Influence of an Internal Reference on ¹H NMR Solvent Shifts. Determination of Reference Independent ASIS Values

MIRJAMI JUTILA

Department of Chemistry, Institute of Biomedicine, University of Turku, SF-20500 Turku 50, Finland

In many studies concerning the aromatic solvent-induced shifts (ASIS) the measurements are made using tetramethylsilane (TMS) as internal standard. However, the solvent effect on TMS in aromatic solvents can be considerable, and the use of internal reference can appreciably modify the real ASIS effect.

In ¹H, ¹³C and ²⁹Si NMR measurements tetramethylsilane has become the accepted standard because of its many favorable properties: Tetramethylsilane dissolves in most organic solvents, it is inert and nonpolar, its signal has a convenient up-field location and it has a comparatively small solvent effect. However, when added to certain solvents, for example, aromatic ones, the solvent effect is not necessarily small. As a matter of fact it can be quite large, as has been shown by Rummens and Krystynak[1] and Laszlo et al.[2] They showed that TMS is just as much a solute as the actual solute. Nevertheless, some recent reports[3⁻5] are still based on the erroneous assumption that the resonance position of the internal standard is independent of the solvent.

The role of the internal standard is very important in the formation of the ASIS. The chemical shifts of the solute in an inert solvent and in an aromatic solvent are measured relative to an internal standard, usually tetramethylsilane. The ASIS is the difference between these two chemical shifts, as shown in eqn. (1).

$$\text{ASIS} = \Delta = \delta_x^{\text{CDCl}_3} - \delta_x^{\text{C}_6\text{H}_6}. \tag{1}$$

To draw conclusions regarding the structure of the solute one should eliminate the influence of the internal standard on the true solvent shifts. Rum-

mens and Krystynak[1] have realized this by reference to an absolute external standard, for which they have chosen the resonance position of zero pressure TMS gas. They found that the ASIS is given by

$$\text{ASIS} = \Delta = (\sigma_{\text{Rm}}^{\text{CDCl}_3} - \sigma_{\text{Rm}}^{\text{B}}) - (\sigma_{\text{xm}}^{\text{CDCl}_3} - \sigma_{\text{xm}}^{\text{B}}) \tag{2}$$

$$= \Delta_{\text{Rm}} - \Delta_{\text{xm}}, \tag{3}$$

eqn. (2) where σ is a chemical shielding and Δ_{xm} is a "true" shift. Subscript x stands for a solute, B for

Table 1. Medium effect of internal TMS in comparison with external TMS.

Solvent	Medium shift shielding/ppm[a]
Carbon tetrachloride	−0.41
1,2-Dichlorobenzene	−0.25
Bromobenzene	−0.20
o-Chlorotoluene	−0.09
Chlorobenzene	−0.05
Benzoyl chloride	0.09
Mesitylene	0.09
p-Xylene	0.12
m-Xylene	0.13
Benzonitrile	0.13
Toluene	0.16
o-Nitrotoluene	0.19
Benzene	0.21
Acetophenone	0.23
Pyridine	0.30
Nitrobenzene	0.30
Benzaldehyde	0.36

[a] The resonance positions were measured from the signal of internally added TMS, the -sign corresponding to an up-field shift from internal TMS.

benzene, m for medium, R for a reference compound. The equation shows that Δ is dependent on the choice of internal standard but independent of the bulk susceptibility of the solvents and of the choice of external standard.

The medium effect of the internal TMS (Table 1) in CCl_4, in comparison with the external one, is -0.41 ppm and in benzaldehyde $+0.36$ ppm, an overall Δ of 0.77 ppm, which is much larger than most of the so-called ASIS values. The chemical shifts appear to be characteristic of the position of the nucleus under examination with respect to the various functional groups in the solute molecule. The best approach[6] to medium effects on NMR chemical shifts is given by the eqn. (4), expressing the contribution of the medium to the nuclear shielding in the form (4), where σ_b is the bulk

$$\sigma_{solvent} = \sigma_w + \sigma_b + \sigma_a + \sigma_E, \qquad (4)$$

susceptibility effect, σ_a takes account of the diamagnetic anisotropy of the solvent molecules, σ_w is the van der Waals contribution, and the "reaction field" term, σ_E, includes contributions from polar effects. The extent to which any or all of these effects contribute depends on the nature of the solute – solvent system. Tetramethylsilane is a symmetrical nonpolar molecule and it behaves as internal

standard in solution just like a "real" nonpolar solute. The $C-Si$ bond is much more susceptible to solvent effects than either the $C-C$ or the $C-H$ bond.[7] Therefore TMS, due to van der Waals' interaction σ_w and factors which arise from solvent anisotropy effects σ_a, exhibits ASIS values like any other solute. The magnitude of σ_w increases with increasing molecular polarizability of the solvent molecules. The interaction of TMS with polar aromatic solvents, such as with pyridine, nitrobenzene, benzaldehyde, benzonitrile and acetophenone, is significant (Table 2) and the use of TMS as internal standard in such solvents clearly leads to less significant shifts.

