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Hertz H G & Zeidler M D. Kernmagnetische Relaxationszeitmessungen zur Frage der Hydratation unpolarer Gruppen in wässriger Lösung (NMR relaxation time measurements relative to nonpolar group hydration in aqueous solutions). *Ber. Bunsen. Ges. Phys. Chem.* 68:821-37, 1964.
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Measurements of ^1H and ^2H magnetic relaxation times show solvent water reorientation times in hydration spheres of alkyl group-containing solutes to be about two times longer than in pure water. Motion inside hydration cages is comparatively fast. Nonaqueous solvents are inactive regarding solvation. [The SC^1 ® indicates that this paper has been cited in over 140 publications.]

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Around 1958 at the Institut für Physikalische Chemie of the University of Hamburg, calorimetric work was done on aqueous solutions of substances that contained methyl groups. All of these solutes showed remarkably high partial molar heat capacities. The effect was ascribed to the iceberg formation around the inert methyl groups as described by Henry S. Frank and M.W. Evans.¹ According to this theory, inert solutes should produce an increase of water structure connected with an enhancement of H-bonding among the water molecules.

At about this time at the Hamburg laboratory we had just completed the construction of a high-resolution nuclear magnetic resonance (NMR) apparatus, one of the few that existed at the time. Almost the first application of this apparatus was to examine whether an increase of H-bonding truly occurred in the solutions in question. The indicator was the proton chemical shift: increased H-bonding should cause a downfield shift, whereas an upfield shift means breakage of H-bonds. Our

measurements showed that methyl-group containing solutes, contrary to expectations, caused an upfield shift.² Thus, H-bonded structure was broken, and Frank's hypothesis obviously was not correct. We were left with contradictory findings within the same laboratory!

In the following years we built a pulse apparatus to measure NMR relaxation times. Again one of the first applications of the new instrument was the investigation of aqueous solutions of molecules (polar or charged) with inert groups. The NMR relaxation time essentially measures the reorientation time of the molecule in the liquid. If a solute produces slower solvent motion, then this solvent becomes more solidlike, resulting in a structure reinforcement. The measurements we performed in 1962 and 1963 showed that in all cases where the solute molecule carries at least one methyl group, the water molecules undergo slower reorientational motion and that the retardation of the motion becomes stronger when more methyl or methylene groups are present. This was the object of the *Classic* paper. We were thus confronted with the surprising result that a positive dynamic structure effect exists, yet the proton chemical shift, as the most frequently used indicator for H-bonding, pointed toward structure breaking. For this effect, now known as hydrophobic hydration, no simple, obvious explanation exists. Later, at lower temperatures (around 0°C), downfield chemical shifts were discovered for certain solutes showing hydrophobic hydration, but this is not typical for this particular hydration effect.³ A number of other dynamic and structural⁴ studies confirmed structure increase of the solvent using viscosity, ^{17}O -relaxation, self-diffusion, and other measurements.⁵

It seems fairly obvious why our publication has been cited so frequently: because hydrophobic hydration and hydrophobic interaction play an important role in many systems of biochemical and biophysical interest.

1. Frank H S & Evans M W. Free volume and entropy in condensed systems. III. Entropy in binary liquid mixtures: partial molar entropy in dilute solutions; structure and thermodynamics in aqueous electrolytes. *J. Chem. Phys.* 13:507-32, 1945. (Cited 1,520 times since 1955.) [See also: Frank H S. Citation Classic. (Thackray A. comp.) *Contemporary classics in physical, chemical, and earth sciences*. Philadelphia: ISI Press, 1986. p. 151.]
2. Hertz H G & Spalthoff W. Über die chemische Verschiebung der Protonenresonanzen des Wassers in Elektrolytlösungen (Chemical shifts of proton resonances of water in electrolyte solutions). *Z. Elektrochem.* 63:1096-110, 1959. (Cited 95 times.)
3. Wen W-Y & Hertz H G. Chemical shifts of aqueous nonelectrolyte solutions. Influence of the polar and nonpolar groups on the water proton shifts at 0° . *J. Solut. Chem.* 1:17-37, 1972.
4. Hertz H G & Wen W-Y. The orientation of the water molecules in the hydration sphere of the tetraethylammonium ion. *Z. Phys. Chem. Neue Folge* 93:313-26, 1974.
5. Huot J-Y & Jolicoeur C. Hydrophobic effects in ionic hydration and interactions. (Dgonadze R R, Kálmán E, Kornyshev A A & Ulstrup J, eds.) *The chemical physics of solvation. Part A. Theory of solvation*. Amsterdam: Elsevier, 1985. p. 417-71.