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A New Description of Nuclear Magnetic Resonance Solvent Shifts for Polar Solutes in Weakly Associating Aromatic Solvents[1]

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Abstract: The chemical shifts for the methyl resonances of camphor have been measured in various aromatic solvents, both polar and nonpolar. By subtracting the corresponding solvent shifts for camphane, one is able to focus on the interaction between the carbonyl group of camphor and the aromatic solvent molecules. The interpretation of the results stresses the inadequacy of a specific 1:1 complex model for weak interactions as encountered here. The notion of a time-averaged cluster of solvent molecules is introduced instead. This general solvation model accounts considerably better for various features of the data. Control experiments, for instance with the solvent shifts for camphorquinone, a molecule with the same skeleton, are reported. As a consequence of this model, solvent shifts can be expressed as product functions of a site-factor term for the various proton groups within the solute, and of a solvent parameter. The detailed meaning of each of these terms is explored.

Striking chemical shift differences are often incurred by the proton resonances of molecules having polar sites if the medium is changed from a solvent such as cyclohexane or carbon tetrachloride to an aromatic solvent like benzene. For instance, it was early observed that the chloroform proton shifts to high field by about 1 ppm upon change of the solvent from cyclohexane to benzene.[2] The interpretation of the effect rightly stressed the large magnetic anisotropy of the benzene ring, which would modify the chloroform chemical shift provided the solute molecules occupy preferentially certain regions of space with respect to the benzene solvent molecule.[3] Such ASIS[4] (Aromatic Solvent-Induced Shift(s)) have proven helpful in structure determination, since they may be decomposed into increments characteristic of the location of a given proton group with respect to a polar site. There has been a plethora of such empirical applications,[4–6] and by and large they have met with considerable success. Predictably, many authors have not resisted the urge to

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speculate about the contents of this particular "black box,"[7] and have supplied interpretations of their data in terms of discrete solute–solvent complexes. Obviously, alternative schemes, in which the solvent is viewed as a continuum,[8] were considerably less attractive because they would not account satisfactorily for the data available on polar solutes. Well-defined stoichiometries and fixed relative orientations of solute and solvent in the complex, generally deduced from the Johnson–Bovey mapping of the benzene ring anisotropy,[9] were presented in no uncertain and very graphic fashion. Ledaal's work on the geometry of solute–solvent collision complexes can be taken as an illustration of this school of thought. Initially, Schneider[2] had proposed an interpretation of the experimental data for the chloroform–benzene molecular association in geometrical terms, and many authors followed this path by postulating specific solute–solvent configurations to account for their data.[4,10,11] It remained for Ledaal to attempt a generalization: "One and the same type of collision complexes exists in all cases. This common model has the dipole axis of the solute molecule located along the sixfold axis of a benzene nucleus with the positive end of the dipole nearest, and the negative end farthest away from it."[10] Such dogmatic statements and the attendant model drawing appear strongly reminiscent of Dolezalek's ill-fated attempts to explain deviations in the properties of binary mixtures of gases from ideal behavior by the formation of discrete complexes.[12] Their interpretations of the ASIS go to three dimensions in order to depict what the postulated complex should look like. The fourth dimension, time, was left out. It will be our concern here. The introduction of this dimension is physically necessary and methodologically useful; it will allow us to reach the core of the phenomenon and to remove unnecessary trimmings. One is thus led to a simple realistic model, which will now be outlined in some detail.

Procedure and Results

(1) Purification of Chemicals and Preparation of Solutions. All chemicals used in this study, except for camphane, were the best available commercial grade. Camphane was prepared from camphor *via* a modification of the Huang-Minlon reduction.[13] Camphor, camphorquinone, and camphane were purified by sublimation before use. Solvents were dried over Fischer molecular sieves.

Solutions contained 1% tetramethylsilane as an internal reference (however, see below), and the solvent shifts were measured on samples containing the minimum detectable amount of solute (*ca.* 1% mol/mol) in the solvent of interest.

(2) Procedure for Recording and Calibration of Spectra. Spectra were obtained with a Varian A-60A spectrometer operating at the normal probe temperature of 39 ± 2°. Chemical shifts were measured using the double-audio-side-band technique, first to calibrate the sweep, and second to calibrate a given line. Five or six separate recordings were performed on each peak and averaged to yield the final value. The standard deviation in all cases was less than ±0.1 Hz.

(3) Problem of the Inert Reference Solvent. The correct inert reference state for solvent shift measurements should be the gas-phase shift of the pure solute, but this is seldom practical. The next best procedure is through recourse to a solvent believed to be inactive. Such an inert solvent must possess a dielectric constant as near unity as possible, since polar solutes are submitted to an electric field shift which increases with the

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(7) "The so called "black box" is the most general kind of model used in science. No objects or mechanisms are specified: we know nothing of what happens inside the box. All that is given is the input and the output.... The black box illustrates that the model is not itself an explanation, as has been mistakenly suggested: it need not specify a causal mechanism. Rather the model is a conceptual scheme we impose on Nature, a necessary tool for obtaining information.": E. M. Hutton in "Philosophy of Science," R. Klibansky, Ed., La Nuova Italia Editoriem, Florence, 1968, p 121.

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(9) C. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(10) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

(11) See for instance: H. Alexandrou and D. Jannakoudakis, *ibid.*, 3841 (1968); K. M. Baker and B. R. Davis, *J. Chem. Soc. B*, 261 (1968); J. Bowie, P. F. Donaghue, and J. Rodda, *ibid.*, *B*, 1122 (1969); P. V. Demarco, D. Doddrell, and E. Wenkert, *Chem. Commun.*, 1418 (1969); J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, 40, 1289 (1962); P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964); R. J. W. Lefevre, D. V. Radford, G. L. D. Ritchie, and P. J. Stiles, *J. Chem. Soc. B*, 148 (1968); J. Ronayne and D. H. Williams, *ibid.*, *B*, 540 (1967); T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1218, 1224 (1960).

(12) F. Dolezalek, *Z. Phys. Chem.*, **64**, 727 (1908).

(13) M. Fétizon, M. Golfier, and P. Laszlo, *Bull. Soc. Chim. Fr.*, 3205 (1965).

dielectric constant of the medium. For this reason we have chosen to use a fluorocarbon solvent (FC-75, 3M Co., ϵ 1.86).[14] Using this "inert" solvent yields slightly larger shifts than the recourse to cyclohexane (ϵ 2.02). However, this solvent has the disadvantage of not dissolving the more highly polar solutes. Thus camphor is soluble, while camphorquinone is not. We have deliverately avoided the use of carbon tetrachloride, since it has been shown to be a poor choice as an inert solvent,[14] but it still possesses many advantages as an nmr solvent.

(4) **Choice of an Internal Reference.** The reliability of tetramethylsilane (TMS) as an internal reference for liquid-phase proton magnetic resonance spectra has been examined earlier.[15] It was shown that TMS gives rise to weak interactions with aromatic solvents such as pyridine, nitrobenzene, aniline, etc., which can lead to extraneous shifts. Given this problem, we have attempted to avoid the use of TMS in the referencing of our solvent shifts. Two independent procedures were followed to circumvent this problem. One involves the referencing of the camphor shifts to its reduced hydrocarbon analog,[16] camphane. The other procedure takes advantage of the fact that the site factor (as defined below) for the C-10 methyl in camphor is very close to zero. We have referenced the chemical shifts to this internal standard and obtained substantially the same results as with the camphane referencing. It should be noted that any peak from the solute may have been chosen for that matter, as implied by the proportionality relationship implicit in

$$\text{ASIS} = (\text{site factor})(\text{solvent parameter}) \qquad (1)$$

That the referencing of a resonance in camphor to its camphane counterpart or to the C-10 methyl resonance in camphor are virtually equivalent practices can be appreciated from Figure 1, in which graphs of the C-9 *vs.* C-8 ASIS obtained from the two procedures are compared. The same functional dependence obtained in both cases implies that it is not an artifact due to the experimental conditions.