The choice of reference has the least effect in the case of chlorine-containing aromatic solvents. As compared proton medium shifts to ^{13}C medium shifts, the magnitude of ^{13}C medium shifts is much higher and anisotropic shifts are less significant.[7]

Many authors[8-10] have preferred cyclohexane to TMS as internal standard for precise work on aromatic solvents. It is seen in Table 2 that the Δ_i-values do not differ very much from the values measured when using TMS as internal standard but the Δ_e-values show that also cyclohexane interacts with solvent molecules and hence fairly incorrect conclusions may have been drawn about the ASIS values if cyclohexane has been used as internal

Table 2. ^1H chemical shifts (Hz) of tetrahydrofuran and cyclohexane in carbon tetrachloride and aromatic solvent-induced shifts (Hz) at 307 K.

Solvent	Tetrahydrofuran 3,4-H		2,5-H		Cyclohexane	
	Δ_i	Δ_e	Δ_i	Δ_e	Δ_i	Δ_e
Carbon tetrachloride	$v_i = 111.0$		$v_i = 225.2$		$v_i = 85.2$	
Toluene	18.5	52.5	3.2	37.2	4.5	38.5
Benzene	22.0	59.0	4.2	41.2	5.3	42.3
Nitrobenzene	4.0	46.6	−2.3	40.3	−5.1	37.5
Bromobenzene	13.4	26.3	2.4	15.3	−0.4	12.5
Chlorobenzene	13.7	35.1	2.2	23.6	0.2	21.6
p-Xylene	17.2	48.7	4.6	36.1	4.0	35.5
m-Xylene	18.0	50.1	6.2	38.3	4.0	36.1
o-Nitrotoluene	5.0	40.7	−0.3	35.4	−3.7	32.0
1,2-Dichlorobenzene	8.0	17.4	0.3	9.7	−0.3	9.1
Benzaldehyde	11.0	57.2	1.7	47.9	−3.2	43.0
Pyridine	10.2	52.5	−0.8	41.5	1.0	43.3
o-Chlorotoluene	13.5	32.9	3.2	22.6	−1.3	18.1
Benzonitrile	5.5	37.7	−1.3	30.9	−4.9	27.3
Benzoyl chloride	7.3	37.1	0.0	29.8	0.7	30.5
Acetophenone	9.0	47.1	1.7	39.8	1.2	39.3
Mesitylene	17.7	47.5	6.6	36.4	4.2	34.0

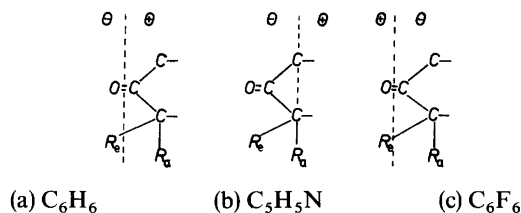(a) C_6H_6 (b) C_5H_5N (c) C_6F_6

Fig. 1. Carbonyl reference plane rules. The dotted line shows a reference plane (Refs. 13 and 16).

standard. It has been assumed in the literature that only polar solutes have significant ASIS values but the present results with cyclohexane show that the Δ_i-values in different aromatic solvents are almost invariant whereas the reference-independent solvent shifts Δ_e are, on the contrary, considerable.

The so-called "carbonyl plane rule" (Refs. 11 and 12) is misleading if, for instance, TMS is used as internal standard. This rule states (Fig. 1) that Δ-values in C_6H_6 are negative for protons lying in front of the carbonyl plane and positive for protons lying behind the carbonyl plane or in practice that in cyclohexanone molecule axial methyl groups or protons are shielded whereas equatorial methyl groups or protons are either deshielded or barely

influenced. The carbonyl reference plane rules in solvents C_5H_5N and C_6F_6 are presented in Fig. 1. These statements, *i.e.* deshielding by solvent or negative ASIS values, are, however, incorrect. The relative difference of the ASIS values in the same solvent remains unchanged, independent of the reference. According to the theory of Rummens and Krystynak, negative ASIS simply means that Δ_{xm} in eqn. (3) happens to be smaller than Δ_{Rm}. This condition therefore depends just as much on the choice of reference compound as on the solute. Negative Δ-values in C_6H_6 and in C_5H_5N (Table 3) are due to the internal TMS standard in the solutions. Barton *et al.*[13] discovered that the direction of hexafluorobenzene-induced shifts observed for some polar solutes is opposed to that of deuterobenzene-induced shifts. It is postulated that benzene tends to lie as far away as possible from the negatively charged region of the dipole and induces up-field ¹H shifts at the positive end, while C_6F_6 shows an opposite behaviour and hence induces up-field shifts at the negative end. The solvent shifts in Table 4 have been corrected by the external reference method and show that negative Δ-values simply arise from the choice of reference.

