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MOLECULAR INTERACTIONS
IN HYDROGEN-BONDING SOLVENTS

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SVMMARIVM — De structuralibus effectibus ligaminis hidrogenii inter-molecularis in aqua et in glicole ethylenico disputat Auctor. Effectus in micellas detergentium efficiunt ut coniici possint similitudines inter eas materias. Glycolis ethylenici structuras ligaminibus hydrogenicis firmatas esse, confirmat eius glycolis analysis.

The role of hydrogen bonding in water

In terms of its molecular structure, water is one of the simplest substances. Nevertheless, many of its physical properties, especially those relating to its behavior as a solvent, differ more or less from the properties of most other simple liquids. These properties extend from simple ones, such as p-V-T behavior, to the thermodynamics of solutions and to interactions in complex biological systems [1-3]. It is generally recognized that the unusual physical properties of water can

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be ascribed to its ability to be linked by several relatively strong hydrogen bonds to neighboring molecules. Each water molecule can form four such bonds (fig. 1), in two of which it acts as a proton donor, and in two as a proton acceptor. This topological feature allows the build-up of an unlimited three-dimensional hydrogen-bonded network, extending beyond the group of molecules shown in fig. 1, and potentially form-
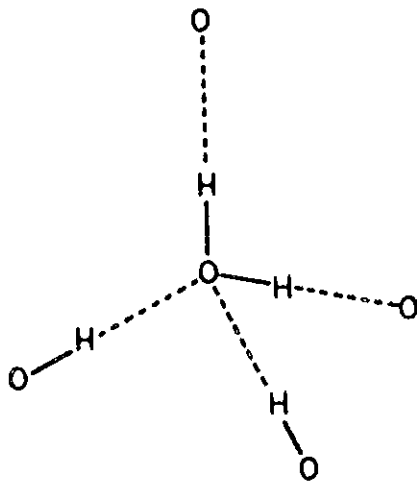

FIG. 1 — Hydrogen-bonded water molecule. The oxygens of the four neighboring molecules are shown with which hydrogen bonds are formed.

ing a space-filling structure. This is illustrated by the structure of ordinary ice (fig. 2) as well as of its many other crystalline polymorphs [4]. It is also a generally accepted concept that liquid water is "structured", i.e., that hydrogen bonding exists to a considerable extent in the liquid as well. However, the structure is not perfect: a certain fraction of the hydrogen bonds may be broken, or the bonds are distorted
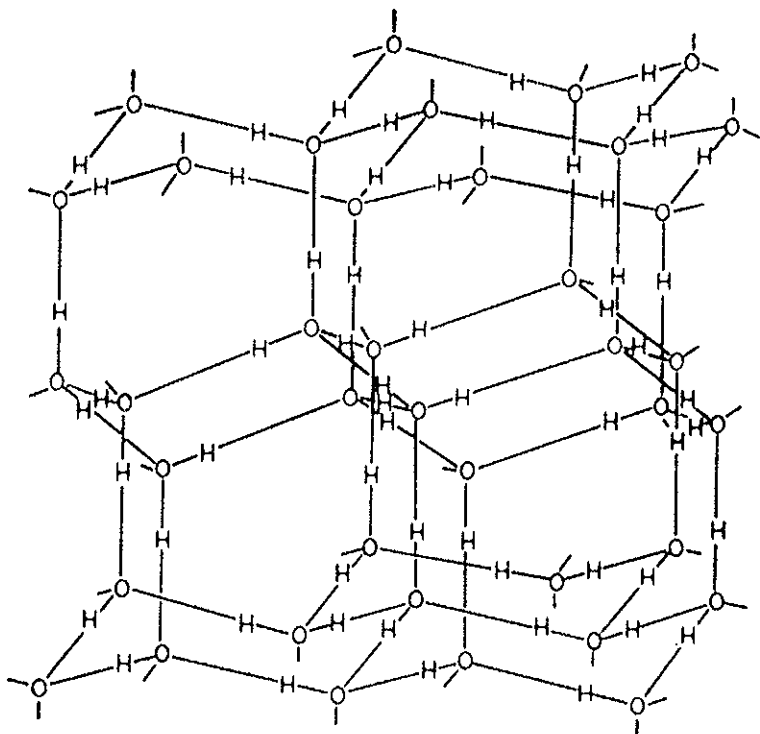
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FIG. 2 — The arrangements of water molecules in the crystal of ordinary ice (ice-I).

