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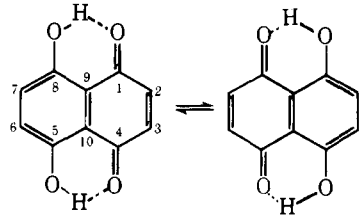
Received June 11, 1979

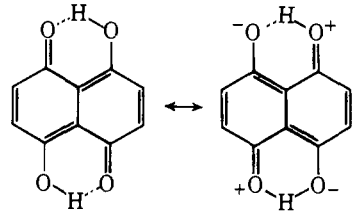
Investigation of Crystalline Naphthazarin B by ^{13}C NMR Spectroscopy Using "Magic Angle" Spinning Techniques and by X-ray Diffraction: Evidence for a Dynamic Disordered Structure

Sir:

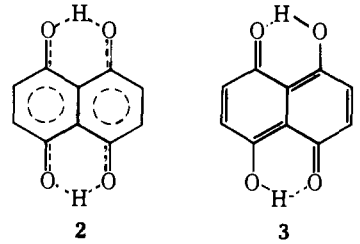
Few organic molecules have been the subject of as many X-ray structural investigations as has naphthazarin.[1,2] Several investigations of each of the three crystalline forms (designated A, B, and C) have led to the conclusion that in the crystalline state the molecule is centrosymmetric and, hence, can best be represented not as **1a** but as a resonance hybrid of structures such as **2a** and **2b**, i.e., the symmetrical form **2**.[3]



1a **1b**



2a **2b**



2 **3**

In contrast, solution studies such as dipole moment determination[5] and NMR[1,3,6] and IR[7] spectroscopy have been interpreted in terms of structures **1a** and **1b** which are in rapid equilibrium on the NMR time scale down to −75 °C; an indirect argument has been made[7] that an isolated molecule of the 1,5-quinone **3** should be very much less stable than **1a**. As a result, there appears to be acceptance of the belief that the molecular structure in the solid state (**2**) is different from that in solution (**1a** or **1b**) owing to the effect of crystal packing forces.[1,7] The structure of naphthazarin is of interest not only in its own right, but because this assembly of functional groups occurs in clinically important antitumor antibiotics[8] as well as in other natural products.[1,2b]

It has recently been shown[9] that, by a combination of high power proton decoupling, cross polarization,[10] and "magic angle" spinning[11] techniques, it is possible to obtain relatively well-resolved high-resolution ^{13}C NMR spectra of solid materials.[12] An important feature of these high-resolution ^{13}C experiments in solids is that the chemical shift values obtained are the "isotropic" values for the solid state and may, therefore, be compared directly with those from solution NMR; these solid-state signals are averaged by chemical exchange processes in the same way as solution spectra[13] and may thus be used to distinguish motions in the solid state which involve chemical exchange from those which do not.

In this communication we report the application of high-resolution solid-state ^{13}C NMR spectroscopy using these techniques and a further detailed X-ray structural study to this problem.

Interchange between the two tautomeric forms **1a** and **1b** involves primarily the movement of only two hydrogen atoms and might thus occur readily in the solid state; this process is accompanied by interchange between carbonyl and hydroxylic carbons which are both well resolved in the ^{13}C NMR spectrum and easily assignable. Our new data strongly suggest that the structure of crystalline naphthazarin is dynamically disordered and involves a tautomeric equilibrium which is fast at room temperature (in the solid state).

The ^{13}C NMR spectrum of a stationary sample of polycrystalline naphthazarin B[2,14] is shown in Figure 1A. Only broad, relatively featureless absorptions are observed, as would be expected since each of the carbons in the molecule should show a large shift anisotropy. The spectrum of the same sample recorded under identical conditions except that it is now also being spun rapidly (~3.5 kHz) at the "magic angle" is shown in Figure 1B. Well-resolved ($\Delta\nu_{1/2} \simeq 25$ Hz) peaks are now observed in the spectrum. The fact that broad absorptions are observed for the stationary sample under the same experimental conditions rules out the possibility that the sharp absorptions in the MAS spectrum are due to very mobile, noncrystalline material or to some experimental artifact. Under a whole variety of experimental conditions only three peaks are observed in the spectrum, and no peak is observed at low field where the carbonyl groups would be expected to absorb, facts that are indicative of a fast chemical exchange process. This is confirmed by comparison of the solid-state spectrum (Figure 1B) with the high-resolution ^{13}C spectrum from solution whose signals have been artificially line broadened (Figure 1C). The two spectra are identical, indicating that the same chemical exchange process is occurring in both phases. The peak assignments given in the caption to the figure are taken from the high-resolution solution spectrum[15] and are confirmed by the different cross-polarization rates in the solid-state experiment where the four equivalent carbons which bear protons cross polarize much more efficiently than the other six.

