

THE SOLID-STATE VERSUS THE SOLUTION STRUCTURE OF
6-HYDROXYPEREZONE

P. JOSEPH-NATHAN,* E. MARTÍNEZ, M. ROJAS, and R.L. SANTILLAN

*Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional,
Apartado 14-740, México, DF 07000, México*

ABSTRACT.—The ^{13}C CPMAS solid-state nmr spectra of 6-hydroxyperezone [2] and 3,6-dihydroxythymoquinone [5] measured at 15.1 MHz show suppression of the exchange equilibrium observed in the high resolution ^{13}C solution spectra. Further evidence for a very slow, if any, exchange process involving the hydroxyl hydrogens was obtained by low temperature measurements and selective saturation experiments that showed no significant variation in the signals. Moreover, crystal structure data for 6-hydroxyperezone [2] were compared with data for perezone [1], 3-hydroxythymoquinone [3], and 6-hydroxythymoquinone [4] showing that the quinonoid ring in 2 is composed of two, unconjugated, enolized β -diketones.

To date most of the interest in nmr spectroscopy has revolved around high resolution measurements in solution; however, modern developments in solid-state nmr have sparked increased interest on the applicability of the methodology to a diversity of organic solids (1-5). Moreover, variable temperature ^{13}C nmr has proved to be a powerful technique not only for the study of fluxional molecules in solution but also for solids (6-9). Although still a developing technique, Cross Polarization Magic Angle Spinning (CPMAS) ^{13}C nmr spectroscopy has established its potential as a probe of structure and dynamics in the solid state, in addition to providing a bridge between X-ray data and solution nmr studies, a point that might be of relevance for natural products.

An interesting class of compounds that has received special attention with the aim of elucidating the structure and the kinetics of intramolecular hydrogen bonds is the enol forms of β -diketones (10, 11) and 3,6-dihydroxy-*p*-benzoquinones, numbered as in monocyclic sesquiterpenes (12, 13). In these molecules only one averaged structure can be detected by ^{13}C magnetic resonance studies in solution owing to the very rapid interconversion between the exchange forms. For the particular case of *p*-benzoquinones, the investigations include the correlation of the solid state ^{13}C CPMAS spectra of members of this family with their crystal structures (14).

This work reports solid-state high resolution ^{13}C nmr spectral analyses of 6-hydroxyperezone [2] and 3,6-dihydroxythymoquinone [5] with reference to their spectra in solution, as well as the X-ray structural study of several *p*-benzoquinones, including 3-hydroxy- [3] and 6-hydroxythymoquinone [4] and naturally occurring perezone [1] and 6-hydroxyperezone [2].

RESULTS AND DISCUSSION

A detailed study describing the interconversion of the two energetically equivalent forms of 2,5-dialkyl-3,6-dihydroxy-1,4-benzoquinones from variable temperature measurements has been described (13). There, we observed that for 6-hydroxyperezone [2] and for 3,6-dihydroxythymoquinone [5] the solution spectra show the four oxygen-bearing carbons (C-1, 3, 4, and 6) as a single, very broad signal around 168.8 ppm. Determination of the spectra at higher temperatures caused resolution of the broad signal into two sharp peaks (C-1, 3 and C-4, 6) that were assigned from long-range heteronuclear $^1\text{H}/^{13}\text{C}$ couplings. The same chemical exchange process was observed at -30° in DMF. However, neither 2 nor 5 was sufficiently soluble in low freezing point solvents to carry out lower temperature measurements.