More accuracy would result from total removal of the effect of the reference, according to a method which has been recently developed.[17] Unfortunately, this was not feasible here, but the magnitude of the shifts is such that small errors from the referencing procedure can be tolerated.

(5) **Camphor–Benzene Equilibrium Measurement.** The equilibrium constant for the interaction between camphor and benzene has been determined according to the procedure of Foster and Fyfe.[18] The value for K was 0.02 l./mol using the C-9 methyl and 0.03 l./mol using the C-8 methyl.[19]

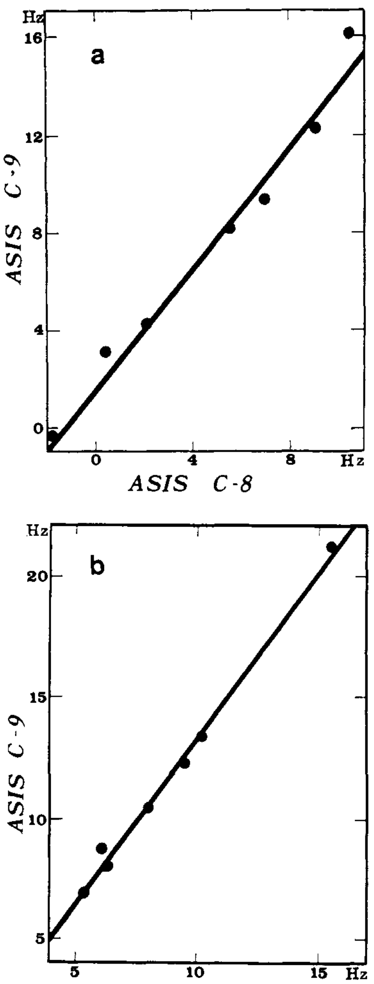

Figure 1. Plot of the C-9 methyl ASIS of camphor *vs.* the C-8 methyl ASIS of camphor for a single series of substituted benzene solvents: (a) for solvent shifts referenced to camphane, correlation coefficient = 0.990; (b) for solvent shifts referenced to C-10, correlation coefficient = 0.995.

(6) **Presentation of Data.** Since TMS has been used so widely in the past, we also report in Table I the chemical shifts relative to TMS for the 8, 9, and 10 methyls in camphor for 50 solvents. The ASIS for the 8 and the 9 methyls have been expressed with respect to the C-10 methyl using FC-75 fluorocarbon as the inert solvent for the reasons already discussed. The chemical shifts of camphor in carbon tetrachloride and in cyclohexane are also included in Table I for comparison purposes. In fact, the magnitude of the solvent shifts discussed here is sufficiently large that our conclusions are virtually unaffected by the choice of the inert solvent and the reference compound; the ASIS bear an uncertainty of ±0.4 Hz.

Inadequacy of a Fixed 1:1 Complex for Nmr Studies

There is little doubt that binary collisions do indeed occur in solution. However, if one evaluates the strength of the interaction between a polar solute, such

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[14] Unfortunately, the volume magnetic susceptibility for this solvent which would be a rigorous index of its "inertness" is not available.

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

[16] M. J. S. Dewar and A. P. Marchand, *J. Amer. Chem. Soc.*, 88, 354 (1966).

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[18] R. Foster and C. A. Fyfe, *Trans. Faraday Soc.*, 61, 1626 (1965).

[19] K. M. Baker and B. R. Davis, *J. Chem. Soc. B*, 261 (1968), have reported a value of 1.21 on a *mole fraction* concentration scale for the same interaction. Their method involved varying the camphor concentration in benzene without recourse to an "inert" solvent. Caution about the use of a mole fraction scale in the measurement of weak interactions has already been expressed.[20] Furthermore, our values are in line with previous uv determinations giving $K = 0.07 \pm 0.04$ l./mol for the closely related acetone–benzene system.[21]

[20] I. D. Kuntz, Jr., F. P. Gasparro, M. D. Johnston, Jr., and R. P. Taylor, *J. Amer. Chem. Soc.*, 90, 4778 (1968).

[21] R. F. Weimer and J. M. Prausnitz, *Spectrochim. Acta*, 22, 77 (1966).

Table I. Chemical Shifts of the Camphor Methyl Groups in 50 Solvents[a]

				ASIS relative to C-10[b]	
Solvent	C-10	C-9	C-8	C-9	C-8
FC-75	53.60	58.69	50.68	0.0	0.0
Cyclcohexane	51.46	56.11	48.30	0.4	0.2
Carbon tetrachloride	51.59	57.08	50.00	−0.4	−1.3
Benzene	53.96	37.97	35.51	21.1	15.5
Toluene	51.46	39.32	35.64	17.2	12.9
o-Xylene	48.95	38.79	34.55	15.25	11.5
m-Xylene	49.74	40.16	35.60	14.7	11.2
p-Xylene	49.94	40.09	35.93	14.9	11.1
Mesitylene	48.78	40.50	35.61	13.4	10.25
Ethylbenzene	51.28	40.75	36.46	15.6	11.9
m-Diethylbenzene	49.94	42.31	37.14	12.7	9.9
p-Diethylbenzene	49.96	42.29	37.34	12.8	9.7
1,3,5-Triethylbenzene	49.37	44.08	38.41	10.4	8.0
Isopropylbenzene	51.32	42.31	37.63	14.1	10.8
p-Diisopropylbenzene	50.43	45.26	39.73	10.3	7.8
1,3,5-Triisopropylbenzene	50.22	47.85	41.72	7.5	5.6
tert-Butylbenzene	50.76	42.85	37.91	13.0	9.9
Fluorobenzene	53.36	45.50	40.43	12.95	10.0
Chlorobenzene	51.62	44.51	39.16	12.2	9.5
Bromobenzene	51.18	44.32	39.03	11.95	9.2
Anisole	51.64	42.54	38.40	14.2	10.3
Aniline	50.55	38.04	35.08	17.6	12.55
N,*N*-Dimethylaniline	49.33	38.89	35.27	15.5	11.1
Nitrobenzene	53.87	52.62	46.39	6.3	4.6
Benzonitrile	52.78	50.97	44.41	6.9	5.45
Benzaldehyde	52.72	47.69	42.15	10.1	7.65
α,α,α-Trichlorotoluene	52.32	46.42	41.06	11.0	8.3
α-Chlorotoluene	51.02	42.34	37.78	13.8	10.3
Benzyl methyl thioether	51.51	45.80	40.27	10.8	8.3
Benzylamine	49.71	41.06	36.38	13.7	10.4
α-Phenylacetone	51.44	46.95	41.11	9.6	7.4
Phenylacetonitrile	50.01	45.55	39.47	9.55	7.6
m-Difluorobenzene	54.04	51.29	44.99	7.8	6.1
m-Dichlorobenzene	51.30	48.16	42.15	8.2	6.2
m-Dimethoxybenzene	50.82	45.59	40.54	10.3	7.4
m-Fluorotoluene	51.30	46.30	40.50	10.1	7.8
m-Nitrotoluene	52.35	52.86	45.82	4.6	3.6
α-Chloro-*m*-xylene	49.93	43.46	38.20	11.6	8.8
m-Tolualdehyde	50.75	48.13	41.75	7.7	6.1
m-Anisaldehyde	51.36	49.38	43.35	7.1	5.1
p-Bromotoluene	49.45	44.92	39.00	9.6	7.5
p-Bromofluorobenzene	52.83	49.36	43.98	8.6	5.9
p-Bromonitrobenzene	54.74	57.24	50.14	2.6	1.7
o-Dichlorobenzene	51.31	47.45	41.83	8.95	6.6
α-Methylnaphthalene	49.51	18.08	22.79	36.5	28.8
α-Chloronaphthalene	50.11	23.55	26.83	31.65	20.4
Pyridine	54.47	47.84	42.65	11.7	8.0
Pyridazine	55.74	52.80	47.74	8.0	5.1
Pyrrole	48.57	41.82	35.11	11.8	10.5
1-Methylfuran	52.35	50.03	43.52	7.4	5.9

