will be able to find a flexible enough fragment description in order to predict correctly the last portion of the electronic structure, while preserving the accurate geometric structure predictions for nitrogen double bond containing molecules.

The final fragments studied, the NH_3-Planar fragments, have been evaluated only on the basis of the electronic structure predicted for pyrrole. The better fragment again appears to be a fragment with the π-type FSGO at 0.1 bohr, *i.e.*, NH_3-Planar-0.1. Preliminary studies on simple amides also indicate that this choice of fragment parameters describes quite well the situation where nitrogen contributes its lone pair to an extended π system. However, further studies of the same nature as those mentioned for the NH_2 fragment are contemplated.

In summary, the studies presented here show that the predicted ordering of the chemically interesting molecular orbital energy levels for the nitrogen-containing molecules is in general in very good agreement with more extensive *ab initio* calculations. The one consistent difficulty that occurs with both types of N-π fragments, *i.e.*, $\cdot NH_3$-Planar and $\cdot NH_2$, is that the molecular orbitals which are primarily lone pair in nature are too high in energy relative to the other molecular orbitals.

These studies further emphasize that, as noted in previous calculations,[2,3,6-8] even the very limited basis sets used in these studies are capable of producing results of a useful qualitative, and often quantitative, nature for several aspects of geometric and electronic structure. In particular, geometric predictions are also quite acceptable. Barriers to rotations are again generally too high. However, this method does appear to be capable of predicting barrier height trends, even as heteroatoms are introduced, with the possible exception of hydrazine. Bond distance predictions, including multiple bonds, average 4.5% from the experimentally accepted values, an improvement over the corresponding results for the hydrocarbons.[3]

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Intermolecular Interactions in Nuclear Magnetic Resonance. VII. The Role of the Internal Reference in Aromatic Solvent Induced Shifts

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Abstract: It is shown, both experimentally and theoretically, that the ASIS (aromatic solvent induced shift) of any solute depends very strongly, both in sign and magnitude, on the chosen internal reference compound. It is pointed out that magnitude and sign of ASIS bears little, if any, relation to presumed specific interactions between solute and solvent. It is also found that additivity of ASIS occurs if two conditions are simultaneously fulfilled: if the ASIS of the parent hydrocarbon is zero and if the differential (between the two solvents) substituent medium effects are additive. Several alternative referencing schemes are discussed. A proposal is made for a modified ASIS which is only a function of interaction effects related to the solute, independent of the reference and independent of the solvent bulk susceptibility. The modified ASIS can be related to the common ASIS by means of conversion terms which have been determined for a number of internal references. The advantages of the modified ASIS for solvent effect studies, in particular specific solute-solvent interactions, are pointed out.

It is well known that proton chemical shifts depend not only on the intrinsic shielding properties of the solute molecule (X), but also on the medium (solvent) in which the solute resides. The most widely used solvent effect is known as "aromatic solvent induced shift" or ASIS for short. In this technique the solute is dissolved in two different solvents, usually deuteriochloroform and benzene, and its chemical shift(s) relative to an internal standard, usually TMS, is measured. The ASIS is then simply the difference between these two chemical shifts (eq 1). While progress on

$$\text{ASIS} = \Delta = \delta_X^{CDCl_3} - \delta_X^{C_6H_6} \quad (1)$$

the quantitative and even qualitative understanding of the parameter Δ is slow,[1-5] the empirical use of the above technique has been rather explosive. Laszlo,[1] in reviewing the first three years of ASIS, gave already some 100 references, while at the present there appear approximately 400 papers a year[6] that make a more or less extensive use of ASIS, with applications mainly

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(1) P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Vol. 3, Pergamon Press, Elmsford, N. Y., 1967.

(2) J. Ronayne and D. H. Williams, *Annu. Rep. NMR Spectrosc.*, **2**, 83 (1969).

(3) J. K. Becconsall, *Mol. Phys.*, **15**, 129 (1968); 18, 337 (1970).

(4) F. H. A. Rummens, *J. Amer. Chem. Soc.*, **92**, 3214 (1970).

(5) E. M. Engler and P. Laszlo, *ibid.*, **93**, 1317 (1971).

(6) Estimated from Current Awareness Service output, Scientific Documentation Centre, Dunfermline (Fyfe), U. K.

in the determination of structural details. It appears that the numerical values of Δ are often characteristic for certain moieties at certain locations in the molecule, that they have some degree of additivity, and even that these values are often transferable from one solute to another (structurally related) one.

Our concern at present is neither with the applications nor with the mechanism of ASIS but rather with the use of an *internal* standard in the ASIS technique. Phenomenologically speaking, an internal reference is just as much a solute as the "real" solute whose properties one wishes to determine. The Δ values as obtained *via* eq 1 at least in principle reflect as much the medium shift experienced by the internal standard as the medium shift of the actual solute. To draw conclusions regarding the structure of the solute from such Δ values seems therefore not well warranted, unless one finds ways to eliminate the contribution of the internal standard. The situation can best be visualized by reference to an absolute external standard, for which we have chosen the resonance position of zero-pressure TMS gas, as indicated in Figure 1.

The following nomenclature has been adopted. σ (for shielding) rather than δ is used, because the δ scale is defined with respect to TMS (as internal standard) only. Superscripts indicate the solvent, with "C" for $CDCl_3$ and "B" for benzene and a "zero" superscript for the gas state. The first subscript indicates the solute; "X_0" for nonsubstituted solute, "X_1" and "X_2" for two different monosubstituted solutes, "X_{12}" for the corresponding disubstituted solute, and "R" for reference compound. The second subscripts indicate the nature of the interactions with "b" for bulk susceptibility, "m" for medium, "w" for van der Waals, "a" for neighbor anisotropy, and "E" for electric field effects. It will be assumed[11] that the shielding can always be written as

$$\sigma = \sigma^0 + \sigma_b + \sigma_w + \sigma_a + \sigma_E + \ldots \quad (2)$$

while we furthermore will define σ_m as the gas-to-solvent shift corrected for bulk susceptibility, as given by eq 3.

