolute molecules on the rates of organic reactions in dilute aqueous solutions directly reflect pairwise interactions between these cosolutes and both the initial state and the activated complex. We have shown how kinetic medium effects can be described using pairwise Gibbs energy interaction parameters.[7] By applying the additivity approach of pairwise group interactions, as proposed by Savage and Wood[8] (SWAG approach), pairwise group interaction parameters can be obtained. These pairwise group interaction parameters reveal the contribution of each functional group in the cosolute to the overall solvent effect.

During the last few years, this analysis has been applied to different types of cosolutes for pH-independent hydrolysis reactions in dilute aqueous media. These cosolutes vary from monohydric and polyhydric alcohols,[7] (acyclic) carboxamides,[9] ureas,[9] sulfonamides,[9] sulfones,[9] alkylpyrrolidinones,[10] sodium alkylsulfates[11] to more complex molecules such as carbohydrates[12] and α-amino acids.[13,14]

In the present study, we describe medium effects of tetraalkylammonium bromides (R = H to butyl), alkylammonium bromides, alkyldimethylammonium bromides and alkyltrimethylammonium bromides (R = propyl to hexyl). This is the first study of the effect of this class of cosolutes on the water-catalysed hydrolysis of 1-benzoyl-1,2,4-triazole (**1**) in dilute aqueous solutions. Using the theory as described above,[7] we can distinguish between the effect of a methylene moiety in the alkyl chain near the cationic group and that further away from this polar ionic group. The SWAG approach turned out to be inapplicable to the methylene moieties inside the hydration shell of the ammonium headgroup; *i.e.* the first two methylene moieties of the alkyl group. This pattern is apparently due to the incompatibility of the headgroup hydration sphere with the hydrophobic hydration sphere of the alkyl group. The SWAG approach is valid for methylene moieties outside this hydration sphere; *i.e.* further than two carbon atoms away from the ionic group. The rate retarding effect of ammonium bromide on the hydrolysis reaction is substantial, despite the absence of hydrophobic groups. Previously, we observed that the anionic sulfate group[11] is also rate retarding. We contend, primarily based on simulation studies,[15] that the two water molecules involved in the activated complex require a very specific orientation and, apparently, this is hampered by the water-demanding ionic groups in these two solutes, including ammonium bromide.

Experimental

Materials

1-Benzoyl-1,2,4-triazole was synthesised according to literature procedures.[16] The alkyl amines, tetraalkylammonium bromides and methyl bromide were purchased from Janssen Chimica, Fluka and Sigma. The alkylamines were distilled before use.

The alkylammonium bromides and the dimethylalkylammonium bromides were prepared *in situ* by acidifying the corresponding alkylamines and dimethylalkylamines, respectively, with aqueous hydrogen bromide to pH 4. The alkyldimethylamines were synthesised by Esch–Weiler–Clark methylation[17] of the corresponding alkylamine.

The alkyltrimethylammonium bromides were synthesised by methylation of the corresponding alkyldimethylamines with methyl bromide −20 °C in acetone. The acetone was carefully removed *via* a steel tube under moderate nitrogen pressure. The salts were dried in a drying pistol until no further loss in mass was observed. The purity of the tetraalkyl- and the alkyltrimethylammonium bromides was checked by ^{1}H NMR and ^{13}C NMR spectroscopy.

Kinetic measurements

Solutions for the kinetic measurements were prepared by mass immediately before use using demineralised water, adjusted to pH 4 with hydrogen chloride. About 5–8 µl of a stock solution containing **1** in acetonitrile were injected into 2.5 ml of reaction medium and placed in a thermostatted cell compartment (25.0 ± 0.05 °C) of a Perkin-Elmer λ5 or λ2 spectrophotometer. The reaction was followed for at least four half-lives and excellent first-order kinetics were obtained by following the change in absorbance at 250 nm. Rate constants were calculated using a fitting program and were reproducible to within 1.5%. Reaction rate constants at each molality were measured in triplicate. A blank reaction in aqueous solution containing no added salt was frequently measured. Kinetic data for each set of solutions were determined at at least four different molalities.†

