Steric Effects on NMR Chemical Shifts Controlled by the Solvent's Accessible Surface

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Steric effects observed on ^{29}Si NMR chemical shifts in trimethylsiloxysteroids are chiefly due to hydrogen bonding which is controlled by solvent accessibility of the oxygen atom in the molecule.

Steric effects observed on NMR chemical shifts are used for structure elucidation in diverse classes of compounds.[1] Various sophisticated concepts have been invoked to explain these effects: sterically induced charge polarization,[2] bond angle changes,[3] electric field effects,[4] local van der Waals interactions,[5,6] *etc.* Despite the fact that a number of compounds containing heteroatoms have been studied in this connection, to the best of our knowledge, no attention has been paid to the possible contribution of association and/or solvent effects to the steric shifts.

The small steric effects observed on ^{29}Si chemical shifts in trimethylsiloxy derivatives of steroids[7] are considerably increased by addition of deuteriochloroform to the measured solution. This is illustrated by the dilution dependence of the ^{29}Si chemical shifts shown in Fig. 1 for four trimethylsiloxysteroids [3α-trimethylsiloxy-5α-cholestane (αα), 3β-trimethylsiloxy-5α-cholestane (βα), 3α-trimethylsiloxy-5β-cholestane (αβ) and 3β-trimethylsiloxy-5β-cholestane (ββ)]. The chemical shifts measured in sufficiently dilute deuteriochloroform solutions become analytically significant and bear a clear relation to the stereochemistry of the compound.[8]

The IR spectra (Fig. 2) prove formation of hydrogen-bonded complexes in the deuteriochloroform solutions of these steroid derivatives: the intensity of the absorption band of $\nu(C\text{–}D)_{free}$ stretching is reduced and the half-width of the band increased by the presence of $\nu(C\text{–}D)_{assoc}$, which is clearly visible in the spectra of αβ and βα derivatives, discernible as a shoulder in the spectrum of ββ, but not obvious in the spectrum of the αα derivative. For a semiquantitative evaluation of the relative basicity[9] another proton donor with a higher acidity and lower steric demands[10] was used. According to $\Delta\nu$ values of phenol [$\Delta\nu = \nu(O\text{–}H)_{free} - \nu(O\text{–}H)_{assoc}$, Fig. 3] the relative basicity decreases in the order αβ ≃ βα ≫ ββ > αα. This order is in agreement with the intensities of ν(O–H) absorption bands and with the shapes of the ν(C–D) bands in the deuteriochloroform solutions (Fig. 2).

The basicity order derived from IR measurements agrees with the estimates of constants of complexation (K_c) for the association equilibrium (Scheme 1), where B stands for the

$$B + HS \rightleftharpoons B\cdots HS$$

Scheme 1

steroid as a base and HS for the proton donor. The constants estimated from the concentration dependence of the chemical shifts (Figs. 1 and 4) according to the method of Nakano *et al.*[11] are given in Table 1.

The reaction cross-section for the association should be proportional to the van der Waals surface (A) of the oxygen atom accessible to the proton of the donor, hence, we can write $K_c = K^{chem} \times A$. Here, K^{chem} denotes the 'chemical' equilibrium constant corrected for the accessibility of the oxygen surface (in analogy to 'symmetry' corrected constants[12]). When coordinates of atoms in the molecule B are known, the accessible surface[13] can be calculated according to the Connolly algorithm.[14] The surfaces A calculated for MM+ optimized geometries[15] of the trimethylsilylated steroids αα, βα, αβ and ββ are 0.4, 1.8, 1.9 and 0.5 Å^2, respectively. Obviously, the order of the relative basicities and the order of the association constants K_c follow the order of solvent accessible oxygen surface A in these compounds suggesting that changes in K^{chem} are not the dominant source of variation in K_c. On the other hand, the relationship between A and the ^{29}Si chemical shifts observed in diluted solutions is more complex. With the usual assumptions