to various extent, or as is most probable, both kinds of disruptions of the crystalline structure occur. In recent years, a large number of theoretical models has been proposed, to account for the properties of liquid water and of aqueous solutions. Several detailed critical reviews of these models are available [1-3, 5]. The great variety of the possible models can be considered as a consequence of the present limitations of the state of art of studies in the liquid state. In setting up a useful model for the liquid, drastic conceptual and mathematical approximations have to be made, in order

to render the model tractable. As a result, in each of the models, certain aspects of the properties of water receive emphasis, at the expense of disagreement with other properties. Broadly speaking, most models for water can be classed into two large groups, referred to as mixture and continuum models (fig. 3). In the "mixture" models, emphasis is placed on differences between molecules with hydrogen bonds formed and those with these bonds broken ([1]), and usually no formal consideration is given to various extents of distortion (such as hydrogen bond stretching and bending) [2, 6]. By contrast, in a continuum model, such distortions are emphasized, and the presence of qualitatively different molecular species is denied [7]. Presumably, the true situation is more complex than that represented by any of these models. Possibly, several of the proposed structures might by present together in the liquid.

While the structure and behavior of water is not completely understood at present, the concepts summarized above could be extended in many cases to a qualitative or quantitative explanation of the behavior of aqueous solutions [2, 3]. In several cases, it was shown that seemingly anomalous thermodynamic and other properties of solutions can be interpreted in terms of changes in the structure of water under the influence of solutes. This is true in particular of solutions of nonpolar substances or substances carrying nonpolar groups [8]. The associating tendency of such groups, usually termed « hydrophobic interaction », has been explained in terms of such structural changes [9-11].

Hydrogen bonding and structure in nonaqueous liquids

Since the molecules of many organic liquids contain functional groups (OH, NH, COOH, etc.) which can form

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([1]) It has to be remembered, though, that water molecules between which no hydrogen bonds are formed can still interact strongly in the liquid.

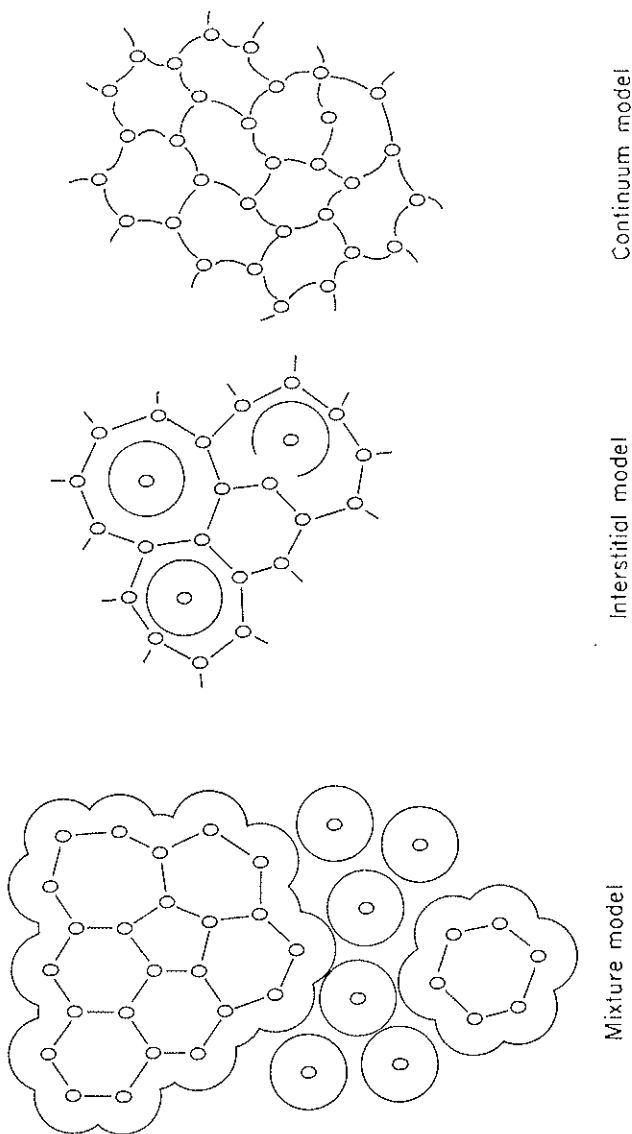Mixture model   Interstitial model   Continuum model

FIG. 3 — Schematic drawing representing characteristic features of different types of theoretical models for the structure of liquid water. "Mixture models" are characterized by the postulated presence of hydrogen-bonded aggregates, possibly of various sizes, as well as non-hydrogen-bonded molecules. In "interstitial models", the molecules of the latter type are assumed to occupy cavities in a network structure formed by hydrogen-bonded molecules. In "continuum models", it is assumed that hydrogen bonds are distorted to continuously varying extents.