$$\sigma_m = \sigma_{g\rightarrow l}(\text{exptl}) - \sigma_b = \sigma_w + \sigma_a + \sigma_E + \ldots \quad (3)$$

From Figure 1 it is clear that both the internal reference and the solute have their resonance positions changed in going from $CDCl_3$ to benzene. Starting from eq 1 one may write

$$\begin{aligned}\Delta = \delta_X{}^C - \delta_X{}^B &= (\sigma_X{}^B - \sigma_R{}^B) - (\sigma_X{}^C - \sigma_R{}^C) = \\ &(\sigma_X{}^B - \sigma_X{}^C) - (\sigma_R{}^B - \sigma_R{}^C) = \\ &(\sigma_{Xm}{}^B + \sigma_b{}^B + \sigma_X{}^0 - \sigma_{Xm}{}^C - \sigma_b{}^C - \sigma_X{}^0) - \\ &(\sigma_{Rm}{}^B + \sigma_b{}^B + \sigma_R{}^0 - \sigma_{Rm}{}^C - \sigma_b{}^C - \sigma_R{}^0) = \\ &(\sigma_{Rm}{}^C - \sigma_{Rm}{}^B) - (\sigma_{Xm}{}^C - \sigma_{Xm}{}^B) \quad (4)\end{aligned}$$

If now the symbol Δ_{Xm} is introduced to indicate for any solute the difference in the medium effect shielding in two solvents, eq 4 reduces to

$$\Delta = \Delta_{Rm} - \Delta_{Xm} \quad (5)$$

Equation 5 shows the dependence of Δ on the choice of (internal) standard as well as the independence of Δ on the bulk susceptibility of the solvents and on the choice of an external standard if any.

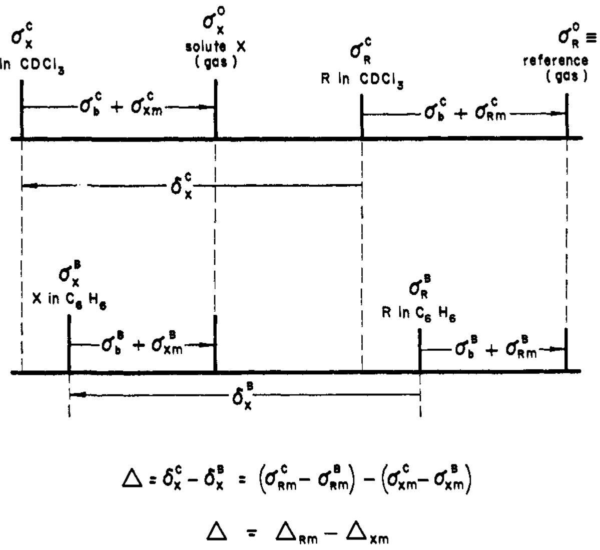

Figure 1. Diagram of internal and external referencing in differential solvent effects.

Internal Referencing. Experimental Results and Discussion

Table I. Experimental ASIS Δ Values (in ppm) for C-19 and C-18 Methyl Protons of 5α-Androstane and Some Keto Derivatives

		Solute			
Internal ref	Signal	Δ_0 5α-A[a]	Δ_1 5α-A-3[b]	Δ_2, 5α-A-17[c]	Δ_{12}, 5α-A-3,17[d]
Tetramethylsilane,	C-19	0.010	0.372	0.123	0.477
TMS	C-18	−0.012	0.078	0.217	0.288
Cyclohexane,	C-19	−0.018	0.341	0.099	0.450
C_6H_{12}	C-18	−0.042	0.046	0.193	0.262
Benzene, C_6H_6	C-19	−0.177	0.180	−0.063	0.287
	C-18	−0.197	−0.115	0.031	0.101
Acetone,	C-19	−0.559	−0.196	−0.442	−0.082
$(CH_3)_2CO$	C-18	−0.582	−0.490	−0.347	−0.270
Chloroform,	C-19	−0.983	−0.604	−0.847	−0.477
$CHCl_3$	C-18	−1.007	−0.896	−0.753	−0.664

[a] 5α-A = 5α-androstane. [b] 5α-A-3 = 5α-androstan-3-one. [c] 5α-A-17 = 5α-androstan-17-one. [d] 5α-A-3,17 = 5α-androstane-3,17-dione.

In Table I the observed Δ values for the C-18 and C-19 methyl groups of 5α-androstane, 5α-androstan-3-one, 5α-androstan-17-one, and 5α-androstane-3,17-dione are given. Measurements were made, not only with the commonly used TMS, but also with cyclohexane, benzene, acetone, and chloroform as internal standards. From these data it is clear that the ASIS Δ values depend very strongly on the choice of the internal standard, as predicted by eq 5.

From the relatively small magnitude of Δ of 5α-androstane (or of any solute for that matter) with TMS or C_6H_{12} as internal standards, it cannot be concluded, as has been done,[7,8] that such internal standards are rather "inert." TMS in $CDCl_3$ has a medium shift of $\sigma_m = -0.333$ ppm, and in benzene a medium shift of $\sigma_m = +0.147$ ppm (Table V), for an overall $\Delta_{Rm} = -0.48$ ppm which is in fact larger than most ASIS values. It may even be noticed (eq 5) that if a reference compound were used of decidedly better

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(7) Reference 1, p 355.

(8) P. Laszlo, A. Speert, R. Ottinger, and J. Reisse, *J. Chem. Phys.*, 48, 1732 (1968).

inertness (such as, for instance, $Si(CH_2CCl_3)_4$ where $\sigma_{Rm}{}^{C}$ and $\sigma_{Rm}{}^{B}$, and there also Δ_{Rm}, are presumably much smaller[4] than for TMS), this would have the effect of producing Δ values that for most solutes would show a *larger* deviation from zero.

The above also shows, *inter alia*, that a search for a "best" reference compound[8] is rather futile since what is "best" inevitably depends just as much on the solute and its properties one wants to investigate.