[a] Shifts relative to TMS. [b] In hertz at 60 MHz.

as acetone, and benzene, using known values for the dipole moment, polarizabilities, etc., one comes up with values for the dipole–induced dipole and induced dipole–induced dipole terms that are of the order of magnitude of RT.[22] Because of thermal agitation, these "collision complexes" can exist only for a time very short compared to the nmr time scale.[4] They might involve a large number of distinct orientations and energies. These sum up to an apparent and entirely fictitious "complex" whose equilibrium constant (K) and limiting shifts (Δ) are in fact weighted averages among all of the species involved. It has been shown that there is strict equivalency between consideration of a plurality of 1:1 complexes having differing values of K and Δ, and that of a single such species.[23] However, such an artificial simplification may be dangerous; as has been shown repeatedly with respect to *weak* interactions of the type we are concerned with, characterized by heats of formation of the order of 1 kcal/mol, Benesi–Hildebrand-type treatment of the experimental data is likely to lead to unacceptable errors in the determination of the resulting K and Δ values.[24] This may be the reason that the apparent equilibrium constants for complex formation determined by nmr for different groups of nuclei in the same solute agree neither with one another[25] nor with independent determinations by calorimetry[27] or by optical methods,[28] whenever K is in the range of 0–*ca.* 0.5 l./mol. In addition, the additivity frequently observed for the ASIS has been shown to be incompatible with a 1:1 complex of fixed geometry.[32]

In weak molecular associations, exemplified by the acetone–benzene system, the component molecules were demonstrated by nmr relaxation measurements to translate and rotate separately; stronger complexes, such as between $CHCl_3$ and DMSO, tumble as discrete entities.[35] Based upon such compelling physical evidence, it seems neither reasonable nor meaningful to extract from the nmr data the characteristics of a species lacking real physical existence. Warnings against interpretation in terms of well-defined and fixed geometries have indeed been issued; a handful of authors have argued that a better model would consider the interaction as general solvation rather than a specific complexation.[22,33,34a,36] This would involve a slight organization of solvent molecules around the polar sites which can be viewed on the nmr time scale as a clustering of solvent molecules. This intuitive notion of a solvent cluster or cage is presented as an alternative to the 1:1 complex model of fixed geometry, which is inadequate for such *weak* interactions. It remained to be

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[22] Y. Ichikawa and T. Matsuo, *Bull. Chem. Soc. Jap.*, 40, 2030 (1967); we have repeated these calculations using the expressions given in J. O. Hirschfelder, C. F. Curtiss, and R. B. Byrd, "Molecular Theory of Gases and Liquids," Wiley, New York, N. Y., 1954, Part III.

(23) (a) I. D. Kuntz, Jr., and M. D. Johnston, Jr., *J. Amer. Chem. Soc.*, **89**, 6008 (1967); (b) B. W. Bangerter and S. I. Chan, *ibid.*, **91**, 3910 (1969).

(24) (a) W. B. Person, *ibid.*, 87, 167 (1965); (b) E. L. Heric, *J. Phys. Chem.*, **73**, 3496 (1969); (c) D. A. Deranleau, *J. Amer. Chem. Soc.*, **91**, 4044, 4050 (1969).

(25) M. I. Foreman, R. Foster, and D. R. Twiselton, *Chem. Commun.*, 1318 (1969); see also K. D. Bartle and D. W. Jones, *J. Chem. Soc. A*, 437 (1969); also they depend on the particular concentration scale used.[20,26]

(26) M. W. Hanna and A. L. Ashbaugh, *J. Phys. Chem.*, **68**, 811 (1964).

(27) M. D. Johnston, Jr., Ph.D. Thesis, Princeton University, 1969.

(28) For instance, under similar conditions, the equilibrium constant for the interaction of 1,3,5-trinitrobenzene and benzene is measured as 0.79 l./mol by nmr techniques and 0.57 l./mol by optical methods.[29] Likewise, the nmr equilibrium constant (0.47 ± 0.03 l./mol)[30] for the *p*-benzoquinone–hexamethylbenzene interaction has been found to differ from the optical determination (0.58 ± 0.02 l./mol).[31]

(29) P. H. Emslie, R. Foster, C. A. Fyfe, and I. Horman, *Tetrahedron*, 21, 2843 (1965).

(30) P. G. Mennitt and E. M. Engler, unpublished work.

(31) R. Foster, D. L. Hammick, and P. J. Placito, *J. Chem. Soc.*, 3881 (1956).

(32) Individual polar sites within a molecule are important, and not whether the molecule possesses an overall net dipole moment. This was not clearly recognized by Brown and Stark[33] and was stressed later.[34]

(33) T. L. Brown and K. Stark, *J. Phys. Chem.*, **69**, 2679 (1965).

(34) (a) P. Laszlo and J. L. Soong, Jr., *J. Chem. Phys.*, 47, 4472 (1967); (b) A. Mackor and H. A. Meinema, unpublished results; we thank Professor Mackor, Utrecht, Holland, for their communication; (c) ref 20; see also ref 23b.

(35) J. E. Anderson, *J. Chem. Phys.*, **51**, 3578 (1969).

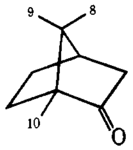
(36) (a) R. C. Fort, Jr., and T. R. Lindstrom, *Tetrahedron*, **23**, 3227 (1967); (b) T. Matsuo, *J. Phys. Chem.*, **72**, 1819 (1968); (c) K. D. Bartle and D. W. Jones, *J. Chem. Soc. A*, 437 (1969).

elaborated upon in detail, so that it would rest on a firm experimental basis and be amenable to a general and quantitative treatment. We shall now outline such a method based on these premises which appears to be entirely satisfactory in accounting for and predicting the experimental data.

Description of Our Approach

Our goal at the outset of this investigation was twofold: not only to try to develop a new physical model based on the notion of solvent clusters, but also to give it a sound experimental foundation, in terms of the only observable parameters which are available, namely chemical shifts. We decided for this reason not to confine this study to the benzene solvent, but rather to examine a wide variety of aromatic solvents. We would thus hope to remedy by the abundance of the data the indeterminacy implicit in the physical model itself.[37] We also decided to examine at first a single solute molecule, which would then necessarily have an approximately constant molecular volume in the solvents used. Philipsborn and coworkers[38] have drawn attention to significant variations of the ASIS upon the molecular size of the solute, even when the solute is a hydrocarbon molecule.[39] We have investigated, ourselves, this effect in the case of polar solutes (see Appendix).

The solute we chose is the camphor molecule (**1**)



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which presents a number of practical advantages. (a) It is abundant and inexpensive. (b) It has a rigid skeleton and the geometry is well defined. (c) There are ten different groups of protons in the molecule and the ASIS for every single resonance have been measured recently at 220 MHz.[40] (d) It is easily purified by sublimation. (e) Possibly owing to its spherical overall shape, it manifests excellent solubility in most nmr solvents. (f) Its interaction with aromatic solvents is very weak (its dilution curve with benzene is "flat;" see Procedure and Results section and Figure 5).