hydrogen bonds, the question arises whether of these liquids posses "structure" in a sense similar to that found in water. It is well known that many such substances associate in solution or in the liquid state. Monohydric alcohols are known to contain aggregates of the following type [12]:

$$O\text{-}H \ldots O\text{-}H \ldots OH \ldots OH$$
$$\quad| \qquad\quad | \qquad\quad | \qquad\quad |$$
$$\quad R \qquad\quad R \qquad\quad R \qquad\quad R$$
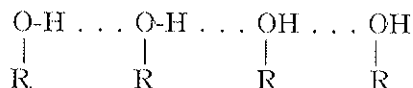
where R is an alkyl group. However, since all protons of the molecules shown are used up in these structures (except that of the terminal OH), no branched structures can form, but only chains or closed rings. Thus, while the behavior of alcohols is rather different from that of simple, nonassociating liquids [12], no unusual properties ascribable to three-dimensional intermolecular structures are to be expected, and none are found indeed.

The situation is different with slightly more complex molecules such as ethylene glycol. In this substance, due to the presence of two OH-groups per molecule, one might conceive the formation of a three-dimensional network (fig. 4b). Thus, a priori, physical and solvent properties intermediate between those of water and the monohydric alcohols are to be expected. A simple consideration of some physical properties is suggestive. In water, the unusually high melting and boiling points, as well as the high dielectric constant and high heat capacity have often been interpreted as evidence for hydrogen-bonded structure. Comparison of these properties for 1-propanol and ethylene glycol (Table 1), two alcohols with almost the same molecular weight, indicates that the values of the first three properties are indeed considerably higher for ethylene glycol. On the other hand, the specific heat does not appear to be abnormal, on first sight. Thus no conclusive deductions may be made on the basis of such a naive comparison of the physical properties.
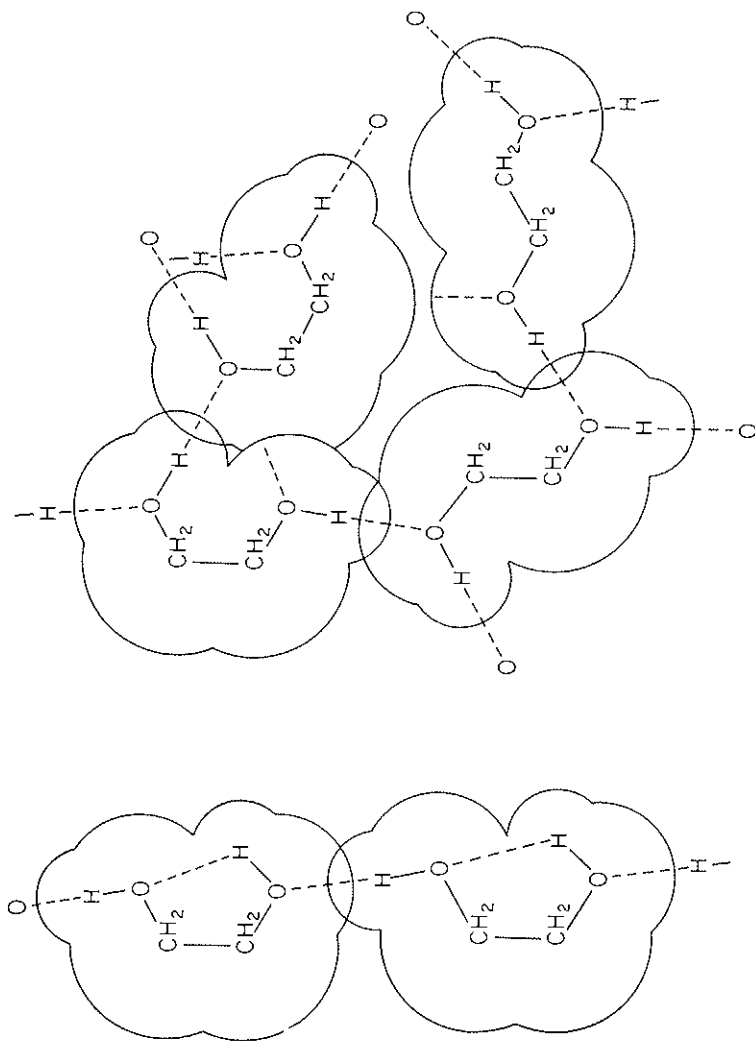
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FIG. 4 — Schematic drawing of possible intermolecularly hydrogen-bonded structures in liquid ethylene glycol. (a) If a bent intramolecular hydrogen bond is formed, only linear aggregates are possible. (b) In the absence of the intramolecular bond, complex three-dimensional structures may be formed.