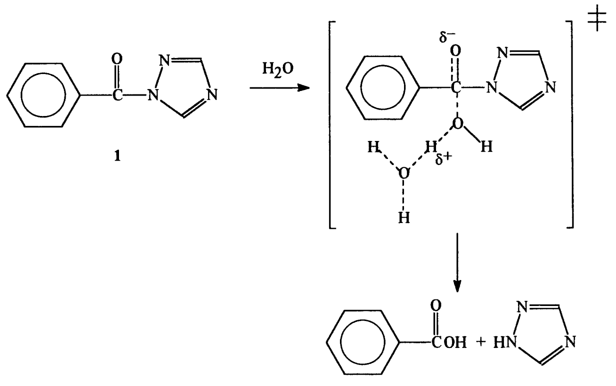
Results and discussion

Previously, we developed a theory in which rate constants can be quantitatively linked to pairwise Gibbs energy interaction parameters,[18,19] G(C) values, which reflect the difference in pairwise interaction Gibbs energy between the cosolute and the initial state, and the cosolute and the transition state of the reaction, respectively, see eqn. (1).

$$\ln\left(\frac{k_{(m_c)}}{k_{(m_c=0)}}\right) = \frac{2}{RT}G(\mathrm{C}) - NM_w\varphi m_c \qquad (1)$$

Herein, $k_{(m_c=0)}$ and $k_{(m_c)}$ are, respectively, the rate constants in aqueous solution and in aqueous solution containing m_c molal of cosolute; N is the number of water molecules involved in the transition state of the hydrolysis reaction; φ is the practical osmotic coefficient, which equals 1 in highly dilute solution and M_w is the molar mass of water. The term $N\varphi M_w m_c$ accounts for the effect of the cosolute on the reactivity of water.

The general-base catalysed hydrolysis of 1-benzoyl-1,2,4-triazole (**1**) is water-catalysed in the pH range of 3–5 and proceeds *via* a dipolar activated complex containing two water molecules [eqn. (1), $N = 2$] with three protons in flight[16,20] (Scheme 1).



Scheme 1 Reaction mechanism for the water-catalysed hydrolysis of 1-benzoyl-1,2,4-triazole

Table 1 Pairwise Gibbs energy interaction parameters for tetraalkylammonium bromides

R	G(C)/J kg mol^{-2}
H	−307 (±7)
Methyl	−324 (±4)
Ethyl	−389 (±15)
Propyl	−655 (±7)
Butyl	−1190 (±13)

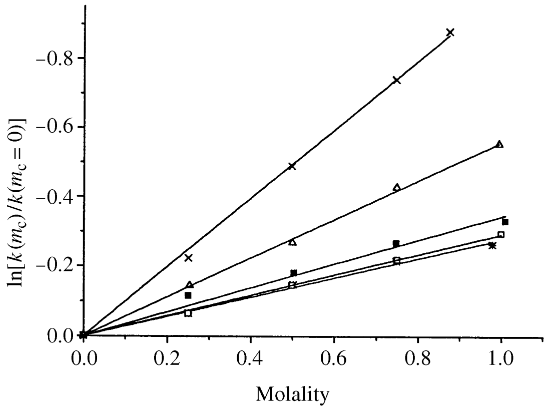


Fig. 1 Medium effects on the pseudo-first-order rate constant for hydrolysis of **1** at 25 °C, plotted as $\ln[k_{(m_c)}/k_{(m_c=0)}]$ *versus* the molality of ammonium bromide, *; tetramethylammonium bromide, □; tetraethylammonium bromide, ■; tetrapropylammonium bromide, △ and tetrabutylammonium bromide, x

The difference in hydrophobicity between the initial state and the transition state is responsible for the marked changes in rate constants which are observed when hydrophobic cosolutes are added. Hydrophobic cosolutes stabilise the initial state to a larger extent than the transition state which increases the Gibbs energy of activation leading to a decrease in rate constant.

In the present study we investigated the effect of tetraalkylammonium, alkylammonium, alkyldimethylammonium and alkyltrimethylammonium bromides on the hydrolysis of **1**, up to a concentration of 1 molal of added cosolute, except for hexylammonium and hexyldimethylammonium bromide. The effects of the latter two cosolutes were measured up to a limit of 0.5 molal, because they showed evidence of aggregation above 0.5 molal. All cosolutes retard the hydrolysis of **1**, as expressed in negative G(C). These retardations are dominated by stabilisation of the initial state of the hydrolysis by the cosolutes through hydrophobic interactions. These alkylammonium solutes can be viewed[21,22] as hydrophobic species. There is convincing evidence that even tetramethylammonium chloride is hydrophobic, according to a neutron diffraction study reported by Finney *et al.*[23]

Medium effects on the neutral hydrolysis of **1**, expressed as the dependence of $\ln[k_{(m_c)}/k_{(m_c=0)}]$ on the molality of added tetraalkylammonium bromides are shown in Fig. 1. The tetraalkylammonium bromides produced excellent linear correlations between $\ln[k_{(m_c)}/k_{(m_c=0)}]$ and the molality of added salt, indicating pairwise (*i.e.* 1 : 1) interactions between cosolute and substrate. G(C) values were obtained from the slopes of these plots; Table 1.

