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AQUEOUS AND IONIC SOLUTIONS: RELIABLE PROTON NUCLEAR RESONANCE SHIELDING VALUES BY INTERNAL REFERENCING.

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The application of nuclear spin resonance (n.s.r.) spectroscopy to diverse fields of study, e.g., classical organic structure determination and functional group identification, stereochemistry and conformational analysis, polymer chain configuration and stereoregularity, polypeptide and protein structure, physical-organic reactivity correlations, "solvent effects" and hydrogen bonding, has been greatly facilitated by the introduction of tetramethylsilane as a homogeneous "internal reference". The several important experimental advantages provided by this technique have been discussed at some length¹ and will not be reviewed here. A major disadvantage is the inapplicability to aqueous solutions. Formamide and certain other polar media fall in the same category.

In view of the importance of aqueous systems we have sought a new reference compound which would be soluble and stable over a wide pH range. A further requirement was that the group responsible for the sharp referencing line should not be part of the group ~~responsible for the sharp referencing line~~ conferring water-solubility. It was reasoned that in the immediate neighborhood of the solubilizing group there would be a considerable degree of

orientation of the solvent molecules, a situation in which magnetic anisotropy and electrostatic-field effects might produce highly specific shifts of the reference line. A final practical requirement was that the reference compound should not contribute additional bands to confuse the proton spectrum.

Our first studies were made with the silicon analogue of neopentyl alcohol, 2,2-dimethyl-2-silapropanol-1, $(\text{CH}_3)_3\text{SiCH}_2\text{OH}$, (termed SNA for convenience); it was found to be suitable for many studies, one of which, dealing with protein ~~in~~ spectra, is being reported elsewhere.² However, "SNA" was found to be unstable in acidic media, had rather poor solubility in water and entirely insufficient solubility in moderately concentrated salt solutions, and its CH_2 group gave an extra line near that for methanol. Thus "SNA" could not be considered satisfactory.

We have therefore designed a structure which we felt might circumvent such disadvantages without forfeiting the desirable features of "SNA". The compound chosen was an anion, namely, 2,2-dimethyl-2-silapentane-5-sulfonate, $(\text{CH}_3)_3\text{SiCH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$, (termed DSS), the sodium salt of which is prepared by addition of sodium bisulfite to allyl trimethyl silane.³ The studies reported here have verified our predictions, as DSS is stable in acid and soluble in concentrated salt solutions. The three CH_2 groups constitute an $\text{A}_2\text{B}_2\text{C}_2$ system, as planned; one obtains a complex, broad, and very low multiplet without salient features. At the concentrations normally employed for internal referencing, 0.3 to 1.0%, this multiplet is not distinguishable from noise.

It is the purpose of the present article to explore the question of shielding value measurements in aqueous media and their correlation with studies previously made in other systems.

Experimental

Materials.- The organic compounds studied were obtained from common suppliers of laboratory chemicals, and were used without further purification. The sample of $(\text{CH}_3)_3\text{SiCH}_2\text{OH}$ was kindly furnished by Paul Lauterbur of the Mellon Institute. The reference compound, DSS, $(\text{CH}_3)_3\text{SiCH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{Na}$, had been synthesized in these laboratories³ from allyltrimethylsilane (Peninsular Chem. Co.). Deuterium oxide of better than 99.5% purity was obtained from the Stuart Oxygen Co.

Apparatus and Techniques.- The equipment used and the measurement techniques employed have been described in detail.¹ Measurements were made at $25^\circ \pm 2^\circ$. Concentrations are given as percentage by volume for liquids, and as weight/volume for solids; all solutions were made up in the n.s.r. sample tubes. All of the compounds studied had strong, sharp n.s.r. bands and were examined in very dilute solution.