Bhacca and Williams[9] in commenting on the low Δ values for C-19 and C-18 for 5α-androstane write, "It therefore appears likely that in the absence of polar functional groups, no preferred geometrical relationship exists between solvent and solute molecules, since the positions of the angular methyl resonances are barely influenced on passing from $CDCl_3$ to benzene as solvent." We wish to observe that these methyl resonances are *strongly* influenced, namely around 0.5 ppm (*i.e.*, just about as much as the TMS internal reference). Furthermore, even the benzene molecules surrounding a quasi-spherical nonpolar molecule like TMS have a preferred geometry relative to such a solute[3,4] which in these cases is the sole reason for a σ_a effect in the first place. Low ASIS values mean only (eq 4 and 5) that Δ_{Rm}, the difference in medium effect for the reference in $CDCl_3$ and C_6H_6, happens to be of about equal magnitude (and same sign) as the corresponding difference for the solute. Since the Δ is made up of four medium effects (eq 2), each of these consisting of several terms such as σ_w, σ_a, and σ_E, the chances for a zero Δ seem slim, unless all the medium effect terms of the reference cancel with the corresponding terms of the solute, and that will only happen if reference and solute are chemically very similar.

Williams and Bhacca also observed negative ASIS for certain signals and solutes[10] and describe these in terms of "deshielding by benzene" and "paramagnetic shift in benzene." Such statements are misleading if not downright erroneous. As far as is known from extensive solvent effect studies,[3,4,11,12] chloroform as a solvent always produces downfield medium shifts and benzene always produces upfield (diamagnetic) shifts. Therefore both Δ_{Rm} and Δ_{Xm} will always be large and negative. Negative ASIS simply means that Δ_{Xm} happens to be smaller than Δ_{Rm}. This condition therefore depends just as much on the choice of the reference compound as on the solute (see also Table I, where several sign inversions occur). To give negative ASIS a discrete physical meaning in terms of the structure of the solute only (according to Bhacca and Williams[9] protons on the oxygen side of a plane through the carbonyl carbon atom and perpendicular to the C=O bond will give negative ASIS) would therefore appear to be a hazardous undertaking which is bound to result in erroneous structural assignments.

ASIS has apparently additivity properties, the ASIS Δ_{12} of a certain proton in a disubstituted solute being often approximately equal to the sum of the ASIS's $(\Delta_1 + \Delta_2)$ of the two corresponding monosubstituted solutes. Such additivity was first reported by Williams and Bhacca[10] and has since been studied rather extensively.

By applying eq 5 three times, *viz.*

$$\Delta_1 = \Delta_{Rm} - \Delta_{X_1m} \tag{6}$$

$$\Delta_2 = \Delta_{Rm} - \Delta_{X_2m} \tag{7}$$

$$\Delta_{12} = \Delta_{Rm} - \Delta_{X_{12}m} \tag{8}$$

the condition for additivity (*i.e.*, $\Delta_1 + \Delta_2 \doteq \Delta_{12}$) can be written as follows.

$$\Delta_{X_1m} + \Delta_{X_2m} \doteq \Delta_{Rm} + \Delta_{X_{12}m} \tag{9}$$

From eq 9 it is clear that the additivity condition involves the properties of the internal reference and therefore cannot be expected to hold in general. In Table II, next to the experimental Δ_{12} values, the calculated $\Delta_1 + \Delta_2$ values are given. While with TMS and C_6H_{12} as internal standards the ASIS's are reasonably additive, using other internal standards (including the nonpolar benzene!) a complete breakdown of additivity is observed.

Table II. Additivity Test for ASIS and for ASIS Substituent Increments (Eq 20–23)[a]

		Solute			
Internal ref	Signal	Δ_{12}	$\Delta_1 + \Delta_2$	$\Delta_{12} - \Delta_0$	$(\Delta_1 - \Delta_0) + (\Delta_2 - \Delta_0)$
Tetramethylsilane	C-19	0.477	0.495	0.467	0.475
	C-18	0.288	0.295	0.300	0.319
Cyclohexane	C-19	0.450	0.440	0.468	0.476
	C-18	0.262	0.240	0.304	0.324
Benzene	C-19	0.287	0.117	0.464	0.471
	C-18	0.101	−0.084	0.298	0.310
Acetone	C-19	−0.082	−0.638	0.477	0.480
	C-18	−0.270	−0.837	0.312	0.327
Chloroform	C-19	−0.477	−1.451	0.506	0.515
	C-18	−0.664	−1.649	0.343	0.365

[a] All data in ppm.

Laszlo, while commenting on Williams and Bhacca's observed additivities in the 5α-androstane series, states,[13] "it is obvious that additivity is obtained *if and only if* the C-18 and C-19 methyl resonances of the *hydrocarbon* skeleton are identical in the reference (inactive) and in the aromatic (active) solvent" (*i.e.*, $\Delta_0 = 0$).

The first premise ("if") can be dealt with by pointing out that if indeed $\Delta_0 = 0$, then all it means is that Δ_{Rm} is numerically equal to Δ_{X_0m} (eq 5), so that Δ_{X_0m} may be substituted for Δ_{Rm} in eq 9. But that still leaves the correlation between three solutes (the additivity) a function of a fourth molecule so that the fulfillment of the additivity condition is still a matter of chance. The hydrocarbon solute X_0 is simply used as an internal reference instead of the regular standard (TMS).

The second premise ("only if") cannot be correct either. For a given series of solutes X_1, X_2, and X_{12} the medium effects in the two solvents are constants. Additivity can only be brought about by a judicious choice of the only variable, the reference compound. The Δ_0 does not even enter into the additivity condition (eq 9).

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[9] N. S. Bhacca and D. H. Williams, *Tetrahedron Lett.*, 42, 3127 (1964).

[10] D. H. Williams and N. S. Bhacca, *Tetrahedron*, 21, 2021 (1965).

[11] A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, 32, 1227 (1960).

[12] F. H. A. Rummens and F. J. A. Louman, *J. Magn. Resonance*, in press.

[13] Reference 1, p 350.