In terms of the SWAG approach, each functional group in one molecule interacts with every functional group in the other molecule. Each of these interactions has a characteristic effect on the pairwise Gibbs energy interaction parameter, G(C). In the case of alkyl-substituted ammonium bromides, G(C) is composed of contributions due to n methylene moieties in the alkyl chain, the ammonium ion and the bromide ion. In the case of perfect additivity, the increment in G(C) of the cosolutes depends solely on the difference in the number of CH_2 groups. In Fig. 2, G(C) is plotted *versus* the number of CH_2 groups (the

---

† Supplementary data are available (Suppl. No. 57211) from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1.

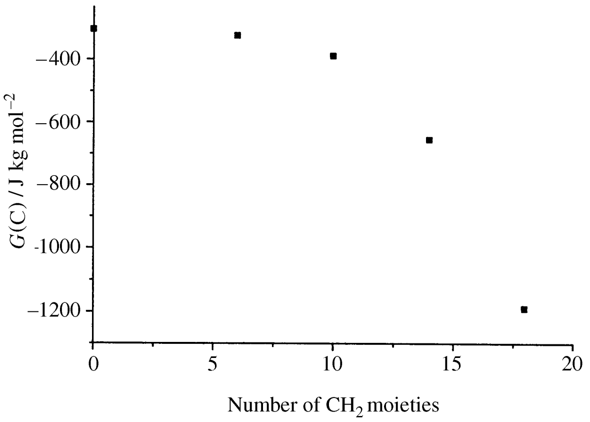


Fig. 2 Medium effects of tetra-alkylammonium bromides on the hydrolysis of **1** at 25 °C. Plot of G(C) *versus* number of CH_2 moieties.

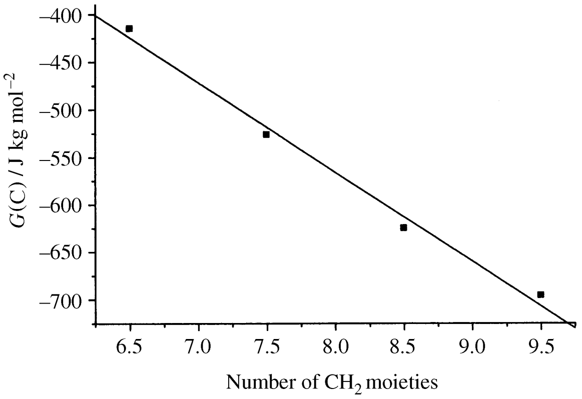


Fig. 3 Medium effects of alkyldimethylammonium bromides on the hydrolysis of **1** at 25 °C. Plot of G(C) *versus* number of CH_2 moieties.

contribution of a CH_3 group equals the contribution of 1.5 CH_2 groups and the contribution of three CH groups).

Almost no effect on the G(C) value is observed when the alkyl chains were extended from zero to two carbon atoms per chain; *i.e.* from ammonium bromide to tetraethylammonium bromide. Hence these groups are not available for hydrophobic interaction with the initial state of the hydrolysis reaction. We contend that this is due to the hydrophilic hydration sphere of the ammonium headgroup, which apparently extends to carbon atom three in the alkyl chain. The influence of ionic hydration shells on the hydrophobicity of nearby methylene groups has also been found in kinetic studies with sodium alkylsulfates,[11] alkylpyrrolidinones[10] and α-amino acids[24] as cosolutes. Gianni *et al.*[25] reviewed partial molal volumes of organic electrolytes at infinite dilution through a simple additivity scheme from which they concluded that the region of influence of a polar group does not extend beyond the β carbon atom. Our results show that outside the hydrophilic hydration sphere additivity is observed for alkyl groups of alkylammonium bromides, $G(CH_2) = -94$ J kg mol^{-2}.