When the temperature is lowered to −160 °C, there is a dramatic change in the spectrum (Figure 2). The highest field line assigned to carbons 9 and 10 is unchanged, and the other two absorptions each clearly split into two lines as would be expected for the freezing out of the dynamic exchange process.[16]

Dark-red prismatic crystals of the B form of naphthazarin from benzene or chloroform solution were examined by X-ray methods. Crystal data: $C_{10}H_{16}O$; mol wt, 190.2; monoclinic; $a = 5.419$ (1), $b = 6.382$ (2), $c = 11.838$ (3) Å; $\beta = 91.51$ (2)°; $V = 409.3$ Å^3; $Z = 2$, space group $P2_1/c$. A total of 635 reflections was considered significantly above zero at the 2σ level out of a possible 699 within the Cu Kα sphere ($2\theta \leq 130°$). Full-matrix refinement of a model with hydroxyl hydrogen

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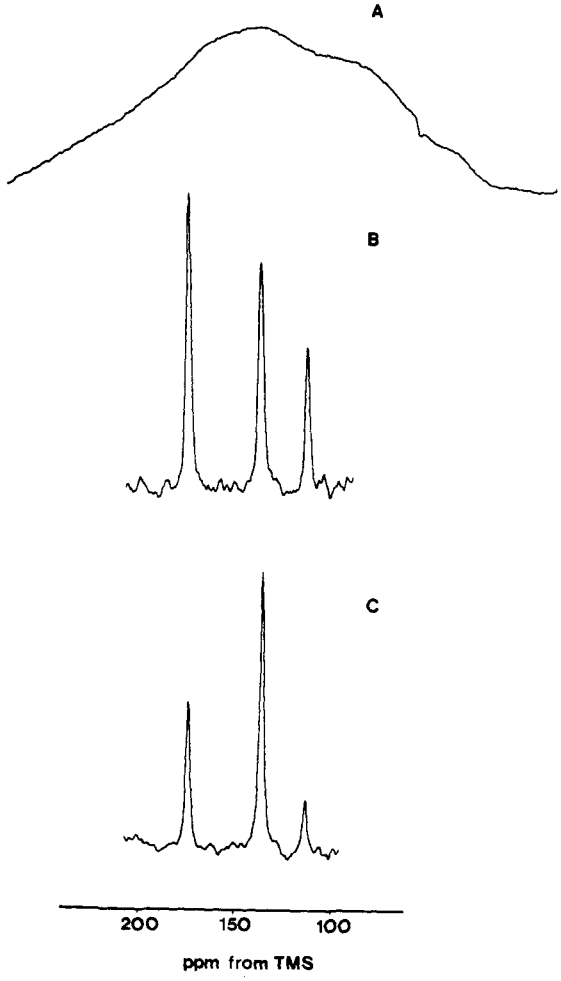

Figure 1. ^{13}C NMR spectra of naphthazarin: (A) nonspinning polycrystalline naphthazarin B, 14064 scans, 40-Hz line broadening, cross-polarization time 1 ms, and recycle time 3 s (the intensity of this peak is exaggerated relative to B and C; (B) polycrystalline naphthazarin B spinning at ~3.5 KHz at the magic angle, 14 930 scans, 15-Hz line broadening, cross-polarization time 1 ms, and recycle time 3 s; (C) solution spectrum of naphthazarin in $CHCl_3$ containing relaxing agent $Cr(Acac)_3$ (nonspinning), 3127 scans, 40-Hz line broadening, ^{13}C 90° pulse time of 7 μs, and recycle time of 20 s. The peaks in B and C are assigned to carbons 1, 4, 5, and 8 (173 ppm), carbons 2, 3, 6, and 7 (134 ppm), and carbons 9 and 10 (112 ppm downfield from Me_4Si).

