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# Importance of Structural Free Space to the Solvent Power of Water

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**Abstract:** The contribution of structural free space to the solvent power of water was examined by a systematic modification of the geometric factor. Gaps and holes, available to foreign molecule occupation, are thought to be filled at low concentrations (max. 1 %) of aliphatic alcohols. The effect upon solvency reached approximately 10 %, which suggests that spatial parameters affect solvent power. The results demonstrate the importance of solvent purity in the dissolution process.

According to the structural model of Eyring (1, 2) liquids represent highly disordered solids containing numerous vacancies and holes (Fig. 1). Under normal conditions each liquid exhibits approximately 3 % empty volume, while at the critical point the fraction of holes reaches 50 %. The vacancies are able to move at random; their formation requires about $10^{-20}$ J work each. In general, the holes of the perforated structure occupy the size of one or several liquid molecules. However, in this form the hole theory and the hole defects model are only applicable to non-polar liquids with low interaction energy of about $10^{-21}$ J (3). Definite numerical data are available for the free volume (hole volume) of several liquids (4, 5).

As far as polar liquids, such as water, are concerned, an "Orientation Defect Model" has been developed (6) on the basis of misorientation of hydrogen atoms. Accordingly, the properties of water could be described as a "Two-State-H-Bond Breaking Equilibrium" between OH-groups with and without hydrogen bondings (in short: Two-State Model). The orientation defects (Bjerrum-Defects) probably cause cluster limitations and cluster interfaces. At the border of ordered zones, however, structural holes may be formed even in the case of polar liquids (Fig. 1) (7). Thus, some authors (8) suggest that water also consists of a perforated structure characterized by holes.

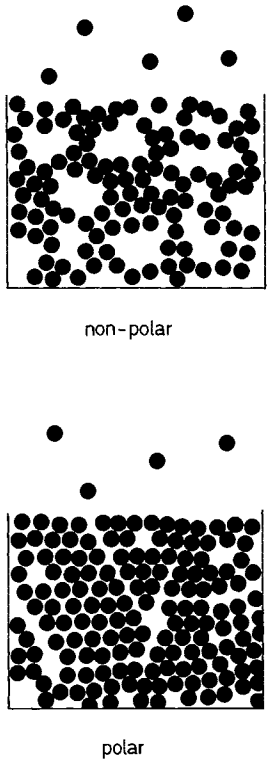


**Fig. 1** Scheme of hole defects in liquid structure.

In addition to the free space caused by disordering, the principle of ordering contributes considerably to the empty volume in solvent structure. The tetrahedral short-range order of water implies such a poor space economy that only 12 % of the volume is occupied by matter. The anomalies of water could be attributed to this low degree of space filling that arises from its highly ordered structure (9). Hence, there are different structural features forming non-occupied places and regions.

We examined the potential importance of structural free space to the solvency of water as a provocative new concept.

## Materials and Methods

The water system was modified with the addition of low aliphatic alcohols of relatively small molecular volumes: methanol, ethanol, *n*-propanol, 1-butanol, 2-butanol, and 2-methyl-2-propanol. As a test substance for the determination of solvent power the new lipophilic steroid dienogest (a peroral gestagen, 17α-cyanomethyl-17β-hydroxy-estra-4,9(10)-dien-3-on; $C_{20}H_{25}NO_2$; MW 311.4) was chosen.

The dissolution kinetics were investigated with a closed flow system using the paddle-principle. The dissolved drug concentration was measured spectrophotometrically at 315 nm.

## Results

With the use of low aliphatic alcohols as solvency-blocking agents, we found that the saturation concentration of dienogest in water as a function of alcohol content showed extreme values in each case (Fig. 2).