Now to the physical model used. To begin with, one can look upon the observed solvent shifts as due to some kind of ordering of the aromatic solvent molecules around the polar solute, owing to its overall shape and polarity. The single most important feature of our model is the notion that, because of the very slow time scale of nuclear magnetic resonance, the interactions between the camphor solute and its aromatic solvents will be *time averaged.* In benzene solution, at a given instant there will be a binary encounter between one camphor and one benzene molecule. This occurs with a certain configuration, which we can imagine, for instance, in terms of the center of the benzene ring occupying a certain position outside the camphor molecule. At another instant, the benzene ring will have yet another position, and so on. This concept of polar sites being preferentially solvated is habitual to organic chemists and physical chemists alike. One may visualize the carbonyl group in camphor, undoubtedly its most polar site, as surrounded on a *time average* by a "cloud" of benzene solvent molecules which represents the cumulative effect of all the encounters which have taken place. The number of encounters is extremely high, therefore their statistical average should be something like a "solvation sphere" of aromatic molecules congregated around the carbonyl group, a shell of solvent molecules. Since the solvent molecules are magnetically anisotropic, any protons within the camphor molecule, for instance the 8-methyl protons, are going to "see" the carbonyl C–O bond with a different magnetic susceptibility tensor in the active aromatic solvent than in an inert reference solvent: the aromatic solvent molecules *superimpose* their magnetic anisotropy on that of the carbonyl bond itself. This statement should not be construed as implying that the carbonyl magnetic anisotropy is modified in going from, *e.g.*, carbon tetrachloride to benzene, only that it will *appear* to have been changed. If we now want to compare the ASIS for the 8-methyl protons to that for the 9-methyl protons, these *must* differ *a priori* simply because these two proton groups do not have the same geometrical relationship with respect to the C–O bond, but see it, as it were, from a different angle. One is led to the conclusion that the ASIS for any particular proton group in the camphor molecule is necessarily made up of two parts, a site factor representing the disposition of that proton group with respect to the solvated polar site, a purely geometrical term, and a solvent parameter, which is expected to include the size of the solvent molecules, the magnitude of their ring current as it might, for instance, be affected by polar substituents, and of course the magnitude of the physical interaction drawing together camphor with these aromatic solvents.[41]

$$\text{ASIS} = (\text{site factor})(\text{solvent parameter}) \tag{1}$$

As a first approximation, we resolved to express the *apparent* change in the magnetic anisotropy of the carbonyl by the dipolar term[42]

$$\text{site factor} = \frac{3\cos^2\theta - 1}{r^3} \tag{2}$$

In the above expression for the site factor, r and θ are respectively the radius vector and the inclination from a point dipole located, *e.g.*, at the oxygen end of the carbonyl, for want of a better origin from within the solvent cluster.[43]

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[37] It should be recalled in this context that Baldwin has remarked to the effect that attempts to devise a 1:1 complex with a certain geometry to account for three experimental ASIS were doomed, since five parameters are needed to specify the position of a benzene ring with respect to another molecule: J. E. Baldwin, *J. Org. Chem.*, 30, 2423 (1965).

[38] J. Becconsall, T. Winkler, and W. v. Philipsborn, *Chem. Commun.*, 430 (1969).

[39] T. Winkler and W. v. Philipsborn, *Helv. Chim. Acta*, **51**, 183 (1968); **52**, 87 (1969).

[40] P. V. Demarco, D. Doddrell, and E. Wenkert, *Chem. Commun.*, 1418 (1969).

[41] It is interesting to note in this respect that Rummens has also used products of solute and solvent properties: F. H. A. Rummens, *J. Amer. Chem. Soc.*, **92**, 3214 (1970).

[42] The familiar McConnell approximation to the magnetic anisotropy of a bond in a molecule; we are resorting to it here in an *inter*- rather than in an *intra*molecular sense: H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).

[43] We thus resist the temptation to infer from the experimental values where the center of the solvation sphere should be. The very notion of a "center" is open to question: that the shell of solvent molecules has no physical reality but is merely a convenient term for the time-averaged picture present in these experiments. It should only be stated here as an empirical observation that the origin of coordinates

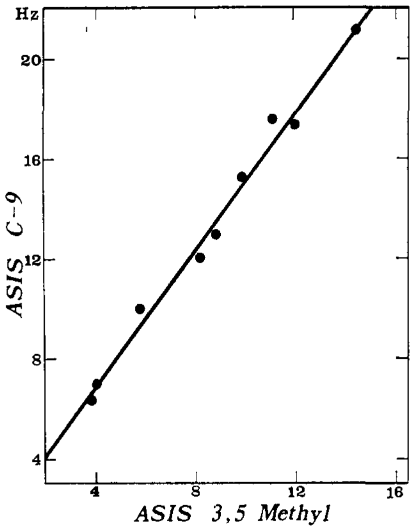

Figure 2. Plot of the C-9 methyl ASIS of camphor *vs.* the 3,5-methyl ASIS of 3,3,5,5-tetramethylcyclohexanone in a series of substituted benzene solvents. Solvent shifts are referenced to the C-10 methyl of camphor. Correlation coefficient = 0.993.

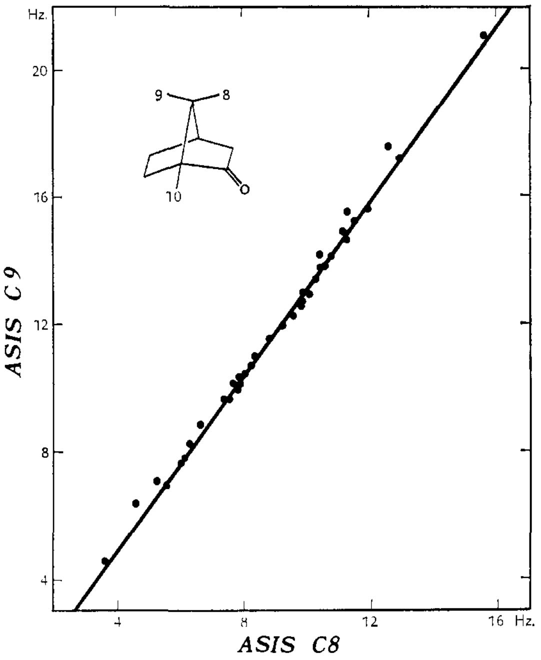

Figure 3. Plot of the C-9 methyl ASIS *vs.* the C-8 methyl ASIS of camphor for a large number of aromatic solvents. See Table I for individual solvent shifts. Correlation coefficient = 0.995.

Assuming the validity of these postulates, it should be possible to eliminate the solvent parameter in eq 1 by comparing the ASIS obtained for different proton groups within the same molecule (an *intra*molecular comparison) or within different molecules (an *inter*molecular comparison). This expectation is indeed realized, as shown in Figure 2, which compares the 9-methyl resonance in camphor with the methyl resonances in an entirely different ketone, 3,3,5,5-tetramethylcyclohexanone.[44] Intramolecular comparisons are equally successful[45] (Figure 3). As another check on the correctness of this approach, one would predict from the expression for the site factor (eq 2) that the 8- and the 9-methyl groups of camphorquinone, a molecule containing two quasiequivalent carbonyls with a very similar geometry to the one in camphor, should display ASIS with very nearly twice the camphor values; this expectation is also realized (Table II). This observation is strongly suggestive of independent solvation of the two carbonyls, which is impossible to reconcile with the notion of a single 1:1 complex with a fixed geometry. Likewise, the existence of the outstanding correlation depicted in Figures 2 and 3 cannot be reconciled easily with the notion of a 1:1 collision complex. For example, in going from benzene to nitrobenzene, both the geometry and the equilibrium constant for the 1:1 complex would have to change drastically in order to comprise the dipolar interaction between the carbonyl and the nitro substituent. It could not be expected that the change in the C-9 ASIS would be linear in that for the C-8 ASIS irrespective of the solvent used.