Yet it appears, from an inspection of Table I and II, that there is indeed a correlation between additivity of Δ_1 and Δ_2 and the near-zero magnitude of Δ_0. For an explanation of this it is necessary to formally write the Δ_{X_m} terms as a sum of a skeletal value Δ_{X_0m} and an appropriate increment $\delta\Delta_{X_m}$ so that one has

$$\Delta_{X_1m} = \Delta_{X_0m} + \delta\Delta_{X_1m} \tag{10}$$

Using this terminology the additivity condition of eq 9 then becomes

$$\delta\Delta_{X_1m} + \delta_{X_2m} \doteq \delta\Delta_{X_{12}m} + (\Delta_{Rm} - \Delta_{X_0m}) \tag{11}$$

From eq 11 it follows that additivity will be achieved if the following two conditions are simultaneously fulfilled: (i) that Δ_{Rm} is equal to Δ_{X_0m} (*i.e.*, $\Delta_0 \doteq 0$) and (ii) that the increments in differential medium effects (as defined by eq 10) are additive.

The first condition has the best chances of being met if the reference is also a hydrocarbon. For hydrocarbons the σ_a effect in benzene is close to a constant, largely independent of the size of the molecule and the site of the proton measured.[4] The σ_w effects vary somewhat more, from about 0.1 to 0.4 ppm,[4,14] while the σ_E effect (operative in $CDCl_3$) is very small so that its variations can be neglected. Therefore, even if the reference compound is a hydrocarbon, the first condition may fail to be fulfilled by as much as 0.3 ppm, which probably explains the lack of ASIS additivity with benzene as a reference (Table II). It may be noted that TMS may be considered as equivalent to a hydrocarbon since its σ_w effects are in the same range as those of hydrocarbons.[14]

The second condition is also often fulfilled. Diehl[15] and also Fétizon and Gramain[16] have already noted the additivity of substituent shift increments in *any* solvent. In such cases the *differential* shift increments are of necessity also additive. (The opposite is apparently not true; Laszlo and Soong[17] have observed that for many heterocyclic compounds the ASIS's are approximately additive, while the substituent shift increments in any single solvent are not.)

It should finally be noted that the two conditions given above are only sufficient; neither of them nor their combination is necessary. In fact, there cannot be any "only if" condition. Suppose condition ii is not fulfilled (which is bound to happen when the two substituents strongly interact); then it is possible (in principle but most likely also in practice) to find a reference compound such that $\Delta_{Rm} - \Delta_{X_0m}$ (eq 11) offsets the nonadditivity of the $\delta\Delta_{X_m}$ parameters.

Alternate Referencing Methods

There are several possible avenues to at least partially, if not wholly, eliminate the undesirable influence of the internal reference in ASIS.

(i) The Δ-Difference Method. This method applies only if there are at least two moieties in the solute in question, whose ASIS's can be measured. Taking the example of the 5α-androstane steroids once more, one may apply eq 5 both on the C-19 and the C-18 methyl signals and subtract the two Δ values resulting in eq 12.

$$\Delta(\text{C-19}) - \Delta(\text{C-18}) = \Delta_{X_m}(\text{C-18}) - \Delta_{X_m}(\text{C-19}) \tag{12}$$

Indeed, when eq 12 is applied to the results of Table I, Δ(C-19) − Δ(C-18) turns out to be a constant for each solute, independent of the internal standard. Results are given in Table III. The major disadvantage is that one obtains only differential information which strongly dilutes the potential for structural interpretation. It is of interest to see whether the Δ-difference method offers advantages for additivity. Application of eq 12 three times (*i.e.*, for X_1, X_2, and X_{12}) renders the following conditions for additivity of the difference in ASIS for two signals A and B.

Table III. Averaged Experimental Values of Δ(C-19) − Δ(C-18), Using Five Different Internal References

Δ(C-19) − Δ(C-18), ppm			
5α-Androstane	5α-Androstan-3-one	5α-Androstan-17-one	5α-Androstane-3,17-dione
0.023 ±0.002	0.294 ±0.002	−0.094 ±0.001	0.187 ±0.001

$$\begin{aligned}(\Delta_{X_1A} - \Delta_{X_1B}) + (x_{2A} - \Delta_{X_2B}) &\doteq (\Delta_{X_{12}A} - \Delta_{X_{12}B}) \\ \Delta_{X_1Am} + \Delta_{X_2Am} - \Delta_{X_{12}Am} &\doteq \Delta_{X_1Bm} + \Delta_{X_2Bm} + \Delta_{X_{12}Bm}\end{aligned} \tag{13}$$

If one uses again the formalism of eq 10, *i.e.*, the subtracting out of the contributions Δ_{X_0m}, then it follows that the condition of Δ-difference additivity is fulfilled to whatever extent that the differential medium effects increments $\delta\Delta_{X_m}$ are additive (except for a deterioration by a statistical factor of $\sqrt{2}$, because eq 13 contains *two* such conditions).

Perhaps the results of Table III are indicative of the best degree of additivity that may be expected; the Δ difference of 0.187 ppm for the dione is to be compared with the 0.200 ppm for the sum of the Δ differences for the two monoketones.

(ii) The Δ-Ratio Method. Rather than subtracting, one may divide the ASIS of two different signals A and B of the same solute which leads to

$$\frac{\Delta_{XA}}{\Delta_{XB}} = \frac{\Delta_{XAm} + \Delta_{Rm}}{\Delta_{XBm} - \Delta_{Rm}} \tag{14}$$

Clearly this method has the disadvantage of not eliminating the reference compound. The right-hand side of eq 14 is a constant for any given solvents and reference material combination, but it can apparently even be a constant if either of these materials is varied.

Assume that the ASIS is measured with $CDCl_3$ as one of the solvents and any number of aromatic solvents S_i as the second solvent. Let the symbol Δ′ be used to indicate that the second solvent is aromatic but not necessarily benzene, and let it be assumed furthermore that upon plotting Δ'_{XA} *vs.* Δ'_{XB} a straight line is obtained with slope *C* and intercept *I*. By differentiation of eq 14 with respect to the second solvent it may be found that the slope is given by

$$C = (\Delta^*_{XAm} - \Delta^*_{Rm})/(\Delta^*_{XBm} - \Delta^*_{Rm}) \tag{15}$$

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[14] F. H. A. Rummens, W. T. Raynes, and H. J. Bernstein, *J. Phys. Chem.*, **72**, 2111 (1968).

[15] P. Diehl, *Helv. Chim. Acta*, **44**, 829 (1961).