TABLE I — *Comparison of Some Physical Properties for Hydrogen-Bonded Liquids* (*).

Property	Water	Ethylene Glycol	1-Propanol
Molecular weight	18.016	62.07	60.09
Melting point (°C)	0.0	− 13	− 126.5
Boiling point (°C)	100.0	198.0	97.0
Density (g/cm³) at 25°	1.00	1.11	0.80
Dielectric constant at 25°	78	38	20
Specific heat (cal/deg · g)	1.0	0.6	0.6
Heat of fusion (kcal/mol)	1.44	2.68	1.24
Heat of vaporization (kcal/mol)	9.71	11.8	9.89

(*) Based on compilations in the Handbook of Chemistry and Physics, Chemical Rubber Co., 50th edition, 1969.

Behavior as a solvent is much more instructive. It was shown recently [13, 14] that micelle formation, which involves the mutual association of nonpolar groups (see below), can occur in ethylene glycol as well as in several other pure liquids whose molecules have two or more hydrogen-bonding functional groups, but not in the monohydric alcohols. On the basis of thermodynamic evidence, it is also proposed [14, 15] that association in the former solvents is accompanied by structural changes in the solvent and thus can be described as due to "solvophobic interactions". Similarities between water and ethylene glycol are also suggested by studies of protein denaturation: ethylene glycol is a much weaker denaturant than are monohydric alcohols [16].

The rest of this communication is devoted to a summary of various lines of recent research in this laboratory, aimed at the elucidation of the properties of ethylene glycol as a hydrogen-bonding solvent.

Formation of detergent micelles in mixed aqueous solutions [2]

Detergents are molecules with two functional moieties: a nonpolar, hydrocarbon tail and a polar, charged or uncharged, head [20]. Above a well-defined concentration, the critical micelle concentration (cmc), the molecules associate into aggregates containing a large number of molecules. These aggregates are called micelles (fig. 5). Very little oligomer (dimer) is present if any [20]. Aggregation is driven by the hydrophobic interaction between the nonpolar tails [3], while the aggregate is kept in solution by the favorable solvent-solute interactions of the polar head-groups. Thus micellar association is a sensitive tool for the investigation of changes in the properties of the solvent.

We studied the behavior of several nonionic detergents in mixed aqueous solutions. The detergent molecules were alkylphenoxy (polyethoxy) ethanols of the following structure:

$$C_m\ H_{2m+1} \bigcirc (OC_2\ H_4)_n\ OH$$

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[2] Detailed description of these studies is published elsewhere [17, 19]. Preliminary reports have been presented at the 157th and the 164th National Meetings of the American Chemical Society, Minneapolis, Minn., April 1969 and New York, N.Y., September 1972, respectively, and at the IV Congresso Nazionale dell'Associazione Italiana di Chimica Fisica, Florence, Dec. 1969.

[3] This is evidenced by the highly positive entropy of micelle formation [18, 20], in contrast to the large negative entropy of association in ideal systems.
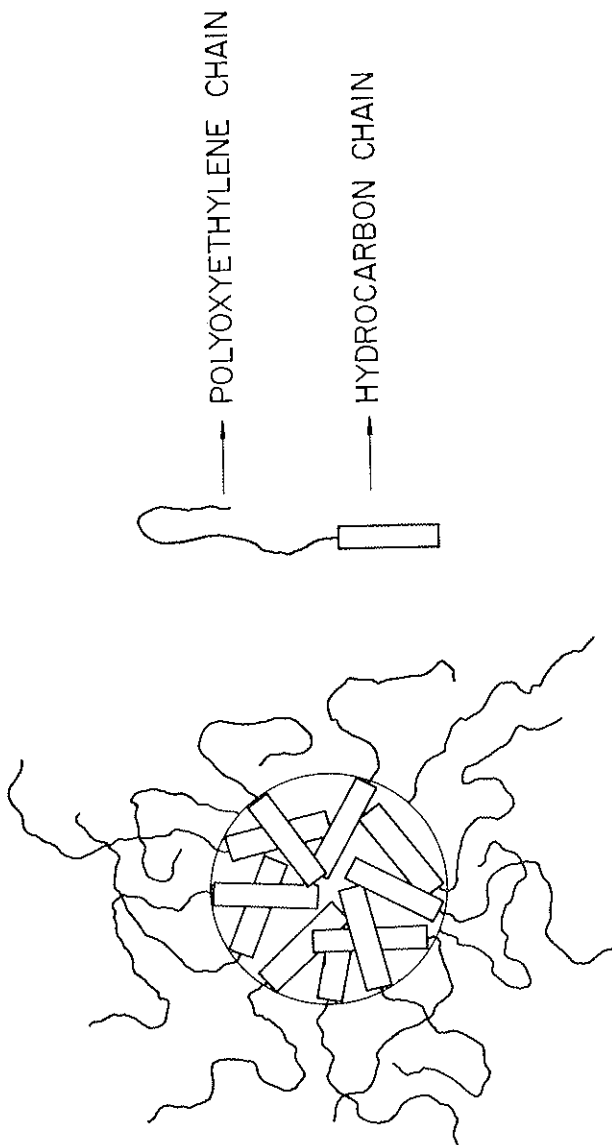
10