Remarkably, ammonium bromide has a rate retarding effect on the neutral hydrolysis of **1**, $G(C) = -307 \pm 7$ J kg mol^{-2}, despite the absence of hydrophobic groups. One would anticipate an increase in rate due to a stabilisation of the transition state by this primarily ionic solute. However, we observed previously that ionic groups can have a retarding effect on the hydrolysis of **1**. In the case of sodium alkylsulfates,[11] $G(OSO_3^-)$ is approximately −600 J kg mol^{-2}. Recently, Berendsen *et al.*[15] calculated the proton transfer rate constant of the rate determining step in the water-catalysed hydrolysis of a carboxylic ester, *p*-methoxyphenyl dichloroacetate, by means of molecular dynamics (MD) simulations and density matrix evolution (DME). The water-catalysed hydrolysis of this substrate proceeds *via* the same mechanism[26,27] as the water-catalysed hydrolysis of **1**. Berendsen *et al.*[15] observed that only a few of the many possible water orientations which lead to reaction can account for the experimental rate constant. We suggest that the strict orientational requirements for the water molecules in the activated complex are further reduced when ammonium bromide is added as a cosolute. Ammonium bromide is extensively hydrated mainly through hydrogen bonding to the four polarised N–H groups, and competes with the transition state for water molecules. The even larger negative G(C) for sodium alkylsulfates[11] might also be rationalised on the basis of electrostriction. In anionic sulfates the charge is less shielded and will have a larger influence on the 3D hydrogen-bond network of water than the cationic ammonium bromides.

Table 2 Pairwise Gibbs energy interaction parameters for alkylammonium bromides

R	G(C)/J kg mol^{-2}
Propyl	−471 (±26)
Butyl	−486 (±4)
Pentyl	−631 (±6)
Hexyl	−735 (±7)

Table 3 Pairwise Gibbs energy interaction parameters for alkyldimethylammonium bromides

R	G(C)/J kg mol^{-2}
Propyl	−415 (±8)
Butyl	−527 (±16)
Pentyl	−625 (±10)
Hexyl	−696 (±8)

Table 4 Pairwise Gibbs energy interaction parameters for alkyltrimethylammonium bromides

R	G(C)/J kg mol^{-2}
Methyl	−324 (±4)
Propyl	−436 (±6)
Butyl	−512 (±14)
Pentyl	−575 (±13)
Hexyl	−782 (±6)

In Tables 2, 3 and 4, G(C) values are listed for alkylammonium bromides, alkyldimethylammonium bromides and alkyltrimethylammonium bromides, respectively. As an example, G(C) values for alkyldimethylammonium bromide are plotted *versus* the number of CH_2 moieties in Fig. 3.

Good additivity is obtained for alkylammonium and alkyldimethylammonium bromides, resulting in the same $G(CH_2)$ value of −94 J kg mol^{-2}. Satisfactory additivity is found for alkyltrimethylammonium bromides, resulting in a $G(CH_2)$ value of −110 J kg mol^{-2}. These values are in good agreement with G(C) values of monohydric alcohols,[7] $G(CH_2) = -90$ J kg mol^{-2}.

As argued above, only methylene moieties outside the hydration sphere of the ionic group (*i.e.* further than two carbon atoms away from the ionic group) are available for hydrophobic interactions with the substrate. Therefore, when the alkyldimethylammonium bromide series is considered, the G(C) value for the $CH_2CH_2N^+(H)Me_2\,Br^-$ group should be similar to the G(C) value for ammonium bromide. We obtain this value by extrapolation of the linear correlation in Fig. 3 to $n(CH_2) = 5$ (Fig. 4).

By extrapolation $G(CH_2CH_2N^+(H)Me_2)$ equals −282 J kg mol^{-2}. Extrapolation of the alkylammonium and alkyltrimethylammonium bromides gives a $G(CH_2CH_2N^+H_3)$ value of −300 J kg mol^{-2} and a $G(CH_2CH_2N^+Me_3)$ value of −245 J kg mol^{-2}, respectively. These are in satisfactory agreement with the

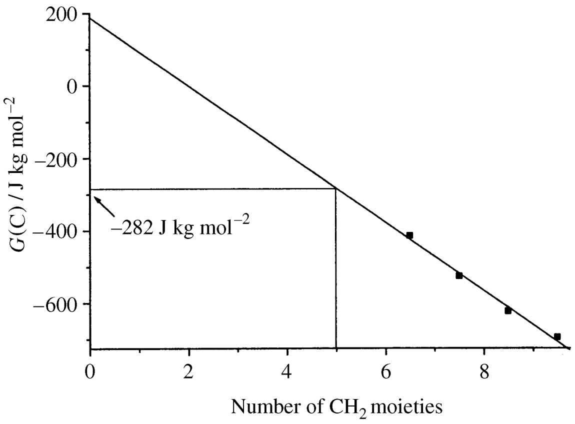


Fig. 4 Medium effects of alkyldimethylammonium bromides on the hydrolysis of **1** at 25 °C. Plot of *G*(C) *versus* number of CH_2 moieties. Extrapolation according to the SWAG approach (five CH_2 moieties = $CH_2CH_2N(H)Me_2$).

experimental *G*(C) value for ammonium bromide of −307 ± 7 J kg mol^{-2}, which indicates again that hydrophobic groups in close proximity to a polar group are masked for hydrophobic interactions with the substrate. The deviation of the *G*(C) value of −245 J kg mol^{-2} for alkyltrimethylammonium bromides is due to less pronounced additivity.