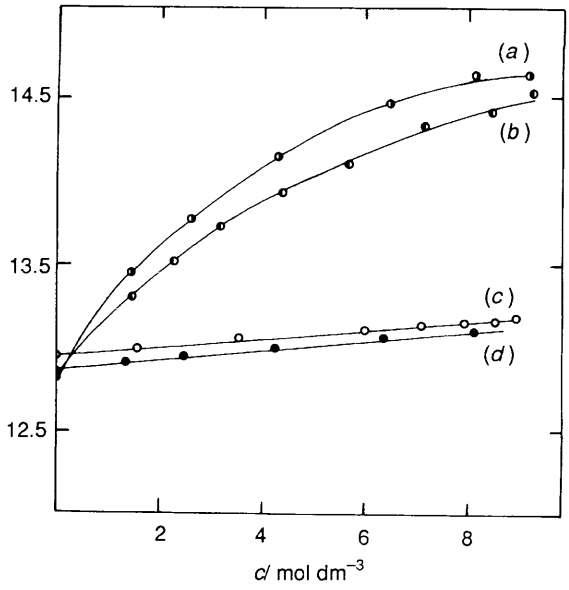

Fig. 1 The dependences of ^{29}Si chemical shifts δ of 3ξ-trimethylsiloxy-5ξ-cholestanes on the concentration of deuteriochloroform in ternary solutions in carbon tetrachloride (concentration of each of the steroids varied in the range 0.03–0.14 mol dm^{-3}, spectrometer Varian Unity 200, INEPT pulse sequence, sample temperature 24 °C, accuracy of δ values better than ±0.02 ppm); (*a*) αβ, (*b*) βα, (*c*) αα, (*d*) ββ

Table 1 Constants of complexation K_c for Scheme 1[a]

	Steroid B			
Solvent HS	αα	βα	αβ	ββ
Chloroform	0.04	0.12	0.18	0.07
Phenol	0.99	2.43	4.56	1.36

[a] K_c in mol dm^{-3}.

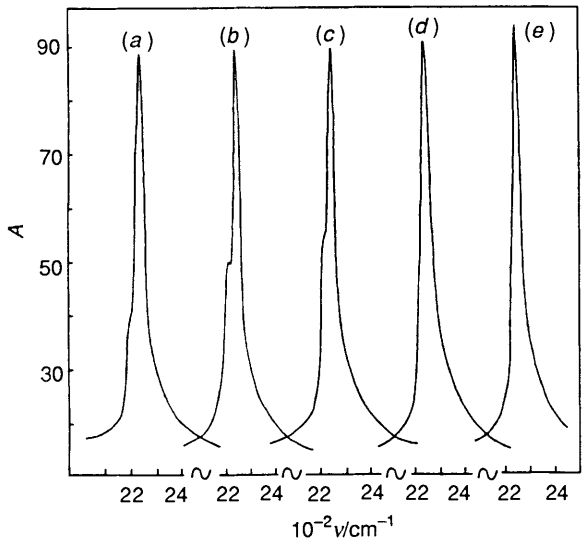

Fig. 2 IR absorption spectra of hydrogen bonds [$\nu(C–D)_{str}$] between deuteriochloroform and 3ξ-trimethylsiloxy-5ξ-cholestanes (Zeiss model IR 75 spectrometer, KBr cell of 0.04 cm thickness, saturated solutions of the steroids in deuteriochloroform); (*a*) ββ, (*b*) αβ, (*c*) βα, (*d*) αα, (*e*) $CDCl_3$