Another area where quite incorrect conclusions can be drawn is that of the use of TMS as internal standard in dilution experiment measurements. Linear plots are often obtained[14,15] when the ASIS values of the solute are plotted for the carbon tetrachloride — benzene system against their concentration ratio. Now, using TMS as internal standard the measurements must be in error because changing the composition of this system leads to a change in the shift of the standard.
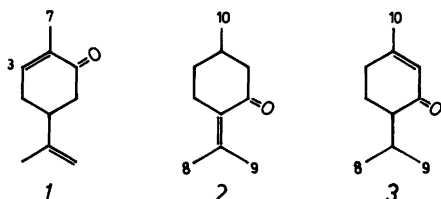
Table 3. Solvent shifts (ppm) of protons of α,β-unsaturated ketones *1, 2* and *3*.

Compound	Protons	$\Delta_{C_5H_5N}^{CCl_4}$		$\Delta_{C_6H_6}^{CDCl_3}$	
		a	b	a	b
1	7 – H	−0.07	0.64	0.00	0.59
	3 – H	0.07	0.78	0.51	1.10
2	9 – H	−0.08	0.63	−0.03	0.56
	8 – H	0.11	0.82	0.22	0.81
	10 – H	0.15	0.86	0.19	0.78
3	2 – H	−0.16	0.55	0.01	0.60
	8 – H	−0.01	0.70	0.02	0.61
	9 – H	0.00	0.71	0.03	0.62
	10 – H	0.17	0.88	0.37	0.96

[a] TMS as internal standard (Ref. 16). [b] Reference-independent solvent shifts, present study.

Table 4. Solvent shifts of solutes in deuterobenzene and hexafluorobenzene (ppm).

Solute		$\Delta^{CCl_4}_{C_6H_6}$		$\Delta^{CCl_4}_{C_6F_6}$	
		a	b	a	b
Tetrahydrofuran	β	0.361	0.971	−0.051	0.489
	α	0.046	0.656	0.105	0.645
Furan	β	0.215	0.825	0.016	0.556
	α	0.228	0.838	0.109	0.649
Pyrrolidine	β	0.229	0.839	−0.113	0.427
	α	0.124	0.734	−0.037	0.503
Pyrrole	β	−0.227	0.383	0.202	0.742
	α	−0.225	0.385	−0.004	0.536
Tetrahydrothiophen	β	0.436	1.046	−0.083	0.457
	α	0.205	0.815	0.038	0.578
Thiophene	β	0.217	0.827	0.036	0.576
	α	0.316	0.926	0.054	0.594

[a] TMS as internal standard (Ref. 13). [b] Reference-independent solvent shifts, present study.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Jeol JNM-PMX 60 NMR spectrometer. Carbon tetrachloride was selected as an inert solvent. The aromatic solvents were chosen in such way that overlapping solute–solvent signals were avoided. The solute concentrations were 3 %. The resonance positions (Hz) were measured from the signal of internal TMS and were corrected with external TMS by using a coaxial sample cell. The outer cell consisted of 3 % of TMS in the aromatic solvent (internal reference) and the inner capillary tube consisted of TMS (external reference). All the spectra were measured at the normal probe temperature of 307 K.

REFERENCES

1. Rummens, F. H. A. and Krystynak, R. H. *J. Am. Chem. Soc. 94* (1972) 6914.
2. Laszlo, P., Speert, A., Ottinger, R. and Reisse, J. *J. Chem. Phys. 48* (1968) 1732.
3. Crabb, T. A. and Jupp, P. A. *Org. Magn. Reson. 13* (1980) 159.
4. Onek, T., Inman, W., Rosendo, H., DiStefano, E. and Nurse, J. *J. Am. Chem. Soc. 99* (1977) 6488.
5. Nikki, K. and Nakagawa, N. *Bull. Chem. Soc. Jpn. 51* (1978) 3267.
6. Buckingham, A. D., Schaefer, T. and Schneider, W. G. *J. Chem. Phys. 32* (1960) 1227.
7. Ziessow, D. and Carroll, M. *Ber. Bunsenges. Phys. Chem. 76* (1972) 61.
8. Nikki, K., Nakagawa, N. and Takeuchi, Y. *Bull. Chem. Soc. Jpn. 48* (1975) 2902.
9. Nikki, K., Nakahata, N. and Nakagawa, N. *Tetrahedron Lett.* (1975) 3811.
10. Jauquet, M. and Laszlo, P. *Tech. Chem. 8* (1975) 195.
11. Bhacca, N. S. and Williams, D. H. *Tetrahedron Lett.* (1964) 3127.
12. Williams, D. H. and Bhacca, N. S. *Tetrahedron 21* (1965) 2021.
13. Barton, T. J., Roth, R. W. and Verkade, J. G. *J. Am. Chem. Soc. 94* (1972) 8854.
14. Bowie, J. H., Ronayne, J. and Williams, D. H. *J. Chem. Soc. B* (1966) 785.
15. Fort, R. C. and Lindström, T. R. *Tetrahedron 23* (1967) 3227.
16. Williams, D. H. *Tetrahedron Lett.* (1965) 2305.