Table II

Solvent	Proton group	ASIS[a] Camphor	Camphorquinone
Benzene	C-9	16.0	33.3
	C-8	10.5	20.2
α-Methylnaphthalene	C-9	31.25	63.5
	C-8	18.5	31.9

[a] ASIS in hertz at 60 MHz referenced to camphane, "inert" solvent cyclohexane.

Analysis of the Site Factors

Calculation of r and θ can be performed so as to obtain estimates of the site factors (eq 2) for various positional relationships within the polar solute. These calculated site factors should then, if our solvation treatment is valid, be proportional to the experimentally determined solvent shifts. This is indeed the case, as evidenced by the values listed in Table III. The agreement between the calculated and experimental site factors is good in all cases, considering the approximate nature of the calculations.[46] It should be noted that the ratio of the *calculated* site factors for the 8- and the 9-methyl groups of camphor is identical with the slope in Figure 3.

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must be located in that region of space containing the carbonyl group rather than elsewhere, and that the physical phenomenon itself must be independent of the system of coordinates chosen to describe it. The procedure we have followed is assuredly incorrect; it need not be more incorrect than alternative procedures.

(44) The success of the intermolecular comparison also serves to rule out the formal possibility that in going from one ketone to another the dipolar approximation to the real magnetic susceptibility tensor with its three different principal axes would vary markedly and therefore lack generality. This and other experiments also serve to extend our conclusions to the entire class of ketones, and not only to camphor itself.

(45) We note in passing that the fact that such correlations obtain as an *a posteriori* justification for our procedure (see Procedure and Results) of referencing the shifts to the 10-methyl resonance: any peak could be chosen for that matter, as implied by the proportionality relationship in eq 1; the 10-methyl resonance has simply the added empirical advantage that the site factor for it is very close to zero.

(46) r and θ were measured using Framework molecular models, with experimental bond lengths (see Procedure and Results). This crude procedure could assuredly be improved upon. For example, computer programs have been developed to calculate the conformations of hydrocarons[47] and are in the process of being extended to other organic molecules; a listing of the site factors, as defined above with respect to each polar site, can easily be made a part of their output.

(47) For a comprehensive review on the subject, see J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968).

Table III. Site Factors for Some Ketones

Proton group	$\frac{3\cos^2\theta - 1}{r^3} \times 10^3$	Benzene ASIS × 0.5, Hz
Camphor		
8-CH_3	7.0	6.4
9-CH_3	9.4	9.2
10-CH_3	−1.5	−1.4
exo-3-H	10.1	7.8[a]
endo-3-H	10.1	8.4[a]
4-H	15.4	13.2[a]
exo-5-H	11.0	10.5[a]
endo-5-H	13.4	13.4[a]
exo-6-H	8.9	9.9[a]
endo-6-H	5.8	4.2[a]
Fenchone		
8-CH_3	3.1	3.0[b]
9-CH_3	3.0	2.4[b]
10-CH_3	−1.5	−0.6[b]
2,2,6,6-Tetramethylcyclohexanone	1.8	1.8[c]
3,3,5,5-Tetramethylcyclohexanone	6.0	6.8[c]
4,4-Dimethylcyclohexanone	11.2	11.5[c]

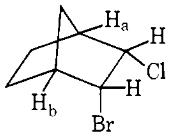
[a] P. V. Demarco, D. Doddrell, and E. Wenkert, *Chem. Commun.*, 1418 (1969). [b] J. D. Connolly and R. McCrindle, *J. Chem. Soc. C*, 1613 (1966). [c] M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

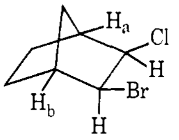
The solvent shifts for all ten proton resonances of camphor (Table III) have been recently measured by Demarco, *et al.*[40] These authors rationalize the magnitude of the observed ASIS in terms of a specific 1:1 complex with a fixed configuration. As seen from Table III, the relative magnitude and the sign of the ASIS are very well predicted solely on the basis of site factors. There is no need for invoking extraneous factors such as a benzene ring associating with camphor according to a given orientation: *the geometry of the camphor solute in itself suffices to account for the solvent shifts observed.*

This paper is mainly concerned with the carbonyl group, yet the site-factor treatment has apparently widespread applicability. For example, we have performed site-factor calculations on *exo*- and *endo*-dihalonorbornanes (Table IV). Assuming additivity of substituent effects, the site factor for the bridgehead proton can be expressed as the sum of increments for each carbon–halogen bond. Thus for *endo*-2-bromo-3-chloronorbornane

$$\begin{aligned} H_a &= 2\text{-}endo\text{-Br} + 3\text{-}endo\text{-Cl} \\ &= 8.5 + 17.3 \\ &= 25.8 \end{aligned}$$

Table IV. Site-Factor Analysis for 2,3-Dihalonorbornanes





	ASIS (endo)[b]	ASIS (exo)[b]
Calcd	~26	~14
Exptl[a]	~27	~18

[a] P. M. Subramanian, *et al.*, *J. Org. Chem.*, **30**, 2624 (1965). [b] In hertz at 60 MHz.

Similarly, for H_b

$$\begin{aligned} H_b &= 2\text{-}endo\text{-Br} + 3\text{-}endo\text{-Cl} \\ &= 25.5 \end{aligned}$$

Aside from the good agreement obtained between experimental and calculated values, it should be noted that a distinction between the endo and exo isomers is clearly possible using site factors, demonstrating the potential utility of such site factors in structural determinations. Conversely, one should also note that the notion that "the two methyl groups in dimethylformamide are equally exposed to solvent molecules"[48] is open to question.

Analysis of the Solvent Parameters

We have just seen how the relative magnitude of the ASIS for various proton groups within a polar molecule can be accounted for in terms of site factors. The solvent—and therefore the solvent parameter in eq 1—was being kept constant. Let us now conversely hold the site factor constant, by examining a given proton group, and vary the solvent. This will give us information on how the solute–solvent interaction is affected by structural changes in the solvent molecules.

These changes amount of course to variations in the steric requirement and in the polarity of substituents on the benzene ring. Let us examine each of these factors in turn, and start by considering the former. The steric bulk of a substituent will modify the overall molecular volume of the solvent molecules, hence their access to the polar sites within the solute. Let us therefore consider solvents with the benzene ring progressively substituted with alkyl groups. When the ASIS obtained for the 9-methyl group of camphor in various aromatic hydrocarbon solvents are compared (Figure 4), they are seen to be strictly proportional to the concentration of benzene rings in the medium, as gauged for instance by the ratio d/M of the molecular weight to the density of the solvent (*i.e.*, the number of solvent molecules per unit volume). Furthermore, the proportionality constant *is the same* as when benzene itself is being diluted with an inert solvent (Figure 5). Again, this observation is not restricted to ketones; the ASIS which had been obtained previously for dimethylformamide[49] can also be shown to follow a similar plot. Likewise, the temperature dependence of the ASIS (Figure 6) or their proportionality to the concentration of the active solvent (Figure 5) is easily accountable in terms of the concentration of benzene rings. This conclusion is of importance: when aromatic benzenoid hydrocarbons are selected as solvents, the overall distribution of benzene rings within the solvent cage or cluster appears, at least from the compounds we have examined, to be unchanged with respect to that for benzene itself. The making of the aromatic ring a better electron donor through alkyl substitution does not appear to modify substantially the interaction with the camphor solute, hence the interaction is better not described as a charge-transfer type. Neither can it be said to conform to a fixed 1:1 complex model: the experimental data clearly rule it out; a steric effect would be expected. The accumulation of alkyl substituents on a benzene ring would be expected to hinder its ap-

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(48) W. T. Raynes and T. A. Sutherley, *Mol. Phys.*, 18, 129 (1970).