POLYOXYETHYLENE CHAIN

HYDROCARBON CHAIN

FIG. 5 — Schematic representation of the structure of micelles formed by the detergents studied in the present work. Rectangles indicate the nonpolar alkylphenoxy groups, forming the hydrophobic core of the micelle. The thin curved lines represent the polyethoxy chains, exposed in part to solvent.

where the alkyl tail was usually a tert-octyl group ($m = 8$), and n ranged between 10 and 30. The presence of a phenoxy group in the molecule enabled us to follow micelle formation by means of a simple spectrophotometric technique. The near UV absorption spectrum of the aromatic group depends on the solvent medium. Thus the spectrum is altered when the monomeric detergent molecules associate into micelles, as described elsewhere [17]. The cmc can be defined as the onset of this change when the concentration of the detergent is raised (fig. 6).

In aqueous solution, the cmc is low. Addition of any organic solvent component raises it strongly. However, in ethylene glycol, this increase is moderate, and seems to conti-
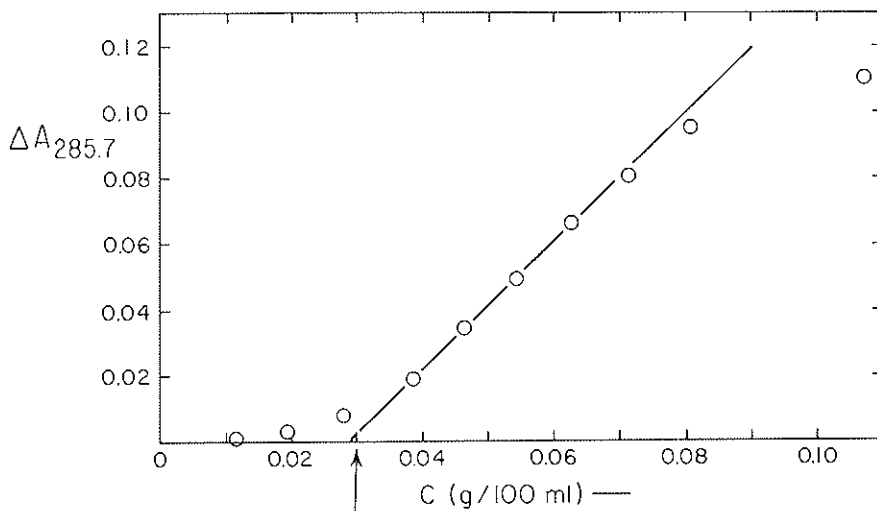

FIG. 6 — Representative example of the uv difference absorption curve used to determine critical micelle concentrations [16]. Difference absorption at 285.7 nm is plotted against detergent concentration. The cmc is shown by the arrow, as obtained from the extrapolated straight line. The circles are the experimental points for a solution of the detergent with $m = 9$, $n = 30$ in a 10% ethylene glycol-water mixture at 45°. (Redrawn after ref. [16]).

nue in a fairly uniform manner over a wide composition range (fig. 7). While the entropy of micelle formation is less positive than in water, it remains much higher than the ideal value [18].

In contrast, the cmc rises much more sharply in water-alkanol mixtures (fig. 7), and no micelles are formed above a certain concentration range [19]. The entropy of micelle formation decreases and becomes negative with an increase of the alkyl chain length of the alcohol. The lack of micelle formation can be explained by the weakening of the hydrophobic interactions between the hydrocarbon tails, due to (a) the increase in the nonpolar character of the solvent when the alkyl chains of the alcohols are present, and (b) the breakdown of water structure as a result of the presence of the second solvent component. The changes in the thermodynamic parameters also reflect these factors [19].