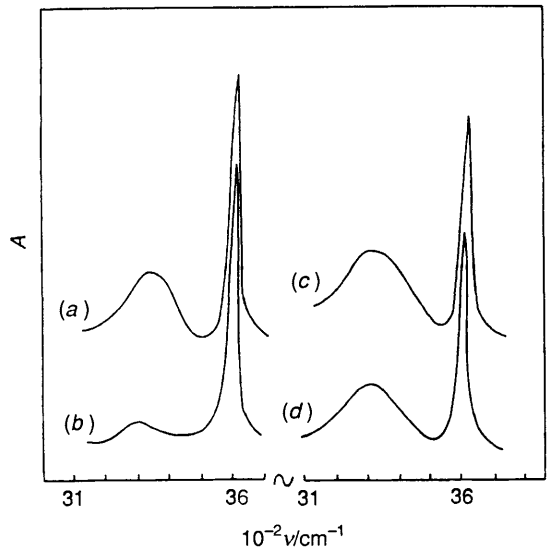

Fig. 3 IR absorption spectra of hydrogen bonds [$\nu(O–H)_{str}$] between phenol (0.02 mol dm^{-3}) and 3ξ-trimethylsiloxy-5ξ-cholestanes (0.05 mol dm^{-3}) in carbon tetrachloride. The low phenol concentration excludes self-association (Zeiss model IR 75 spectrometer, two KBr cells of 0.1 cm thickness each: the sample cell with the ternary solution and the reference cell with the same steroid concentration in carbon tetrachloride to compensate steroid absorptions); (*a*) ββ, (*b*) αα, (*c*) βα, (*d*) αβ

(a sufficient excess of a proton-donor solvent),[16] it can be shown that the observed chemical shift, δ_{obs}, is given by eqn. (1), where

$$\delta_{obs} = \delta_B + \frac{K^{chem} \times A}{1 + K^{chem} \times A}(\delta_{BHS} - \delta_B) \qquad (1)$$

δ_B and δ_{BHS} are the chemical shifts in the free and associated molecules B, respectively. The constant K^{chem} incorporates all other contributing factors to the constant of complexation (*e.g.*, acidity of HS). In a series of closely related compounds the changes in A can be dominant as demonstrated on the above examples. Since A can be easily calculated for various considered structures the above expression provides a tool for

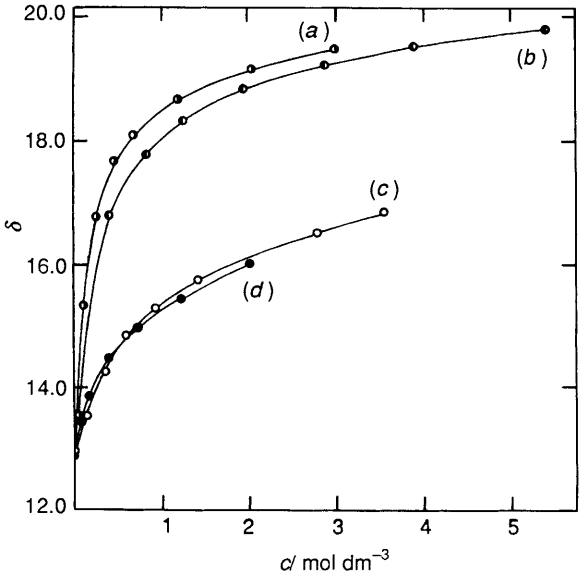

Fig. 4 The dependences of ^{29}Si chemical shifts δ of 3ξ-trimethylsiloxy-5ξ-cholestanes on the concentration of phenol in ternary solutions in carbon tetrachloride (concentration of the steroids varied in the range 0.06–0.08 mol dm^{-3}, spectrometer Varian Unity 200, INEPT pulse sequence, sample temperature 24 °C, accuracy of δ values better than ±0.02 ppm); (*a*) αβ, (*b*) βα, (*c*) αα, (*d*) ββ

NMR differentiation between closely related molecular structures with similar K^{chem} and considerably different solvent accessible surfaces A.

Obviously, similar association effects can be important in NMR of other nuclei including ^{13}C, especially when the nucleus in question is in the α position to a heteroatom. No general theory of steric effects can ignore this aspect as the solvent effects can be of a magnitude comparable to the steric shifts.

This work was supported by a grant No. 472 03 from the Granting Agency of Czechoslovak Academy of Sciences.

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Paper 3/06360G
Received 28*th October* 1993
Accepted 1*st November* 1993