(49) A. A. Sandoval and M. W. Hanna, *J. Phys. Chem.*, 70, 1203 (1966).

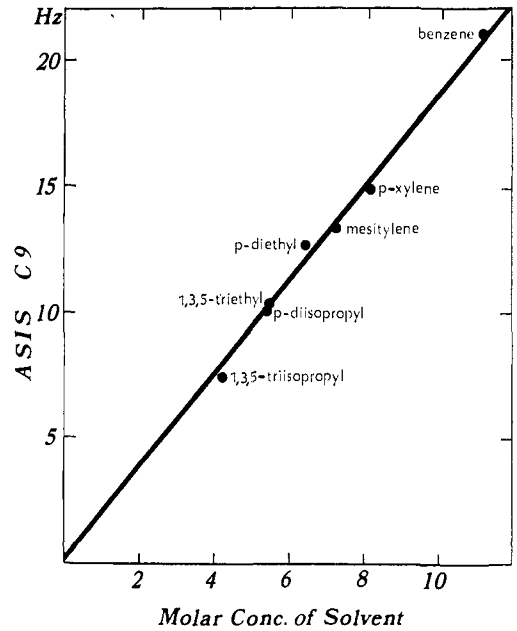

Figure 4. Plot of the C-9 methyl ASIS of camphor *vs.* the molar concentration of the aromatic solvent (*d*/*M*) for a series of symmetrically substituted alkyl benzenes. Solvent shifts are referenced to the C-10 methyl of camphor. Correlation coefficient = 0.998, slope = 1.87 ± 0.04. Densities were taken from "Selected Values of Properties of Hydrocarbons and Related Compounds," American Petroleum Institute Research Project 44, prepared by The Thermodynamics Research Center, Department of Chemistry, Texas A&M University, College Station, Texas, 1963.

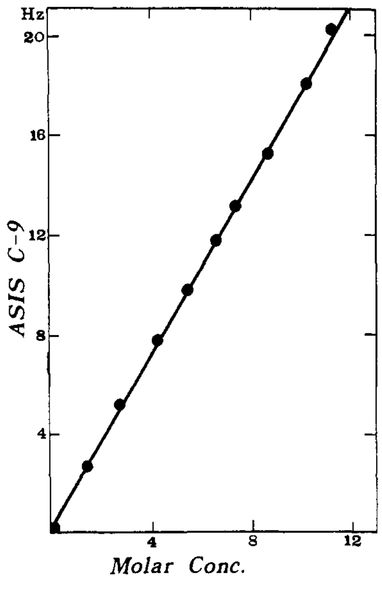

Figure 5. Benzene dilution curve for the C-9 methyl of camphor. Solvent shifts are referenced to C-10 of camphor. Correlation coefficient = 0.999, slope = 1.78 ± 0.02.

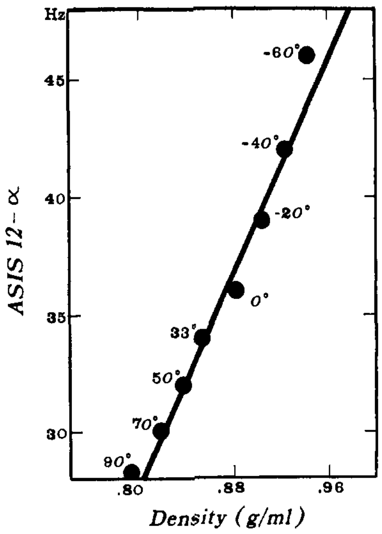

Figure 6. Plot of ASIS for the 12-α proton resonance of 5-α-androstan-11-one [P. Laszlo and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 2799 (1966)] *vs.* the density of the toluene solvent at various temperatures (densities taken from "International Critical Tables," Vol. III, E. W. Washburn, Ed., McGraw-Hill, New York, N. Y., 1928, p 29).

proach to the polar solute, hence decreasing K and changing the value of Δ. Again, the data are nicely accounted for in terms of general solvation rather than specific complexation. The distinction we are making here is somewhat subtle: we submit that the clustering model corresponds to the *mean* value of the interaction for a distribution of configurations differing in energy, somewhat in the sense of Boltzmann statistics, whereas the fixed-complex model corresponds to the *most probable* value for the energy of interaction, as one could conceivably measure by infrared spectroscopy.

There are two further points to be made about the fact that the ASIS, in, for instance, mesitylene solution, are dependent only upon the concentration of the benzene rings, and are not affected by the presence of the methyl substituents. This observation strongly supports our original assumption of binary solute–solvent collisions, since higher order collisions would entail either steric hindrance from the alkyl groups or some kind of geared or cooperative tumbling of the solvent molecules, both of which would be expected to affect the chemical shift. Finally, even though we find here that the aromatic hydrocarbons do not manifest any preference for solvating camphor relative to one another, we do fully expect, of course, that more strongly interacting solutes—characterized by K values above *ca.* 1 l./mol—would be preferentially solvated, for example, by durene if it were pitted against benzene. It may well be that the clustering model presented here would be invalidated in the presence of strong steric hindrance of the polar site within the solute, a point about which we do not have any evidence for or against currently.

We are now in a position to separate empirically the intrinsic effect of a substituent on the benzene ring due essentially to its polar character from its intrinsic effect on the pure solvent concentration, simply by using Figure 4 as a calibration curve. For example, Table V indicates how this separation is performed in the cases of benzaldehyde and of α,α,α-trichlorotoluene, two solvents for which very similar gross ASIS are observed, yet in which the actual substituent effects differ markedly. The ASIS arising purely from molecular volume is read off of Figure 4 using the molar concentration of the solvent. This ASIS can then be subtracted from the benzene ASIS to give the size contribution of the solvent relative to benzene. The difference between the observed ASIS and that arising purely from molecular volume represents the electronic contribution of the

Table V. Breakdown of the Solvent Parameters into "Size" and "Electronic" Contributions

Solvent	Benzene	Benzaldehyde	α,α,α-Trichlorotoluene
ASIS$_{obsd}$, Hz	21.1	10.1	11.0
Molar concn, *d*/*M*	11.3	9.9	7.0
ASIS purely due to mol vol	21.15	18.6	13.2
Size contribution rel to benzene	0	−2.5	−7.9
Perturbation by subst (ASIS)$_R$	0	−8.5	−2.2

Table VI. Isolation of the Intrinsic Interaction Term (ASIS)$_R$ for the 9-Methyl Group in Camphor