Remarkably, small amounts of the alcohols influenced the solubility of the steroid negatively, although they repre-

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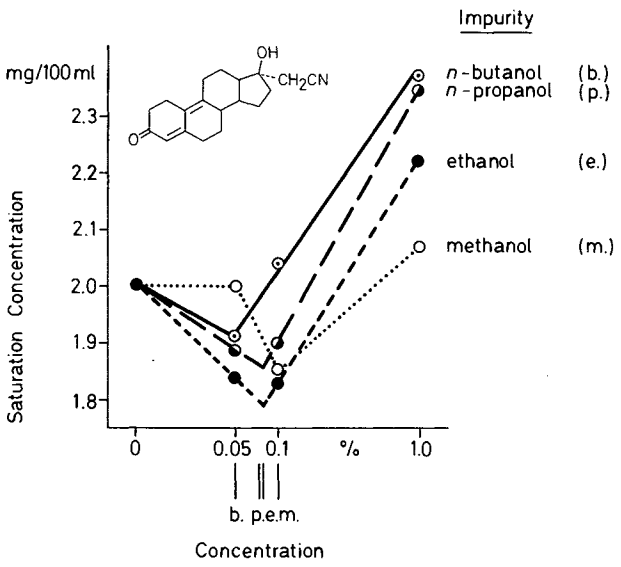
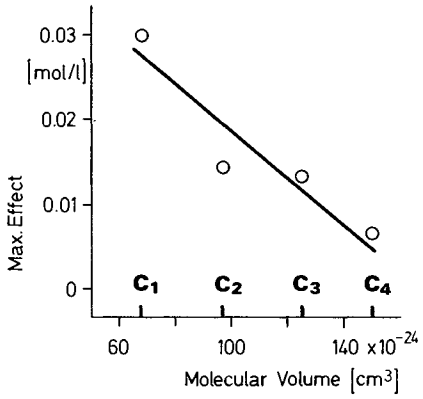



**Fig. 2** Effect of increasing concentrations of different aliphatic alcohols upon solvency of dienogest (saturation concentration).

sent good solvents for the drug. The decrease of water solvency continues with increasing alcohol content until a limiting value is reached. Above the threshold value, however, further amounts of alcohol functioned as cosolvents and increased the solvent power. (Individual drug concentration-time-curves are of lesser importance and were omitted here.) The point of minimum drug solubility was shifted toward higher alcohol concentrations with decreasing molecular size of the alcohol. An apparently linear correlation existed between alcohol concentration producing a maximal inhibitory effect and the molecular volume of the alcohols (Fig. 3). The figure also shows the number of alcohol molecules and their total volume necessary for the maximal reduction of dienogest solubility (presumably, the compensation of the free space available).

The isomeric butanols were compared for their effect on the drug's solubility; the three isomers showed equal inhibitory effects. Thus, variations in molecule shape are without influence on this phenomenon. The high motility of water molecules and the dynamics of empty regions are able to negate the geometric differences among the isomers. The molecular volumes of the three butanols are similar (4). The solubility of the steroid, however, differs considerably and increases in the order tertiary, primary, secondary butanol. Therefore, equal inhibitory effects demonstrate that the drug's solubility in the alcohols per se has no relevance. Only the molecular volume of the alcohol seems to be decisive.




| | Number of Molecules/l x $10^{22}$ | Total Volume [$cm^3$/l] |
|---|---|---|
| $C_1$ | 1.690 | 1.147 |
| $C_2$ | 1.205 | 1.169 |
| $C_3$ | 0.723 | 0.904 |
| $C_4$ | 0.319 | 0.479 |

**Fig. 3** Correlation between the maximal inhibitory effect of alcohols (see alcohol concentration at the solubility minimum of dienogest, Fig. 2.) and molecular volume of the alcohols. Number of molecules per liter and the associated total volume occupied by the four alcohols at their maximal inhibitory concentration are given in the table below.

The solvent power of water was reduced to 90 % by modulation with small amounts (below 1 %) of alcohols. Hence, the solvent capacity of water depends on such an effect to the extent of approximately 10 %. Inversely, the cosolvency of the alcohols is impaired by the water structure. At low concentrations the cosolvent properties disappear (perhaps, because the alcohol molecules get lost in the "pitfalls" of water structure).