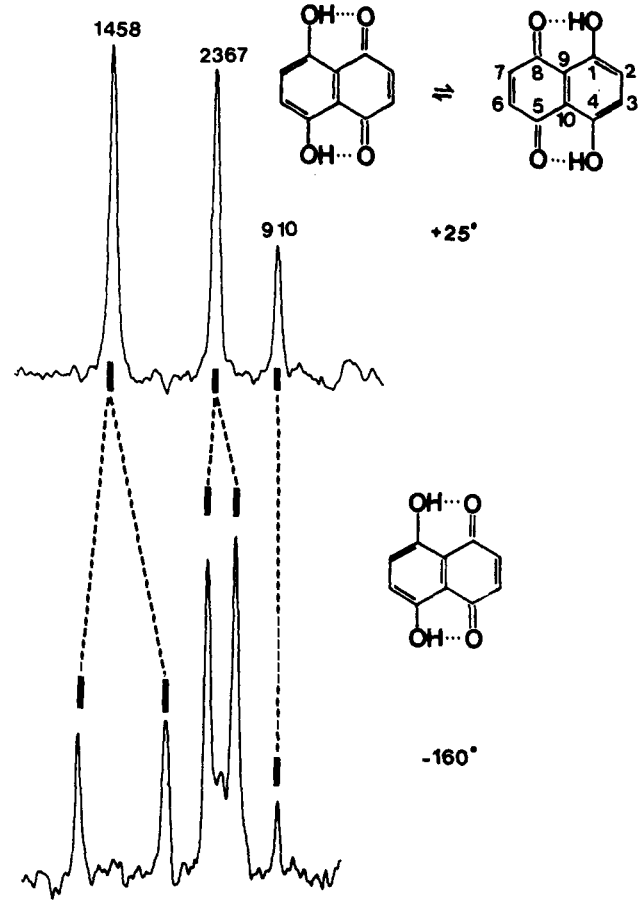

Figure 2. ^{13}C NMR spectra of solid naphthazarin obtained using CP/MAS techniques (600 scans, 30-Hz line broadening, cross-polarization time 1 ms, and recycle time 3 s): upper spectrum, 25 °C; lower spectrum, −160 °C.

atoms at 50% occupancy attached to both O(1) and O(8) gave values of R and R_2 of 0.049 and 0.078, respectively.[17,18,19,20] While the X-ray results are best interpreted by a two-hydrogen model, they provide no information as to whether this is caused by a static disorder or a dynamic process taking place in the crystal. However, taken in conjunction with the NMR study, they do strongly suggest that a proton-switching process takes place in the solid state. The relationship of proton switching to crystal symmetry in naphthazarin B has been discussed previously.[21]

The question of whether crystal sites are occupied exclusively by molecules with structures **1a** and **1b** in rapid equilibrium is a subtle one as is the question of the mechanism of proton transfer. The similarity of the solid-state NMR results to those in solution is consistent with an equilibrium involving only **1a** and **1b**. The transfer of the two protons may be formulated either as a two-step process through a 1,5-quinoid intermediate **3** or as a one-step two-proton transfer proceeding through the centrosymmetric species **2**. A further attractive possibility might involve proton tunneling synchronized with the C–O stretching motions in such a way that tunneling occurs when the oxygen atoms are in the most favorable orientation. Such a mechanism has been proposed for the hydrogen switching in the formic acid dimer in the vapor phase.[22] It is hoped that low-temperature NMR studies and further X-ray studies will provide additional clarification of these points.

Supplementary Material Available: The final positional and thermal parameters for the two half-hydrogen model, the bond lengths and angles, and the list of observed and calculated structure amplitudes (5 pages). Ordering information is given on any current masthead page.

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(16) Preliminary spectra obtained at intermediate temperatures show the superposition of the low- and high-temperature limiting spectra in proportions which depend on the temperature indicating that the exchange process is controlled by the occurrence of a second-order phase transition in the solid. We are currently investigating this phenomenon in more detail.
(17) $R = \sum ||F_{obsd}| - |F_{calcd}|| / \sum |F_{obsd}|$; $R_2 = [\sum w(|F_{obsd}|^2 - |F_{calcd}|^2)^2 / \sum w|F_{obsd}|^2]^{1/2}$.
(18) A difference map calculated prior to the inclusion of the hydroxyl hydrogen atoms revealed a large positive peak (height 0.3 e/Å^3) greatly elongated toward the two hydroxyl oxygen atoms. Refinement of a two-hydrogen (disordered) model varying positional and thermal parameters for all atoms (isotropic for hydrogen, anisotropic for all others) gave an R of 0.049 and an R_2 of 0.078; the thermal parameters for the hydrogen atoms were reasonable. After this refinement, a difference map in the hydroxyl hydrogen region was quite smooth. Refinement of a single hydrogen model (the hydroxyl hydrogen positioned initially at the centroid of the large peak) gave an R of 0.051 and an R_2 of 0.082. However, the position of this hydrogen atom oscillated rather than converged to a definite position, the temperature factor increased to 10.9 (1.1) Å^2, and a difference map indicated considerable residual electron density.
(19) A number of other models have been tried without any improvement in the R values. A full discussion of the X-ray analysis and refinement is in preparation.
(20) See the paragraph at the end of paper regarding supplementary material.
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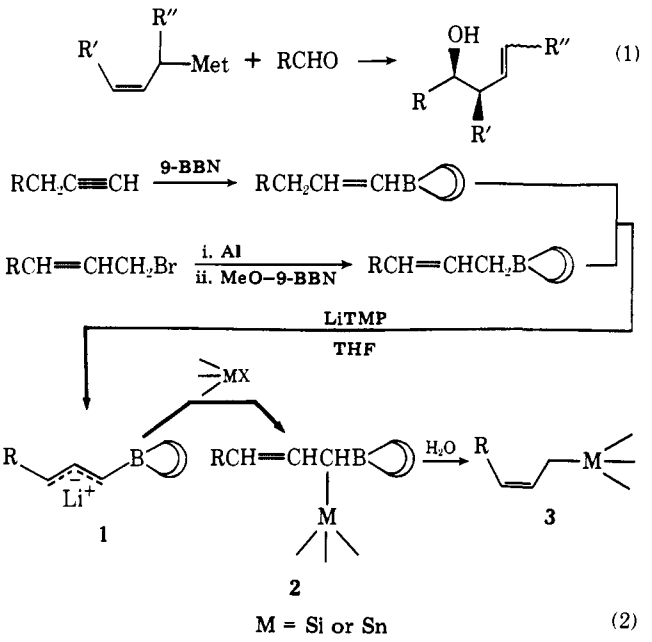
Received February 4, 1980