The experiments summarized here represent only indirect evidence for the role of hydrogen-bonding structural effects in the solvent. Nevertheless the latter appear to be the most reasonable interpretation.

Conformational analysis of ethylene glycol in solution (⁴)

While it is reasonable to assume the presence of three-dimensional structures in ethylene glycol, as discussed above (fig. 4b), the existence of such structures cannot be taken a priori as granted. In the ethylene glycol molecule, a weak intramolecular hydrogen bond can form. If such a bond is formed, the molecule is effectively monofunctional, as far as intermolecular hydrogen bonding is concerned; thus it should behave very similarly to the monohydric alcohols (fig. 4a). A mixture of the two forms depicted in fig. 4, with and
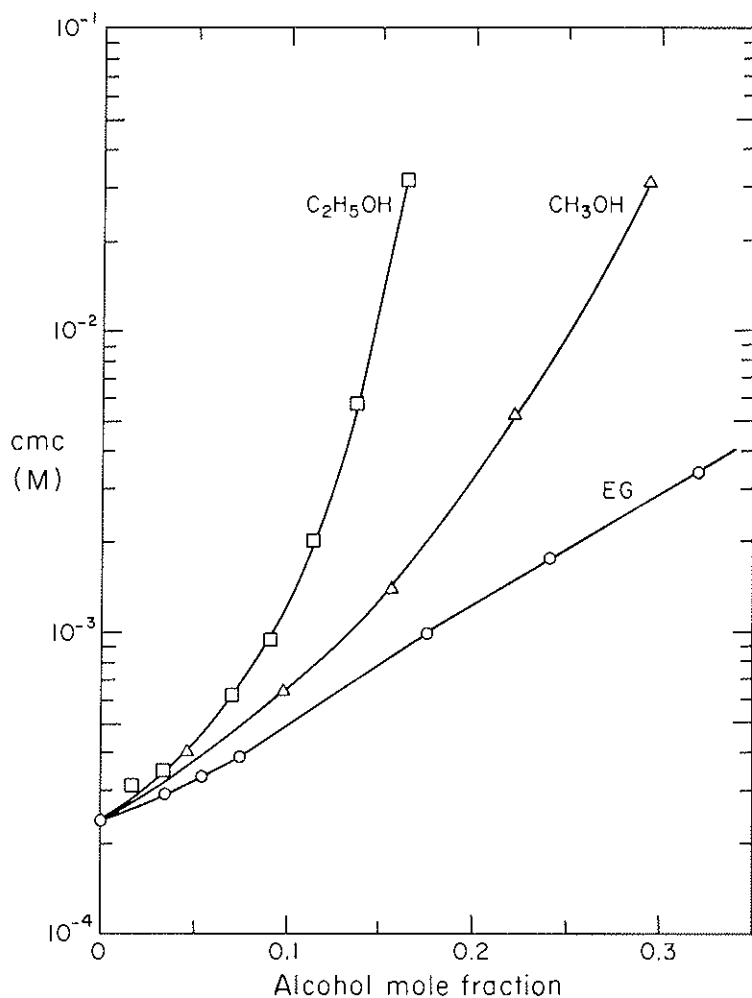
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FIG. 7 — A comparison of the critical micelle concentrations of Triton X-100 ($m = 8$, $n = 9$-10) in aqueous mixtures of various alcohols at 35°. (Cf. ref. [18]).

without the intramolecular hydrogen bond, would still allow the possible formation of three-dimensional networks, as long as a nonnegligible fraction of molecules exists without this bond. Determination of the distribution of ethylene glycol molecules among various possible conformational isomers was therefore very important for the description of its liquid structure. We undertoook a theoretical conformational analysis of ethylene glycol as well as two of its derivatives, methoxyethanol and dimethoxyethane, in which one or both of the OH groups are replaced by an OCH₃ group, thus reducing or eliminating the hydrogen bonding ability of the molecule [21]. This work was carried out in parallel with a conformational study of the same three molecules in solution and the liquid state by means of nuclear magnetic resonance [22].