Results and Discussion

There is no absolute way to relate the scale of shielding values based on tetramethylsilane (τ -values)¹ with the new scale (entitled τ' -values) based on DSS, since DSS is insoluble in CCl_4 and other liquids of low polarity, while Me_4Si is insoluble in D_2O . It is only possible to compare them in certain media of intermediate character, and, since

their peaks overlap, it is necessary to compare each separately to some other peak such as that due to the solvent; this has been done in Table I. It is apparent that the two reference compounds do not behave in precisely identical fashion in the six solvents studied; however, the variability is indeed small, apparently not correlated with dielectric constant, and averages to virtually zero. Accordingly the DSS reference peak position will be taken as $10.000\tau'$ in aqueous systems.

In Table II is given the τ' -value for methyl groups of neopentyl alcohol in a wide variety of solvents. There is a very weak solvent effect upon τ' , but it is too is not correlated with dielectric constant, or, for that matter, with polarizability (as evidenced by refractive index).

The results listed in Table III illustrate the generally good agreement between τ' and τ -values, measured in D_2O and in CCl_4 respectively. The correspondence is best for those compounds in which the group studied is somewhat distant from the solubilizing group, an observation which tends to validate our presupposition (it must be noted that τ -values measured in CCl_4 are not wholly independent of solvent^{4,5}). It is apparent that the entries in the column entitled "difference" ($\tau' - \tau$) are not simply explained, and may reflect a combination of effects. In this connection the τ' -values given in Table IV, which show for the most part a lack of variation in τ' with pH or salt concentration, provide valuable evidence and should be elaborated.

It is interesting to note that the tetramethylammonium

a suitable ion, which is the only example of an internal reference for aqueous systems that we have noticed in the scientific literature,⁶ proves to be rather good, only minor pH or salt effects being found in D₂O. However, its τ' -value is somewhat solvent dependent, as may be seen in Table V, in which shielding values measured in formamide are compared with those from D₂O. Again, relatively good correspondence of τ' -values is found.

TABLE I

A Comparison of Shielding Values, τ (Tetramethylsilane as Internal Reference), and τ' (2,2 - Dimethyl-2-Silapentane - 5 - Sulfonate Ion, DSS, as Internal Reference), Measured in Similar Solutions.

Solvent	Compound & Peak Measured	Conc. (%)	Me ₄ Si τ	Std. Dev.	DSS τ'	Std. Dev.	Corr. for DSS (Aver.)
CH ₃ CO ₂ H	CH ₃ *CO ₂ H	98	7.934	.004	7.945	.001	-.011
CH ₃ OH	CH ₃ *OH	99	6.650	.003	6.659	.005	} -.012
	Me ₃ *CCH ₂ OH	0.6	9.117	.004	9.133	.001	
CH ₃ CN	CH ₃ CN	99	8.033	.004	8.022	.002	+.011
CH ₃ NO ₂	CH ₃ NO ₂	98	5.640	.002	5.646	.004	-.006
(CH ₃) ₂ SO	(CH ₃) ₂ SO	99	7.457	.001	7.434	.001	} +.017
	Me ₃ *CCH ₂ OH	0.6	9.175	.005	9.165	.003	
CH ₃ CONHCH ₃	Me ₃ *CCH ₂ OH	0.8	9.109	.001	9.124	.001	-.015

"Best" value for correction: -.003

TABLE II
The Shielding Value, τ' , for Methyl Groups in Neopentyl Alcohol:
Minor Solvent Effects.

Solvent	τ'	Std. dev.	Dielectric Const., 25°	n _D ²⁰
CH ₃ CO ₂ H	9.120	.002	6.2	1.3718
D ₂ O/H ₂ SO ₄ ^a	9.121	.001	>78.	
CH ₃ CONHCH ₃	9.124	.001	175.	
HCONH ₂	9.129	.003	105.	1.4464
HCON(CH ₃) ₂	9.132	.001	36.7	
CH ₃ OH	9.133	.001	32.6	1.3290
CH ₃ CON(CH ₃) ₂	9.136	.001	37.8	
D ₂ O	9.136	.001	78.2	1.3330
D ₂ O/NaCl ^b	9.138	.002	>78.	
D ₂ O/K ₂ CO ₃ ^b	9.140	.002	>78.	
CH ₃ CN	9.144	.003	36.7	1.3445
CH ₃ NO ₂	9.146	.002	36.7	1.3818
(CH ₃) ₂ SO	9.160	.003	45.	1.4791

(a) 5.0% by volume. (b) 4.6% by weight; approx. 5g./100 ml.