In contrast to the solution spectra, the CPMAS spectra of solid 6-hydroxyperezone [2] and 3,6-dihydroxythymoquinone [5] at ambient temperature show nonequivalence

of the ring carbonyl carbons. A comparison for the case of naturally occurring **2** is depicted in Figure 1. It appears that in the solid state none of the exchange processes that are seen in solution are allowed between the carbons labeled as 1,4 and 3,6 over the temperature range from -140° to room temperature. This is probably due to a solid-state packing effect, as has been observed for semibullvalene (**2**). In contrast, 5,8-dihydroxy-1,4-naphthoquinone, known as naphthazarin B (**8**), which also shows the chemical exchange associated with labile hydrogen atoms, gave a CPMAS ^{13}C spectrum strongly dependent on temperature. The differences among semibullvalene (**2**), naphthazarin B (**8**), and the presently studied *p*-benzoquinones seem to confirm that it will be difficult to predict dynamic behavior of molecules on the basis of molecular structure alone.

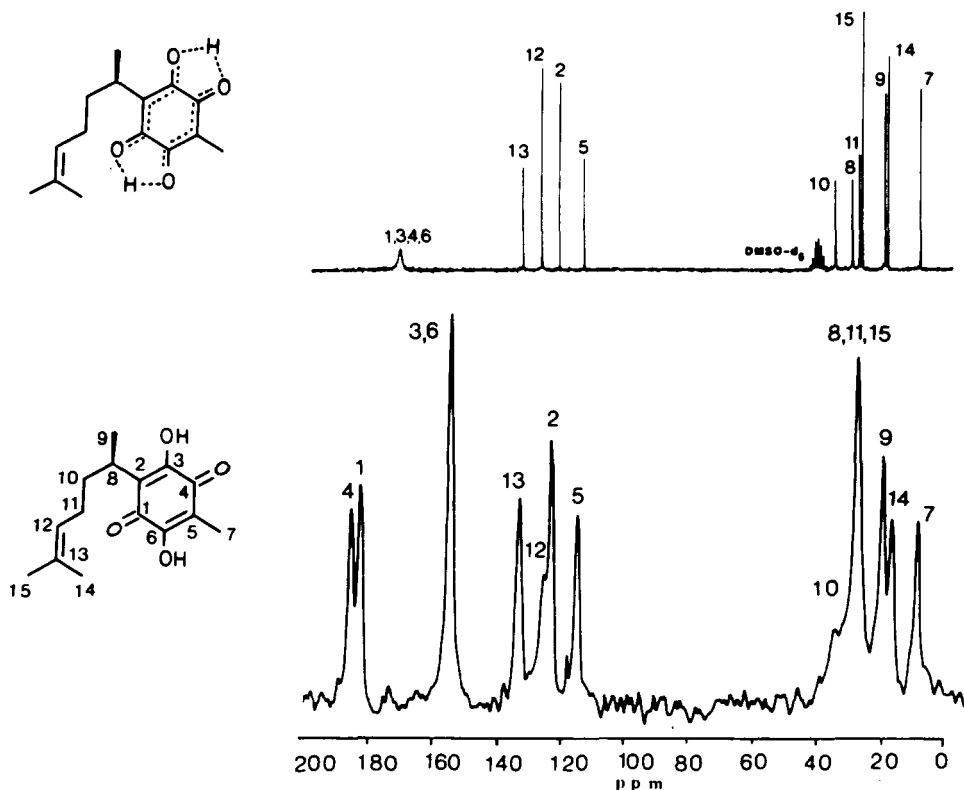


FIGURE 1. ^{13}C -nmr spectra of 6-hydroxyperezone [**2**]; upper: solution spectrum in $\text{DMSO}-d_6$; lower: CPMAS solid-state spectrum.

In order to obtain evidence for the existence of a very slow exchange involving the hydroxyl hydrogens, selective saturation experiments (15) of the C-3,6 peak of 6-hydroxyperezone [**2**] and 3,6-dihydroxythymoquinone [**5**] were performed. Because neither molecule showed a change in the C-1,4 peak under these conditions, it can be inferred that there is no saturation transfer and, therefore, the exchange rate must be extremely low, if any.

It can be concluded that the tautomeric interconversion of the two equivalent forms of the 3,6-dihydroxybenzoquinones **2** and **5**, which proceeds with extreme facility in solution, is extremely slow or absent in the solid state as shown by ^{13}C measurements. The ready interconversion between the exchange forms in solution could be responsible for the unusual chemical behavior observed in the BF_3 catalyzed, intramolecular cycloaddition of 6-hydroxyperezone [**2**] (**16**).