[16] M. Fétizon and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 2289, 3444 (1966).

[17] P. Laszlo and J. L. Soong, *J. Chem. Phys.*, **47**, 4472 (1967).

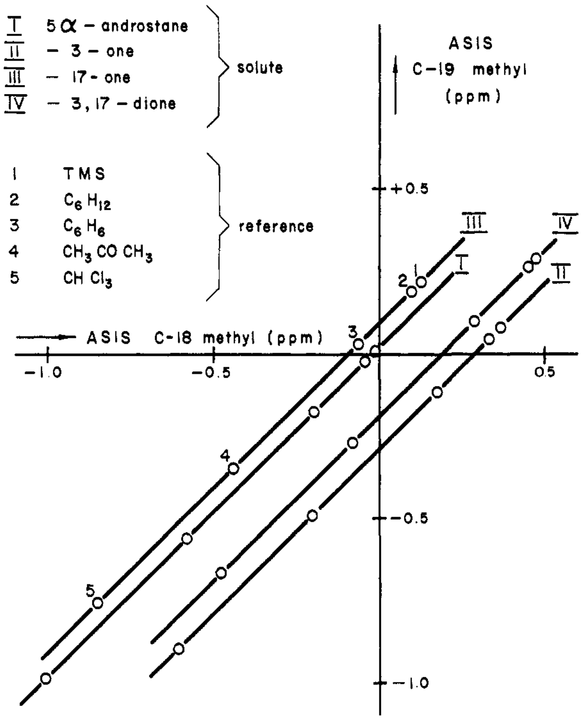

Figure 2. C-19 *vs.* C-18 ASIS plot as a function of reference compound.

where the symbol $\Delta^*{}_{\mathrm{m}}$ indicates a difference in medium effect in two *aromatic* solvent; $\Delta^*{}_{\mathrm{Xm}} = \sigma_{\mathrm{Xm}}{}^{\mathrm{S}_i} - \sigma_{\mathrm{Xm}}{}^{\mathrm{S}_j}$. Equation 15 may be rewritten as

$$\Delta^*{}_{\mathrm{XAm}} = C\Delta^*{}_{\mathrm{XBm}} + (1 - C)\Delta^*{}_{\mathrm{Rm}} \qquad (16)$$

Similarly the intercept is given by

$$I = (1 - C)\Delta'{}_{\mathrm{Rm}} - \Delta'{}_{\mathrm{XAm}} + C\Delta'{}_{\mathrm{XBm}} \qquad (17)$$

From eq 16 and 17 it is clear that both slope and intercept are still a function of the reference compound.

If, however, one furthermore imposes the condition

$$\Delta^*{}_{\mathrm{XAm}}/\Delta^*{}_{\mathrm{XBm}} \doteq \Delta'{}_{\mathrm{XAm}}/\Delta'{}_{\mathrm{XBm}} = C \qquad (18)$$

then this leads to unity slope ($C = 1$) according to eq 16 and to zero intercept ($I = 0$) according to eq 17. The condition as given by eq 18 appears to be very unlikely since it says that the difference in shielding of group A in two solvents is linearly related to that of group B in the same two solvents, but *totally independent of the choice of the two solvents.* Conversely, it may also be stated that if a plot of $\Delta'{}_{\mathrm{XA}}$ *vs.* $\Delta'{}_{\mathrm{XB}}$ is found to be linear, with unity slope and zero intercept, then the ASIS's must be a pure product of a solute factor and a solvent factor, with the changes entirely due to the solvent factor while at the same time the ASIS's must be independent of the reference. Even if all these conditions are not exactly met, the degree to which they apply (or deviate) can be taken as an indication for the degree to which solute factor and solvent factor of the ASIS are separable. An excellent example of this is formed by Engler and Laszlo's work on camphor.[5] Using a fluorocarbon as the "inert" solvent and a series of substituted benzenes as second solvents and using camphane as an internal reference they find that the ASIS of the C-9 methyl relates linearly to the ASIS of the C-8 methyl with a correlation coefficient 0.990, slope 1.39, and intercept 0.025 ppm. Repeating the experiment with the C-10 signal of camphor itself as a reference, the correlation factor is better (0.995), the slope is closer to unity ($C = 1.35$), and the intercept is closer to zero (0.017 ppm).

Engler and Laszlo have stated[5] that the linearity alone is sufficient to warrant a formal separation of solute factor and solvent factor, but the analysis given above indicates that in addition unit slope, zero intercept, and independence of reference are required. At this stage it is not clear, however, to what extent the above noted nonadherence to three of the four conditions influences the quantitative reliability of the solute and the solvent factors such as given by Engler and Laszlo.

Equation 14 can also be differentiated with respect to the internal reference. It is then found that any plot of Δ_{XA} *vs.* Δ_{XB} with the reference as a variable should be exactly linear with a slope of unity, completely independent of solute and of choice of solvent pair. The intercept of such plots is given by

$$I = \Delta_{\mathrm{XBm}} - \Delta_{\mathrm{XAm}} \qquad (19)$$

In Figure 2 such plots are given for the data of Table I. Plots as given in Figure 2 have probably little analytical value, particularly since the intercept value ($\Delta_{\mathrm{XBm}} - \Delta_{\mathrm{XBm}}$) can also be obtained by direct subtraction of the ASIS values for A and B (eq 5). Furthermore, any specific interaction of the reference compound with one or both of the solvents would go unnoticed. If the reference compound interacts specifically with the solute, this would influence the individual ASIS's but normally not their difference. Such specific interactions can be deduced, however, from the position of the points on the lines. In Figure 2 all the distances 1–2 (TMS–C_6H_{12}) are equal; so are the distances 1–3 and the distances 1–4, but the distances 1–5 (TMS–$CHCl_3$) are not the same. In terms of the data of Table I this means that using C_6H_{12} rather than TMS as the internal reference results in a decrease in ASIS (of 0.028 ± 0.003 ppm) irrespective of the solute and irrespective of whether the C-19 or the C-18 ASIS is chosen. Similarly constant ASIS shifts of −0.188 ± 0.003 ppm for the replacing of TMS by benzene and −0.565 ± 0.005 ppm for the replacement of TMS by acetone as reference compound are observed. However, upon using $CHCl_3$ rather than TMS as a reference the ASIS shift for 5α-androstane is −0.994 ppm; for the two monoketo derivatives it is −0.973 ppm, while for the 3,17-dione it is −0.953 ppm, with these results applying both to the C-19 and the C-18 signals. Since the effect for the dione (0.041 ppm) is about twice that for the monoketo derivatives (0.021 ppm), it may be surmised that this effect is due not so much to a change in the shift of $CHCl_3$ itself but rather a secondary effect such as perhaps a change in the benzene cluster[5] around the solute.