Solvent	ASIS C-9	Molar concn	Size contribution rel to benzene	(ASIS)$_R$
Benzene	21.1	11.25	0	0
Toluene	17.2	9.4	3.4	0.5
o-Xylene	15.25	8.45	5.2	0.7
m-Xylene	14.7	8.1	5.75	0.7
p-Xylene	14.9	8.1	5.8	0.3
Mesitylene	13.4	7.2	7.5	0.2
Ethylbenzene	15.6	8.2	5.7	−0.2
m-Diethylbenzene	12.7	6.4	8.9	−0.6
p-Diethylbenzene	12.8	6.4	9.0	−0.6
1,3,5-Triethylbenzene	10.4	5.3	11.0	−0.3
Isopropylbenzene	14.1	7.2	7.5	−0.55
p-Diisopropylbenzene	10.3	5.3	11.1	−0.3
1,3,5-Triisopropylbenzene	7.5	4.2	13.1	0.5
tert-Butylbenzene	13.0	6.5	8.9	−0.8
Fluorobenzene	12.95	10.65	1.05	7.1
Chlorobenzene	12.2	9.8	2.6	6.3
Bromobenzene	11.95	9.5	3.2	5.9
Anisole	14.2	9.2	3.8	3.1
Aniline	17.6	11.0	0.5	3.0
N,*N*-Dimethylaniline	15.5	7.9	6.2	−0.7
Nitrobenzene	6.3	9.8	2.7	12.05
Benzonitrile	6.9	9.7	2.8	11.4
Benzaldehyde	10.1	9.9	2.5	8.4
α,α,α-Trichlorotoluene	11.0	7.0	7.8	2.25
α-Chlorotoluene	13.8	8.7	4.7	2.6
Benzyl methyl thioether	10.8	7.2	7.55	2.7
Benzylamine	13.7	9.2	3.85	3.5
α-Phenylacetone	9.6	7.6	6.8	4.7
Phenylacetonitrile	9.55	8.7	4.75	6.8
m-Difluorobenzene	7.8	10.15	2.0	11.2
m-Dichlorobenzene	8.2	8.8	4.6	8.3
m-Dimethoxybenzene	10.3	7.6	6.7	4.1
m-Fluorotoluene	10.1	9.1	4.0	7.0
m-Nitrotoluene	4.6	8.4	5.2	11.3
α-Chloro-*m*-xylene	11.6	7.5	6.95	2.6
m-Tolualdehyde	7.7	8.5	5.1	8.3
m-Anisaldehyde	7.1	8.2	5.6	8.4
p-Bromotoluene	9.6	8.1	5.8	5.7
p-Bromofluorobenzene	8.6	8.5	5.0	7.5
p-Nitrofluorobenzene	2.6	9.4	3.35	15.1
o-Dichlorobenzene	8.95	8.9	4.4	7.8

solvent. Thus the effect of a polar substituent can be decomposed with respect to two contributing factors: an electronic effect, (ASIS)$_R$, which turns out to be approximately four times greater for the CHO than for the CCl$_3$ group, and an effect of size which privileges the bulkier trichloromethyl group with respect to the smaller aldehydic grouping also by a factor of the order of 4.[50]

Thus one gains access to this quantity (ASIS)$_R$ which is truly representative of the interaction under study. This is the meaningful part of the solute–solvent interaction and this is the parameter we should endeavor to understand. Values of (ASIS)$_R$ for the 9-methyl group in camphor are listed in Table VI.

How do we expect these (ASIS)$_R$ terms to change with the nature of the group R? What are the factors which must be involved, and what is their relative importance? In terms of our clustering model, we submit that these questions may be answered as follows, in what might be the order of decreasing importance.

1. The polarity of the substituent R on the solvent molecule must perforce affect the strength and character of the interaction with the solute. The total strength of the interaction must in fact be *increased* by the introduction of a polar substituent and by the attending energy gain in the dipole–dipole energy term.[51] As we increase the polarity or the number of such polar groups, the interaction must become stronger. Its description therefore should become less and less adequate in terms of a clustering model, and more and more adequate in terms of the fixed 1:1 complex model: the distribution of the solvent molecules congregated around the polar site should start to favor certain configurations to the detriment of others. One could expect the quantity (ASIS)$_R$ to be related, for instance, to the magnitude of the group dipole moment for R.

2. The presence of the R group in the solvent molecule will affect the chemical shift of the solute protons in its vicinity[52] depending upon its magnetic anisotropy—which can be very substantial, as for the nitro group—the electric field effect, and London–van der Waals interactions. All of these contributions would have to be summed for all the positions taken by a substituent R with respect to, say, the 9-methyl group of camphor, as the solvent molecules tumble around the solute molecule.

3. A somewhat unlikely possibility is that the solvent possesses enough structure in the liquid state[53] that there might be a competition between polar solute molecules such as camphor and the solvent molecules for association with a given aromatic solvent molecule. As the polarity of the R group is increased, such ordering of the solvent molecules on the microscopic scale—and also on a very short time scale—would be augmented, leading to a relative depletion in the solvent molecules available for solvation of the solute. However, it seems that statistical mechanics have successfully accounted for a number of properties of aromatic liquids by treating their molecules as being quasi-spherical.[54] Maybe the ASIS attest to a very slight ordering of the solvent which other methods are not sensitive enough to detect.

4. Upon substitution of the benzene ring by a substituent R the magnitude of the ring current is not expected to vary by more than 10–20%.[55]

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(50) This is not to say that CCl$_3$ is four times bigger than CHO, only that the corresponding *increases* in molecular volume with respect to benzene are approximately in that ratio.

(51) In which the attractive part surpasses the repulsive part.

(52) R. F. Zürcher, *Progr. Nucl. Magn. Resonance Spectrosc.*, 2, 205 (1967).

(53) R. L. Schmidt and J. H. Goldstein, *J. Chem. Phys.*, 50, 1494 (1969), have recently proposed such a model for benzene itself.

(54) Private communication from Professor I. McLure, University of Sheffield, England.

(55) (a) H. P. Figeys and R. Flammang, *Mol. Phys.*, 12, 581 (1967); (b) R. J. Abraham and M. A. Cooper, *J. Chem. Soc. B*, 202 (1967);

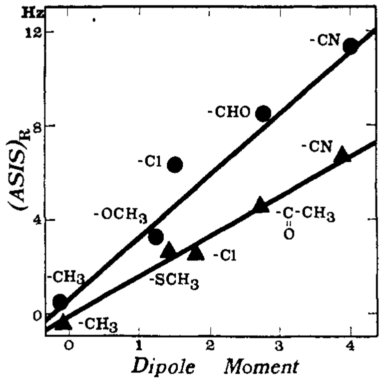


Figure 7. Plot of (ASIS)$_R$ *vs.* the group dipole moment: ○, phenyl-R; △, benzyl-R.

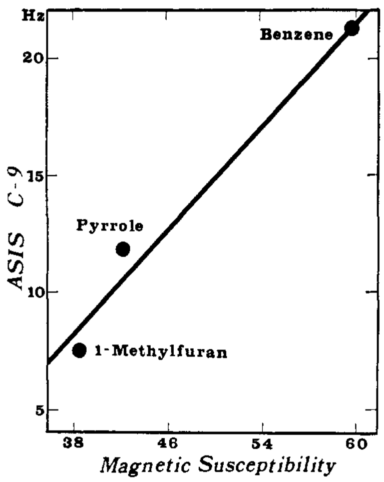


Figure 8. Plot of the C-9 methyl ASIS of camphor *vs.* the magnetic susceptibility for some aromatic solvents.

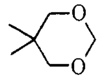
Examination of the results (Table VI) is more or less in line with these expectations. It is possible, for instance, to elicit rough correlations of the quantity (ASIS)$_R$ with the group dipole moment of R (Figure 7)—it is not surprising to find that the slope decreases with the distance of the polar group from the aromatic ring—and with the magnetic susceptibility of the aromatic molecule[56] (Figure 8). On the other hand, the clustering model and the attendant site factors do not give evidence of breaking down as the solvent molecules are made more and more polar. It is a little more surprising that these electronic (ASIS)$_R$ terms seem always to contribute to *depress* the ASIS, and that the effect is not exactly cumulative when several such R groups are present. We are now addressing ourselves to these unsolved problems.