In ethylene glycol (as well as the two derivatives mentioned), several rotational isomers (rotamers) exist, due to the possibility of internal rotation about three single covalent bonds (fig. 8). Rotation around these bonds is not completely
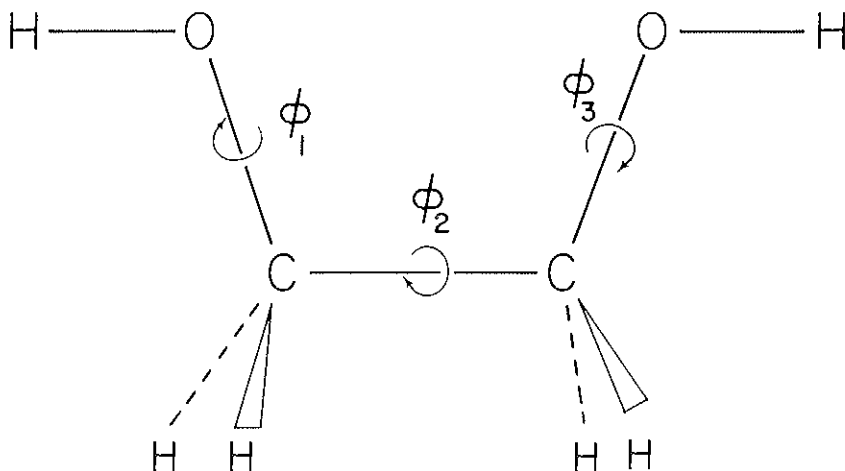

FIG. 8 — Structural formula of the ethylene glycol molecule, indicating the angles around which internal rotation occurs. The dihedral angles $\Phi_1 = \Phi_3 = 180°$ and $\Phi_2 = 0°$. (Redrawn after ref. [21]).

free. Due to the presence of energy barriers [23], three
stable conformations may occur with respect to rotation about
each of these bonds, corresponding to the "staggered" positions
of the substituents (fig. 9). In theory, the molecule might
have 27 rotamers. Actually, some of these differ only with
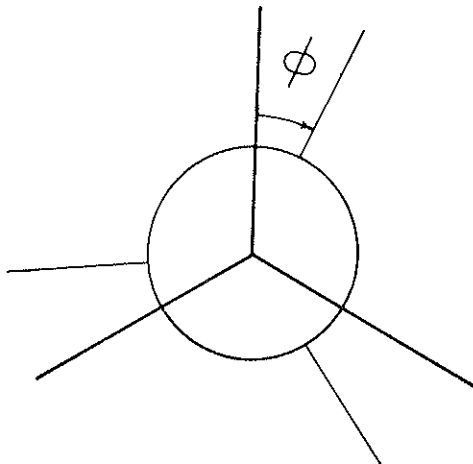respect to symmetry operations, and therefore are not dif-

Fig. 9 — Definition of a dihedral angle of internal rotation on a Newman
projection diagram along the bond being rotated. $\Phi = 0°$ corresponds, by
definition, to the eclipsed (cis) position of the atoms used to define the
rotation (generally main-chain atoms). Stable conformations usually cor-
respond to staggered positions, i.e., angles near the values $\Phi = 60$, 180
or 300° (also denoted as g^-, t, and g^+, respectively).

ferent molecular species. Some are not stable, due to unfa-
vorable intramolecular nonbonded interactions. Thus the
actual number of different rotamers is 10 for ethylene glycol,
and 12 and 9 for its two derivatives mentioned, respectively.
Of these, only a few possess an intramolecular hydrogen bond
(3 in ethylene glycol and 2 in methoxyethanol). Using semi-

empirical energy functions [24], we computed the actual geometry and the potential energy (^{5}) of each rotamer (fig. 10). From this, the distribution of molecules between various observable conformations, as well as between internally hydrogen-bonded and nonbonded forms could be computed, as a function of temperature and of solvent dielectric constant. So far, the computations were carried out only for dilute solutions in noninteracting (non-hydrogen-bonding) solvents. Some of the results are summarized in Table II. The computed results agree well with experimental studies of dipole moment and the fractional extent of hydrogen bonding (obtained from infrared spectra). Both properties depend very little on temperature. This was interpreted in the past [25-28] as evidence for the presence of only one conformation. However, our computations show that this observation is consistent with a distribution over many conformational states. Thus the detailed analysis carried out in this work is necessary for a correct interpretation of the experimental results, including the dependence of the conformational equilibria on dielectric constant. Analyses, applicable to simpler molecules [29], have to be amplified, to take into account the diversity of possible rotamers in these molecules. If this is done, the computed results are in good agreement with the conformational analysis based on nmr measurements, as shown elsewhere [22].