(iii) Subtraction of ASIS of Hydrocarbon Skeleton. If $\Delta_0 = \Delta_{\mathrm{Rm}} - \Delta_{\mathrm{X_0m}}$ is the ASIS of the hydrocarbon analog of the substituted compounds of interest, then the influence of the varying reference can be seemingly eliminated by taking differences $\Delta_1 - \Delta_0$ (eq 20). This

$$\Delta_1 - \Delta_0 = (\Delta_{\mathrm{Rm}} - \Delta_{\mathrm{X_1m}}) - (\Delta_{\mathrm{Rm}} - \Delta_{\mathrm{X_0m}}) = \Delta_{\mathrm{X_0m}} - \Delta_{\mathrm{X_1m}} \qquad (20)$$

is equivalent to taking the hydrocarbon analog as the reference. The advantage is that such a reference is chemically very similar to the compounds of interest and that these modified ASIS's can be expected to more accurately reflect the properties of the functional groups alone. The additivity condition for instance now becomes

$$(\Delta_1 - \Delta_0) + (\Delta_2 - \Delta_0) \doteq (\Delta_{12} - \Delta_0) \qquad (21)$$

or

$$\Delta_1 + \Delta_2 \doteq \Delta_{12} + \Delta_0 \qquad (22)$$

or

$$\Delta_{X_1m} + \Delta_{X_2m} \doteq \Delta_{X_0m} + \Delta_{X_{12}m} \qquad (23)$$

In Table II, columns five and six, the additivity of the modified ASIS is tried out. It may be concluded that the modified ASIS's are independent of the choice of internal standard (apart from a small interaction effect with $CHCl_3$). The additivity is very good, although there is a small systematic deviation of $\Delta_1 + \Delta_2$ being somewhat larger than $\Delta_{12} + \Delta_0$, namely 0.008 ppm for C-19 and 0.018 ppm for C-18. It may also be noted that the additivity holds equally well using the data with $CHCl_3$ as an internal standard although the individual ASIS's are different.

These results are expected since in this method $(\Delta_{Rm} - \Delta_{X_0m})$ is zero by definition, so that the new additivity condition (see also eq 11) now becomes

$$\delta\Delta_{1m} + \delta\Delta_{X_2m} \doteq \delta\Delta_{X_{12}m} \qquad (24)$$

a condition which is fulfilled whenever the substituent effects (in any solvent) are additive.

Notwithstanding the apparent success, it must be stressed that the above is only an additivity of substituent effects, not of interactions, since eq 22 and 23 indicate that it is still a matter of the sum of two (differential) interactions equalling the sum of two others.

External Referencing. A Proposal

The obvious solution to eliminating the effect of the reference is to use the reference *externally*, for instance, by direct measurements employing coaxial sample tubes. Alternately one may continue to use internal referencing supplemented by one-time measurements of the gas-to-solution shifts of the internal reference material(s). The latter is preferred and proposed here mainly because it is completely equivalent to the former and because it allows the continued use of the convenience of internal referencing. Taking a gas-phase shift as a reference has the added advantage that *any* gas shift, including that of the solute, is equally suitable; the actual difference is $\sigma_R^0 - \sigma_X^0$ (see Figure 1) which, being a constant, is eliminated upon taking the difference $\Delta = \delta_X^C - \delta_X^B$. It is therefore valid to speak of "referencing relative to the gas state" without having to state which molecule was in fact measured in the gas phase. In actual practice one will choose a compound which is a suitable internal reference, whose gas shift can be measured easily and whose differential shift $\Delta_{Rm} = \sigma_{Rm}^C - \sigma_{Rm}^B$ can be found accurately.

Becconsall, *et al.*,[18] have made essentially the same suggestion, but their method necessitates the simultaneous use of two nmr spectrometers of different sample geometry (a convential magnet with the sample perpendicular to the field and a superconducting magnet with the sample parallel to the field). It can be shown, however, that their method is equivalent to measuring the gas-to-solution shift of the reference compound as presently proposed.

Following Becconsall, we introduce a new ASIS parameter Δ defined as

$$\bar{\Delta} \equiv -\sigma_{Xm}^C + \sigma_{Xm}^B = -\Delta_{Xm} \qquad (25)$$

Using eq 4 we may also write

$$\begin{aligned}\bar{\Delta} = \Delta - \sigma_{Rm}^C + \sigma_{Rm}^B = \Delta - \Delta_{Rm} = \\ \Delta - (\sigma_R^C - \sigma_b^C) + (\sigma_R^B - \sigma_b^B) = \\ \Delta - (\sigma_R^C - \sigma_R^B) + (\sigma_b^C - \sigma_b^B) \qquad (26)\end{aligned}$$

A one-time measurement of the gas-to-solution shifts in $CDCl_3$ and C_6H_6 for the reference compound of choice plus a bulk susceptibility correction is sufficient to convert internally referenced Δ values to the reference and susceptibility independent $\bar{\Delta}$ parameters. This is to be compared with Becconsall's one-time measurements of the reference compound in each solvent, and this in both magnet configurations.

For the reference compounds of this study these measurements and calculations were carried out. (For details see the Experimental Section.) In Table IV the data of Table I have been converted to the new $\bar{\Delta}$ ASIS scale using the experimental data of Table V and eq 26.