TABLE III

A Comparison of Shielding Values Measured in D₂O and in CCl₄.

Compound	τ' (D ₂ O)	Std. dev.	τ (CCl ₄)	Std. dev.	Difference
Me [*] ₃ SiCH ₂ OH	9.959	.001	9.962	.001	-.003
Me [*] ₃ CCH ₂ OH	9.136	.001	9.114	.003	+.022
Me [*] ₃ CNH ₂	8.859	.006	8.906	.001	-.047
Me [*] ₃ CCO ₂ H	8.812	.002	8.773	.001	+.039
CH ₃ CN	7.946	.002	8.026	.002	-.080
CH ₃ CO ₂ H	7.913	.004	7.930	.004	-.017
Acetone	7.777	.003	7.915	.003	-.138
2-Methyl* Pyrazine	7.472	.006	7.476	.003	-.004
Me ₂ SO	7.285	.002	7.489	.003	-.204
CH ₃ [*] OH	6.658	.001	6.622	.003	+.036
Dioxane	6.251	.001	6.426	.002	-.175
ClCH ₂ [*] CO ₂ H	5.736	.002	5.921	.003	-.185
CH ₃ NO ₂	5.610	.005	5.720	.002	-.110
Imidazole (4,5-H ₂)	2.897	.005	2.955	.003	-.058
(2-H)	2.27	.02	2.363	.003	-.09
H [*] CO ₂ H	1.772	.002	1.991	.002	-.219
2-Methyl pyrazine*	1.570	.006	1.660	.002	-.090

TABLE IV

Shielding Values, τ' , in D₂O Solutions: Effects of pH
and of Added Salt.

Compound	D ₂ O	NaCl ^a	K ₂ CO ₃ ^a	H ₂ SO ₄ ^b
Me [*] ₃ SiCH ₂ OH	9.959	9.957	9.961	---
Me [*] ₃ CCH ₂ OH	9.136	9.138	9.140	9.121
Me [*] ₃ CNH ₂	8.859	8.814	8.810	---
Me [*] ₃ CCO ₂ H	8.812	8.810	(8.912) salt	---
CH ₃ CN	7.946	7.926	7.932	7.934
CH ₃ [*] CO ₂ H	7.913	7.903	(8.095) salt	7.896
Acetone	7.777	7.774	7.79	---
2-Methyl* Pyrazine	7.472	7.466	7.468	---
Me ₂ SO	7.285	7.269	7.282	---
Me ₄ N ⁺	6.824	6.811	6.797	6.794
CH ₃ [*] OH	6.658	6.656	6.644	---
Dioxane	6.251	6.251	6.253	6.249
ClCH ₂ [*] CO ₂ H	5.736	5.697	(5.943) salt	---
CH ₃ NO ₂	5.610	5.585	---	5.598
Imidazole (4,5)	2.897	2.870	2.873	(2.499) salt
(2)	2.27	2.23	2.23	(1.29) salt
H [*] CO ₂ H	1.772	1.744	(1.550) salt	---
2-Methyl Pyrazine*	1.570	1.558	1.568	---

(a) 4.6% by weight in D₂O; approx. 5g./100 ml.
(b) 5.0% by volume in D₂O.

TABLE V

A Comparison of Shielding Values, τ' , Measured
in D_2O and in Formamide.

<u>Compound</u>	τ' <u>D_2O</u>	τ' <u>$HCONH_2$</u>	$\Delta\tau'$ <u></u>
$Me_3^*CCH_2OH$	9.136	9.129	-.007
$Me_3^*CCO_2H$	8.812	8.803	-.009
MeCN	7.946	7.911	-.035
Me_2SO	7.285	7.292	+0.007
Me_4N^+	6.824	6.783	-.041
$MeNO_2$	5.610	5.560	-.050