Conclusions

In the present study, the effects of tetraalkylammonium, alkylammonium, alkyldimethylammonium and alkyltrimethylammonium bromides on rate of the neutral hydrolysis of 1-benzoyl-1,2,4-triazole have been measured. All cosolutes retard the hydrolysis reaction which is interpreted as a dominant stabilisation of the hydrophobic initial state through hydrophobic interactions with the cosolute. The kinetic results are expressed in pairwise Gibbs energy interaction parameters [*G*(C)]. Analysis of these *G*(C) values suggests that the ionic hydration shell of the ammonium group is incompatible with the hydration shell of the alkyl groups attached to it. The ionic hydration shell dominates the medium effect up to two carbon atoms; *i.e.* the effect of the alkyl groups is only observed for alkyl groups with more than two carbon atoms. For those methylene groups outside the ionic hydration sphere, additivity is observed.

The results presented here provide an important contribution to the rank of understanding the hydration of polyfunctional molecules and their noncovalent interactions with solutes in aqueous solution.

References

1 M. J. Blandamer, J. Burgess and J. B. F. N. Engberts, *Chem. Soc. Rev.*, 1986, **14**, 237.
2 J. B. F. N. Engberts, *Water. A Comprehensive Treatise*, ed. F. Franks, Plenum, New York, 1979, vol. 6, ch. 4.
3 H. A. Scherega, *Acc. Chem. Res.*, 1979, **12**, 7.
4 J. H. Fendler, *Membrane Mimetic Chemistry*, Wiley, New York, 1982.
5 H. Wennerström and B. Lindman, *Phys. Rep.*, 1979, **52**, 1.
6 W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem.*, *Int. Ed. Engl.*, 1993, **32**, 1545.
7 W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1990, **112**, 1197.
8 J. J. Savage and R. H. Wood, *J. Solution Chem.*, 1976, **10**, 733.
9 R. P. V. Kerstholt, M. J. Blandamer and J. B. F. N. Engberts, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 49.
10 J. Apperloo, M. J. Blandamer and J. B. F. N. Engberts, unpublished results.
11 W. H. Noordman, W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts, *J. Org. Chem.*, 1993, **58**, 7111.
12 S. A. Galema, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1990, **112**, 9665.
13 L. Streefland, M. J. Blandamer and J. B. F. N. Engberts, *J. Chem. Soc.*, *Perkin Trans. 2*, in the press.
14 L. Streefland, M. J. Blandamer and J. B. F. N. Engberts, *J. Phys. Chem.*, 1995, **99**, 5769.
15 M. F. Lensink, J. Mavri and H. J. C. Berendsen, unpublished results.
16 W. Karzijn and J. B. F. N. Engberts, *Tetrahedron Lett.*, 1978, 1787.
17 S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, 1971, **36**, 829.
18 W. Blokzijl, J. Jager, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1986, **108**, 6411.
19 W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer, *J. Phys. Chem.*, 1987, **91**, 6022.
20 H. J. Mooij, J. B. F. N. Engberts and M. Charton, *Recl. Trav. Chim. Pays Bas*, 1988, **107**, 185.
21 J. Y. Huot and C. Jolicoeur, *The Chemical Physics of Solvation, Part A*, ed. R. R. Dogonadze, Elsevier, New York, 1985.
22 G. Jakli and L. Marko, *Models Chem.*, 1995, **132**, 225.
23 J. L. Finney, A. K. Soper and J. Z. Turner, *Pure Appl. Chem.*, 1993, **65**, 2521.
24 L. Streefland, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1996, **118**, 9539.
25 P. Gianni and L. Lepori, *J. Solution Chem.*,1996, **25**, 1.
26 J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1974, **96**, 1231.
27 J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1975, **97**, 1563.

Paper 6/06693D
Received 30*th September* 1996
Accepted 19*th November* 1996