Table IV. ASIS $\bar{\Delta}$ Values (in ppm) for C-19 and C-18 Methyl Protons of 5α-Androstane and Some Keto Derivatives

		Solute			
Internal ref	Signal	$\bar{\Delta}_0$ 5α-A[a]	$\bar{\Delta}_1$ 5α-A-3[b]	$\bar{\Delta}_2$, 5α-A-17[c]	$\bar{\Delta}_{12}$, 5α-A-3,17[d]
Tetramethylsilane	C-19	0.490	0.852	0.603	0.957
	C-18	0.468	0.558	0.697	0.768
Cyclohexane	C-19	0.481	0.841	0.598	0.949
	C-18	0.457	0.546	0.693	0.761
Benzene	C-19	0.499	0.856	0.613	0.963
	C-18	0.479	0.561	0.707	0.777
Acetone	C-19	0.513	0.873	0.631	0.990
	C-18	0.491	0.583	0.725	0.803
Chloroform	C-19	0.527	0.907	0.664	1.033
	C-18	0.504	0.615	0.758	0.847
Av value	C-19	0.496	0.856	0.611	0.965
($CHCl_3$ excluded)	C-18	0.473	0.562	0.706	0.777

[a] 5α-A = 5α-androstane. [b] 5α-A-3 = 5α-androstan-3-one. [c] 5α-A-17 = 5α-androstan-17-one. [d] 5α-A-3,17 = 5α-androstane-3,17-dione.

It may be noted from Table IV that the $\bar{\Delta}$ parameters are independent of the choice of internal reference. The uncertainty in the averaged values is somewhat higher than in the internally referenced Δ parameters. This is due to the various experimental errors in the gas-to-liquid shifts of the reference materials. The accuracy of the $\bar{\Delta}$ parameters cannot be expected to be better than ±0.015 ppm (± 1 Hz) for this reason.

It should be stressed that for future use of $\bar{\Delta}$ it is not necessary to follow the highly circuitous experimental route used in this paper. The correction term $\sigma_{Rm}^B - \sigma_{Rm}^C = -(\sigma_R^C - \sigma_R^B) + (\sigma_b^C - \sigma_b^B)$ of eq 26, once determined for a particular reference and solvents combination, can be added to the ASIS Δ values determined in the conventional way. Recommended values of these correction terms are given in Table VI, in

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[18] J. K. Becconsall, G. D. Daves, and W. R. Anderson, *J. Amer. Chem. Soc.*, 92, 430 (1970).

Table V. Experimental Shielding of Reference Compounds (in ppm) at 38°

Ref compd	$-\sigma_R$ relative to zero-pressure ethane In $CDCl_3$	 In C_6H_6	$-\sigma_R{}^0$ (gas) internal In ethane	Gas-to-liquid shifts $-\sigma_{Rm}$ In $CDCl_3$	 In C_6H_6
TMS	0.963	0.237	−0.882	0.333	−0.147
C_6H_{12}	2.387	1.636	0.543	0.231	−0.268
C_6H_6	8.311	7.387	6.355	0.443	−0.233
$(CH_3)_2CO$	3.111	1.791	1.053	0.548	−0.525
$CHCl_3$	8.214	6.455	6.238	0.468	−1.046

Table VI. Correction Terms to Convert Conventional ASIS Δ Values to the $\bar{\Delta}$ Scale for the $CDCl_3$–C_6H_6 Solvent System (in ppm) for Various Internal References

TMS	C_6H_{12}	C_6H_6	$(CH_3)_2CO$	$CHCl_3$
+0.487	+0.514	+0.676	+1.052	+1.48

which the data were obtained by first averaging the $\bar{\Delta}$ data for each solute to eliminate most of the uncertainty in the various gas-to-liquid data of the reference compounds (see bottom line Table IV), followed by averaging for each reference compound over the eight solute signals. The accuracy of the data of Table VI is estimated to be about ±0.01 ppm, except for $CHCl_3$ (possibly ±0.03 ppm) where the data on the keto steroids had to be omitted because of specific interaction.

The $\bar{\Delta}$ parameters are not additive, nor could this be expected since $\bar{\Delta}$ parameters indicate the total medium shift, not just the increments due to substituents. Substituent increments can be calculated, of course, by subtracting $\bar{\Delta}_0$ from all other $\bar{\Delta}$'s. These increments show very good additivity, just as good as for the original Δ increments (last two columns of Table II). In fact the results are identical because in general the following relation holds (see also eq 26).

$$\bar{\Delta}_{X_i} - \bar{\Delta}_{X_j} = \Delta_{X_i} - \Delta_{X_j} \tag{27}$$

For any discussions in terms of substituent increments (or referencing with respect to the carbon skeleton molecule) the use of $\bar{\Delta}$ parameters has no advantage; in such cases the Δ parameters are still to be preferred, because of their better accuracy. The same is true for the internal Δ-difference method (eq 12 and 26).

The $\bar{\Delta}$-ratio method, however, is quite different from the Δ-ratio method. Using the definition of $\bar{\Delta}$ (eq 25) for two different solute signals A and B, one finds

$$\bar{\Delta}_{XA}/\bar{\Delta}_{XB} = \Delta_{XAm}/\Delta_{XBm} \tag{28}$$

Therefore, if $\bar{\Delta}_{XA}$ is plotted *vs.* $\bar{\Delta}_{XB}$ (varying one of the solvents), the resulting line will have a zero intercept and a slope given by eq 29. The above relation (eq 28)

$$C = \frac{\Delta^*_{XAm}}{\Delta^*_{XBm}} = \frac{\sigma_{XAm}{}^{S_i} - \sigma_{XAm}{}^{S_j}}{\sigma_{XBm}{}^{S_i} - \sigma_{XBm}{}^{S_j}} \tag{29}$$

may be important for the study of medium effects in terms of product functions. Malinowski, *et al.*,[19] and Bernstein[20] as well as others[4,14,21] have investigated whether medium effects σ_m can be written as pure products of a solute factor and a solvent factor.[22] If such a separation is possible then eq 29 reduces to the ratio of solute factors (eq 30), which is a constant.

$$C = \frac{\text{solute factor of XA}}{\text{solute factor of XB}} \tag{30}$$

Conversely, if a plot of $\bar{\Delta}_{XA}$ *vs.* $\bar{\Delta}_{XB}$ (varying one of the solvents) produces a straight line, then this may be taken as evidence for the existence of product functions of the medium shifts in the solvents investigated. The $\bar{\Delta}$-ratio method has therefore clear advantages over the Δ-ratio method employed by Engler and Laszlo.