In terms of the present communication, the most significant result is the following: while a large fraction of the ethylene glycol molecules possesses the intramolecular hydrogen bond (Table II), sufficient numbers of molecules exist in the non-hydrogen-bonded conformations to allow for the possibility of three-dimensional structure formation, as postulated initially. The actual demonstration of the presence of

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(^{5}) The potential energy includes terms for various intramolecular interactions, as well as a first approximation term for interaction with the surrounding solvent medium [21].
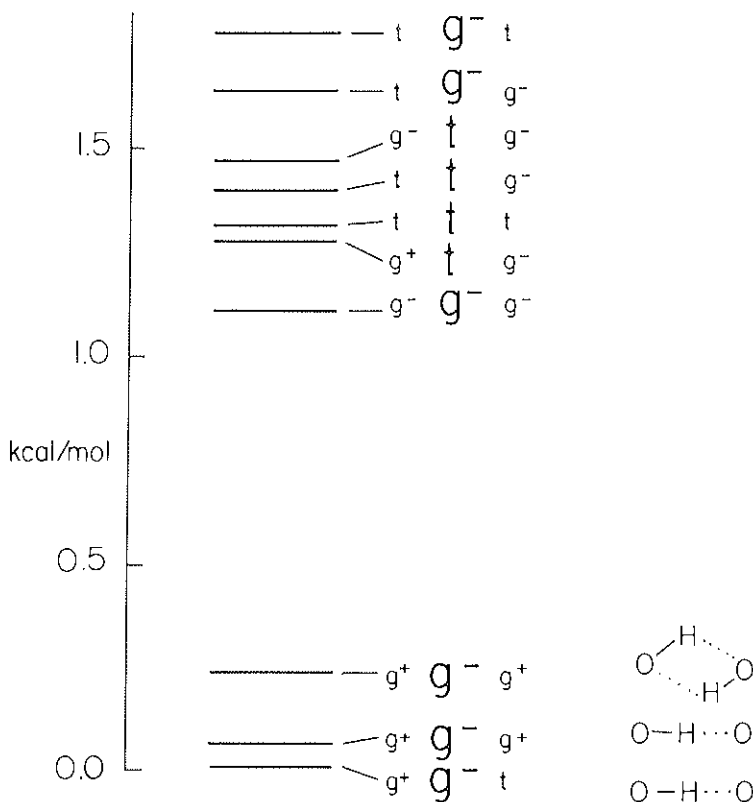
Energies of EG (gas) rotamers

FIG. 10 — Calculated energies of the various rotamers for the ethylene glycol molecule in the gas phase. The letters indicate the position around each of the rotatable bonds (cf. legend of fig. 9). The rotational state corresponding to Φ_2 is indicated with heavier letters. The existence of intramolecular hydrogen bonds in some of the rotamers is indicated in the last column. The energy scale is written with zero corresponding to the energy of the relatively most stable rotamer.

TABLE II — Computed Properties of Ethylene Glycol and its two Methyl Ethers, Related to Conformational Equilibria (*).

Substance	Phase	Temp. °C	n_t	n_g (NB)	n_g (HB)	f_H	μ_{calc} D	μ_{exp}(**) D
Ethylene glycol	gas	25	0.09	0.06	0.85	0.49	2.13	2.3 ± 0.1
	solution (†)	28	0.12	0.09	0.79	0.48	2.10	2.3 ± 0.1
Methoxyethanol	gas	25	0.11	0.11	0.78	0.78	1.63	
	solution (†)	28	0.14	0.18	0.68	0.68	1.65	
Dimethoxyethane	gas	25	0.43	0.57	—	—	1.03	
	solution (†)	28	0.39	0.61	—	—	1.05	

(*) Explanation of symbols used in the heading of the table: n_t = fraction of molecules in the *trans* conformation ($\Phi_2 = 180°$); n_g (NB) = fraction of molecules in the *gauche* conformation ($\Phi_2 = 60$ or $300°$) *without* an intramolecular hydrogen bond; n_g (HB) = same, *with* one or two intramolecular hydrogen bonds; f_H = fraction of hydrogen-bonded OH groups; μ = dipole moment.

(**) Refs. 25, 26.

(†) Computed for a dielectric constant $\varepsilon = 2$.

such structures as well as of their extent in the liquid has
to await the outcome of further experimental and theoretical
studies.

Conclusion

There is now evidence that hydrogen bonding can play
an important role in determining solvent properties in several
ways, besides direct solvent-solvent and solvent-solute interac-
tions through the formation of hydrogen bonds. In some
cases solvent-solvent hydrogen bonding leads to the formation
of "solvent structure", which itself has a profound effect on
the properties of solutions. While this effect has been known
for many years in water, we propose that it may be of
importance in ethylene glycol and its mixtures with water
as well.

Acknowledgment

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