A New Procedure for the Stereoselective Synthesis of (*Z*)-2-Alkenylsilanes and -tins and Their Application to Erythro-Selective Synthesis of β-Alkyl Alcohol Derivatives

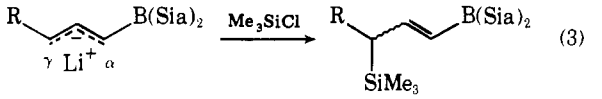
Sir:

The erythro-selective synthesis of the β-methyl alcohol units of macrolide antibiotics is a problem of pressing concern in organic synthesis. The usual solution to this problem is to use the stereoselective cross-aldol condensation.[1] An alternative approach, which has not yet been studied extensively but is highly promising, is use of the erythro-selective addition of (*Z*)-2-alkenyl metal derivatives to carbonyl compounds (eq 1).[2,3] Unfortunately, however, no methodology with a wide applicability has yet been established to realize the stereoselective synthesis of such an organometallic compound.[4] We report here for the first time a convenient one-pot procedure for the synthesis of (*Z*)-2-alkenylsilanes and -tins (eq 2) and



their application to erythro-selective synthesis of β-alkyl alcohol derivatives (eq 4 and 5).

It was reported that the treatment of alkenyldisiamylborane with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) generated boron-substituted allyl carbanion which reacted with trimethylsilyl chloride at the γ position owing to the steric repulsion between bulky siamyl and trimethylsilyl group[6] (eq 3).



It appeared that the regioselective reaction at the α position may be realized by replacing the siamyl group with less bulky 9-BBN. Actually, the boron-stabilized allyl carbanion (**1**), prepared from 1- or 2-alkenyl-9-BBN,[7] reacted with trialkylsilyl and -tin halides exclusively at the α position to produce **2**, which subsequently underwent protonolysis by H_2O. To our surprise, the resulting 2-alkenyl derivatives (**3**) drastically favored the *Z* configuration. The results are listed in Table I. The exclusive formation of the *Z* olefin, as well as the regiocontrol, is particularly remarkable for synthetic application.

The following procedure for the synthesis of (*Z*)-2-hexen-

Table I. Stereoselective Synthesis of (*Z*)-2-Alkenylsilanes and Tins[a]

9-BBN derivative	electrophile	product[b]	yield, %[c]	isomeric purity, %[d]
n-BuCH=CH—B	Me_3SiCl	*n*-PrCH=CHCH$_2$SiMe$_3$	72	~100
n-BuCH=CH—B	*n*-Bu_3SnCl	*n*-PrCH=CHCH$_2$Sn(*n*-Bu)$_3$	76	~100
n-BuCH=CH—B	Me_3SnBr	*n*-PrCH=CHCH$_2$SnMe$_3$	70	~100
CH$_3$CH=CHCH$_2$—B	Me_3SiCl	CH$_3$CH=CHCH$_2$SiMe$_3$	40[e]	~100
CH$_3$CH=CHCH$_2$—B	Me_3SnBr	CH$_3$CH=CHCH$_2$SnMe$_3$	(72)	70[f]

[a] All reactions were performed as described in the text. [b] All products were fully identified by spectroscopic methods and by comparison with the corresponding *E* isomers.[8] [c] Isolated yield (GLC yield). The product arising from the attack at the γ position was not detected. [d] Determined by IR spectra and by GLC with a capillary column. [e] High vapor pressure of crotyltrimethylsilane made the separation from solvents difficult, resulting in low isolated yield. [f] Crotyltin underwent facile isomerization in contrast to other derivatives; see also ref 8.

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