Another area where the new $\bar{\Delta}$ scale is bound to be superior to the Δ scale is that of complex formation of solutes with benzene and other aromatic solvents. The literature is replete with examples[1,2] where equilibrium constants have been determined by using ASIS (or similar internal reference techniques) by varying the benzene concentration or by temperature variation. There is now a growing body of evidence[1–5] that in many cases no benzene complexes exist at all. At least part of the effects are apparently due to the *shape* of the solute molecule and the consequent changes in stacking of surrounding molecules. In such cases where the complex is real, any technique designed to calculate properties of complexes must take full cognizance of the above noted nonreal or apparent complex effect. Furthermore, as this paper shows, it is necessary to correct for the effects undergone by the internal reference. With one notable exception,[23] none of the proposed techniques fulfills these two conditions. It seems therefore likely that most of the published data on equilibrium constants and enthalpies of formation are considerably in error.

Experimental Section

Instrumental. All solvents used were commercial spectrograde quality; they were freshly distilled on a vacuum line shortly before usage, to remove dissolved oxygen. The ethane was research grade (Phillips Hydrocarbons). The steroids (Steraloids Inc.) were used without further purification. The five reference compounds were mixed in a ratio to give equal signal strength and a drop (about 10 μl) of this mixture was added to the steroid solution (10 mg/400 μl). Several checks were made to ensure that admixture of reference compounds results in chemical shifts not different from those of test solutions with only one reference material. Wilmad Type 516 coaxial tubes were used for all liquid measurements. The annular space of these tubes always contained acetone as an intermediate standard. Before and after each solution measurement a measurement was made with an inner tube filled with 11.7 normal atm of ethane, to relate all measurements directly to ethane gas. A correction for the medium effect of the ethane (2.16 Hz) was made based on previous experimental data.[24] The acetone–ethane shifts

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(21) A. A. Bothner-By, *J. Mol. Spectrosc.*, **5**, 52 (1960).

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also served to measure the probe temperature, these shifts previously having been calibrated against the methanol nmr thermometry data of Van Geet.[25] Where necessary all data were related to $t = +38°$. For the gas shifts of the reference materials, these were mixed with some ethane and measured internally; the possible error due to different van der Waals shifts of gaseous reference and ethane is estimated to be less than -0.1 Hz at the low pressures employed. All reference compound solutions were measured at four concentrations (2 to 10%) and graphically extrapolated to zero concentration. A Varian A-60A spectrometer was used throughout. Audio side-band techniques were used to ensure accurate line positions (usually ± 0.1 Hz, but somewhat larger for some of the steroid methyl groups which showed unresolved long-range coupling). Molecular susceptibilities of $\chi_M = -54.85 \times 10^{-6}$ and $\chi_M = -59.30 \times 10^{-6}$ for benzene and chloroform, respectively, were used.[26] Densities[27] were calculated for the temperature prevailing at each experiment. It was assumed that the volume susceptibilities of $CDCl_3$ and $CHCl_3$ are the same, which is corroborated by the density data of $CDCl_3$.[28]

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Proton Nuclear Magnetic Resonance Study of Diamagnetic Cation Association with Hydroxylic Substrates. Interpretation of Ionic Molal Shifts in Methanol and Water

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Abstract: Association constants and hydroxyl proton nmr shifts have been measured for one-to-one complexes in acetonitrile of six diamagnetic cations with six hydroxylic substrates, including water and methanol. Their values follow the trend appropriate to a simple electrostatic association of the cation with the oxygen of the substrate. Molal shifts, Δ_m, of small cations in methanol and water may be adequately accounted for by a model which takes explicit account of nearest-neighbor interactions only. It leads to an equation of the form $\Delta_m = (nM/1000)(\Delta_c + \Delta_h)$, where n is the solvation number, M the molecular weight of the solvent, Δ_c the cation complex shift, and Δ_h a desolvation shift characteristic of the solvent. n appears to have a value near six for small and/or polyvalent cations. Δ_h has a value of about 1.5 ppm for cations in methanol at $-69°$ and water at $+25°$. It decreases with increasing temperature, and presumably reflects the amount of hydrogen bonding in the solvent. Deviations from the predicted behavior by Rb^+ and Cs^+, and the molal shifts of the larger halide ions, are most plausibly interpreted in terms of a disordered primary solvation shell, so that the effective solvation numbers of these ions are less than the number of nearest-neighbor solvent molecules. It may be possible to interpret the desolvation shift in terms of structure making by small cations and structure breaking by large anions.

Hydroxylic solvents, in particular water and the alcohols, are the principal media of ionic chemistry. Thus their mechanisms of ionic solvation are of great significance. Nuclear magnetic resonance can follow a hydroxylic molecule through the solvation process, since the shielding of the hydroxyl proton is extremely sensitive to the associations which distinguish the isolated, bulk liquid, and solvated states. It has been observed that, when an ionic salt is added to water or methanol, at most temperatures only a single time-averaged OH signal is observed, which shifts with concentration.[1] In the limit of low concentration, the molal shifts have been shown to be additive in the ions.[1-3]

It is reasonable to postulate that when ions are added to a hydroxylic solvent, those solvent molecules which interact with the ions undergo a change of state characterized by at least two effects: partial desolvation (that is, separation from one or more nearest-neighbor molecules) and polarization by the ion. It would be desirable to separate the net time-averaged shielding change caused by the ion into two corresponding terms. If these could be evaluated, then it would be possible to investigate secondary effects. For example, it has been postulated that structure-making and structure-breaking phenomena must be invoked to account for the molal shifts of ions in methanol[3] and water,[4] though the significance of these effects has been questioned.[5]

It is possible to observe 1:1 association of ions with hydroxylic substrates in an inert solvent.[6-8] If the desolvation effect is small, or if it can be evaluated, then the direct ion–molecule polarization shift is accessible to experimental observation. Ormondroyd, *et al.*,[7]

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