## Discussion

The experiments designed to test the hypothesis that relates occupancy of free solvent space to solvency power were based upon the following concept:

1. If the solvency of water is influenced by the free structural space, a "competitive inhibition" of the dissolution process can occur by occupying the empty volume available (Fig. 4).
2. The inhibitory effect by an impurity should depend upon molecular size, and it should increase with increasing molecular volume of the filling substance. Saturation of the empty space should be reached by lower concentrations of large molecules than of small ones. A widening or rearrangement of the holes may occur during inclusion of foreign molecules, thereby allowing for the capture of even larger molecules.
3. The reduction of solvent power must also occur (up to a certain limit) if the added substance represents a cosolvent that dissolves a test compound better than does water. After saturation of the available free volume by cosolvent molecules the paradoxical negative effect should change into a positive one. Therefore, such additives are best suited to test the free space occupancy hypothesis.

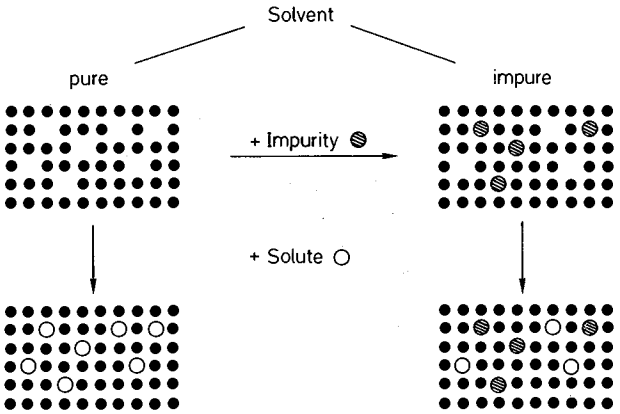



**Fig. 4** Principle of competitive inhibition of solvent power, on the basis of the space filling hypothesis. In this study, impurity refers to the alcohols and solute to dienogest.
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4. Only a finite part of the entire free structural volume may be available to occupation.

The presented results support a spatial mechanism in principle. There appears to be a competition between space filling cosolvent and dissolving molecules for "binding places", which depends upon the molecular size of the cosolvent (impurity). Therefore, the volume of the space filling agents probably is the crucial parameter. Molecules equal in their volume show the same intensity of the effect (example: isomeric butanols).

Interpretations other than solvent topology are possible, but there are further aspects that support our concept. The free space in the water structure makes it possible to dissolve apolar gases at about 0° C without entropy change (8). In this case a simple inclusion takes place occupying empty places without deformation of water order. When the temperature increases, the situation changes and the "interstitial solvent" becomes a "substitutional solvent". In other words: The free space (inclusion) effect decreases with rising temperature. The free volume of the tetrahedral arrangement disappears by breaking up its voluminous structure, comparable with the densification during melting of water.

X-ray studies of alcohol-water mixtures have shown that the foreign molecules at concentrations as high as 0.2 to 0.3 mole fractions (8) can enter the water "lattice" without changing the water structure. Within this concentration range the alcohol molecules can be accomodated by the free structural space. In the experiments presented here, the alcohol concentrations were far below these levels (Fig. 3). Therefore, an interstitial incorporation of the alcohols can be assumed.

We see that the dissolution of a substance may be caused by different simultaneous mechanisms. The spatial mechanism occurs when the molecular dimensions and the temperature conditions make it possible. We must differentiate between entropy-changing and entropy-indifferent mechanisms of the dissolution process. Compounds that enhance or weaken the structure of water may influence both types (10). Consequently even small amounts of impurities may alter the solvent power; the purity of the solvent gains special importance under this aspect.

The exceptional conditions of the free space effect (very small foreign molecules, low concentrations) prevented its previous consideration (11). Usually, binary polar solvent mixtures are assumed to change their solvency continuously according to the mixing ratio (12–16). The observed discontinuity (Fig. 2) contradicts the rule. Hence, solvency is not only determined by polarity and density of cohesion energy but also by a third, likely a geometrical, factor. The determination of intermolecular interaction by various methods and the calculation of polarity from constitutional parameters (11, 17) are insufficient to completely characterize a solvent.

Nevertheless, we should keep in mind that the existence of free space within a liquid structure represents an unproven concept that allows us to better understand water behavior. The present investigation does not provide a direct detection method of empty volume. However, since all dissolution theories are still under debate, although highly sophisticated techniques have been applied to elucidate the problem, the hypothetical character of the structural hole model is not exceptional; rather, it broadens the current experimental approach to understanding the dissolution process.

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