Conclusion

We have sought in this paper a better understanding of the *weak interactions* between a ketone solute and a number of aromatic solvents. Specific complexation is not necessary to explain the large shifts observed for such polar solutes in aromatic solvents. These solvent shifts arise from general solvation. According to the notion of a clustering of solvent molecules around the polar sites of the solute, and owing to the time averaging implicit in the nmr experiment itself, the solvent shift can be nicely decomposed into a site factor and a solvent parameter. The former depends only on the geometry of the solute, while the latter reflects the size of solvent molecules plus the truly intrinsic part of the solute–solvent interaction. We have indicated the factors that are to be discerned. They are primarily dipolar and magnetic susceptibility contributions from within the solvent molecule.

Appendix. Influence of the Molecular Volume of the Solute (in Collaboration with Mr. A. Greenberg)

For simple polar solutes, the magnitude of the benzene-induced solvent shift has been known for some time to depend on the magnitude of dipole moments within the solute as well as on the molecular volume of the solute. Schneider[2] was able to obtain rough correlations of the ASIS for a series of polar CH_3X compounds with the dipole moment divided by the molecular volume of the solute (μ/V). The molecular volume comes in because, after rotational averaging, this quantity determines the mean distance of approach to the benzene solvent molecules. It remained for Philipsborn, Becconsall, and their coworkers[38,39] to explore this effect in greater detail and to thus examine more generally the influence of the molecular "shape." They found that solvent magnetic anisotropy shifts for hydrocarbons in benzene solution show a systematic decrease with increasing size of the solute molecule, in agreement with predictions from a simple geometrical model. van der Waals and nonpolar solvent anisotropy effects are thus primarily dependent on the size of the solute, and if possible should be maintained constant by not varying the molecular size of the solute. We have gathered experimental data bearing on this point. 1,3-dioxane molecules **2**–**6** were synthesized according to standard procedures,[57] and the ASIS were measured for the methyl and for the 4- and 6-methylene protons (Table VII). The ASIS differ markedly in molecule **2** from their values in molecules **3**–**6**, not so



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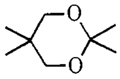

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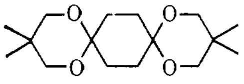

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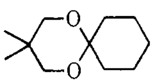

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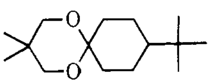

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(c) Professor H. A. O. Hill of Oxford (private communication) has also observed virtual independence of the ring current with respect to the substituent in palladium square-planar complexes in which one of the sulfur ligands bears a *p*-C_6H_4–X group.

(56) J. M. Pochan and W. H. Flygare, *J. Amer. Chem. Soc.*, **91**, 5928 (1969).

(57) See A. Greenberg and P. Laszlo, *Tetrahedron Lett.*, 2641 (1970).

Table VII. Solvent Shifts for a Series of 5,5-Dimethyl-1,3-dioxanes

Compound	ASIS,[a] Hz at 60 MHz	
	CH_3	CH_2
2	10.22	10.09
3	7.08	5.35
4	6.56	6.05
5	6.36	5.52
6	5.30	

[a] Cyclopentane to toluene, at room temperature.

much because of "steric hindrance" of the oxygen heteroatoms,[58] but simply because there is a conformational change, a flattening of the dioxane ring upon introduction of an axial methyl group in position 2.[57,59]

Compounds **3–6** nicely exhibit the effect of molecular size discovered by Philipsborn and Winkler, a slight depression of the ASIS upon an increase of the molecular volume. We believe these to be the first polar solutes in which the effect of size is demonstrated simply by attachment of a variable hydrocarbon residue at a position distant from the polar sites. Notice in particular the intermediate position of the ASIS for molecule **4** between those for **3** and **5**: there are two dioxane rings in **4** and the moieties which would result in a formal sense from cleavage of the central cyclohexane ring along the middle would be in between **3** and **5**. The comparison of molecules **5** and **6** is also instructive: assuredly, the conformation of the dioxane ring is the same in both molecules, yet attachment of the bulky *tert*-butyl group modifies very significantly the ASIS perceived by the methyl protons situated at the other end of the molecule. It is for such reasons that we have maintained the solute's size constant throughout our study.

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[58] J. E. Anderson, *Tetrahedron Lett.*, 4713 (1965).

[59] (a) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968); (b) unpublished ^{13}C work by Professor F. G. Riddell, University of Stirling, Scotland.

Ion Cyclotron Resonance Studies of Ionic Reactions in Ethane and of Hydrogen Exchange in D_2–C_2H_6 and H_2–C_2D_6 Mixtures[1]

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Abstract: Ionic reactions in pure gaseous ethane and in D_2–C_2H_6 and H_2–C_2D_6 mixtures have been investigated with the technique of ion cyclotron resonance spectroscopy. The observations on ethane lead to the establishment of mechanisms for the formation of $C_2H_4^+$, $C_2H_5^+$, C_3, and C_4 ions and the protonated species $C_2H_7^+$ and $C_3H_9^+$. The results resolve conflicting conclusions about these ions derived from previous high-pressure mass spectrometric experiments. The mechanisms of exchange of hydrogen isotopes during the ionic reactions that take place in D_2–C_2H_6 and H_2–C_2D_6 mixtures have also been determined. The modes observed serve as the basis for the sequences of reactions proposed to account for the nuclear-decay-induced and radiation-induced Wilzbach labeling of ethane by tritium.

The simple method devised by Wilzbach[2] for preparing tritium-labeled organic compounds has found widespread practical application in the tagging of complex molecules of biological and medical importance.[3] In this method a mixture of a compound and tritium is allowed to stand for some time, and the various tritiated products are then separated by radiogas chromatography. Interest in the fundamental hydrogen-exchange reactions taking place in this approach has resulted in several studies of the mechanisms of "Wilzbach labeling." Pratt and Wolfgang[4] have reported on an investigation of the kinetics of exchange in methane–T_2 mixtures, while Gant and Yang[5] have studied a number of gaseous mixtures of tritium with organic compounds, including ethane.[6] There was agreement between these pairs of workers that two modes of labeling were occurring: a decay-induced mechanism initiated by reaction of the T^3He^+ daughter formed directly from nuclear transformation of T_2 and a radiation-induced mechanism provoked by excitation and ionization of the compound and tritium by β particles released in the nuclear decays and by secondary electrons (self-radiolysis). Cacace, *et al.*,[7] have also investigated C_2H_6–T_2 mixtures under conditions where the former mode of tagging was predominant. In all these investigations the mechanisms proposed to account for the results were based on reactions of positively charged transient species.

The techniques of "high-pressure" mass spectrometry[8,9] and ion cyclotron resonance spectroscopy[10]

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[1] Work performed under the auspices of the U. S. Atomic Energy Commission.

[2] K. E. Wilzbach, *J. Amer. Chem. Soc.*, **79**, 1013 (1957); J. E. Wilzbach and P. Riesz, *J. Phys. Chem.*, **62**, 6 (1958); see also W. R. Ahrens, M. C. Sauer, and J. E. Willard, *J. Amer. Chem. Soc.*, **79**, 3284 (1957).

[3] "Proceedings of the 5th Annual Symposium on Advances in Tracer Technology," Vol. I, R. Rothchild, Ed., Plenum Press, New York, N. Y., 1963.

[4] T. H. Pratt and R. Wolfgang, *J. Amer. Chem. Soc.*, **83**, 10 (1961).

[5] P. L. Gant and K. Yang, *J. Chem. Phys.*, **32**, 1757 (1960); **31**, 1589 (1959); *J. Phys. Chem.*, **66**, 1619 (1962).

[6] P. L. Gant and K. Yang, *J. Chem. Phys.*, **30**, 1108 (1959).

[7] F. Cacace, R. Cipollini, and G. Ciranni, *J. Amer. Chem. Soc.*, **90**, 1122 (1968).

[8] S. Wexler, *ibid.*, **85**, 272 (1963); *Exch. React. Proc. Symp., 1965*, 301 (1965).