The ^{13}C chemical shifts of **2** and **5** are summarized in Table 1. The resonance of all

TABLE 1. ^{13}C Chemical Shifts of 6-Hydroxyperezone [2] and 3,6-Dihydroxythymoquinone [5] (in ppm)

| Carbon atom | Compounds | | | |
|-------------|-----------------------|-------|-----------------------|-------|
| | 2 | | 5 | |
| | Solution ^a | Solid | Solution ^a | Solid |
| C-1 | 168.8 | 183.8 | 168.5 | 183.2 |
| C-2 | 119.1 | 123.9 | 120.2 | 121.8 |
| C-3 | 168.8 | 155.7 | 168.5 | 154.6 |
| C-4 | 168.8 | 186.3 | 168.5 | 185.8 |
| C-5 | 111.6 | 115.6 | 111.5 | 113.7 |
| C-6 | 168.8 | 155.7 | 168.5 | 154.6 |
| C-7 | 7.6 | 8.8 | 7.3 | 7.9 |
| C-8 | 28.8 | 27.8 | 23.4 | 23.2 |
| C-9 | 18.6 | 19.7 | 19.9 | 18.9 |
| C-10 | 34.1 | 34.1 | 19.9 | 18.9 |
| C-11 | 26.6 | 27.8 | | |
| C-12 | 124.7 | 126.0 | | |
| C-13 | 130.6 | 134.3 | | |
| C-14 | 17.6 | 16.9 | | |
| C-15 | 25.7 | 27.8 | | |

^aFrom Joseph-Nathan *et al.* (13).

but the oxygen-bearing ring carbons correspond closely to those in solution (13). However, C-1,3,4,6, which are observed as a single broad signal in the solution spectra, give rise to three well-defined signals in the solid. One signal corresponds to the carbons supporting the hydroxyl groups and the other two correspond to each of the carbonyl carbons (C-1 and C-4). They were individually assigned in analogy to the solution spectrum of the derived dimethyl ether (13).

Inasmuch as the results derived from the solid-state versus the solution nmr studies show a marked difference in the molecular structure of both 2 and 5, X-ray studies were carried out to complement the information on the structure of these molecules. The importance (17) of understanding the arrangements of the quinone molecules in their crystal is clear, because this information provides a bridge between the structure and much of the chemistry of the molecules.

In the quinone ring of compounds 1 to 4 (Figure 2) the C=O (1.22 Å) and C-Me bond lengths are similar to the values found in other quinones (17-18), the O-H bonds show distances around 0.9 Å, and there is a weak hydrogen bond showing a H...O separation around 2.1 Å. The average distance for the side chain of 1 and 2 can be considered as normal and are 1.53 for C(sp³)-C(sp³) bonds, 1.50 for C(sp²)-C(sp³), and 1.34 for C=C.

Comparison of compounds 1, 3, and 4 with 6-hydroxyperezone [2], which contains an additional OH group, shows that a significant feature of the structure of 2 is the large difference between the bond C1-C2 (1.44 Å) and C3-C4 (1.52 Å) of the two 1-oxo-propen-3-ol fragments forming the quinone ring. Thus, there are unconjugated C-C single bonds between two sp²-sp² hybridized carbon atoms (C3-C4 and C1-C6) and conjugated C-C bonds between sp²-sp² carbons (C1-C2 and C4-C5). These two significantly different bond lengths indicate that the quinone ring in 2 is composed of two enolized β-diketone systems showing no π-electron delocalization between them. To our knowledge such a situation has been observed previously only for 2,5-dihydroxy-1,4-benzoquinone [6] when studied at low temperature (18) and is in clear contrast with other quinones (17) such as 2,5-dimethyl-1,4-benzoquinone [7] (19) (Figure 2).

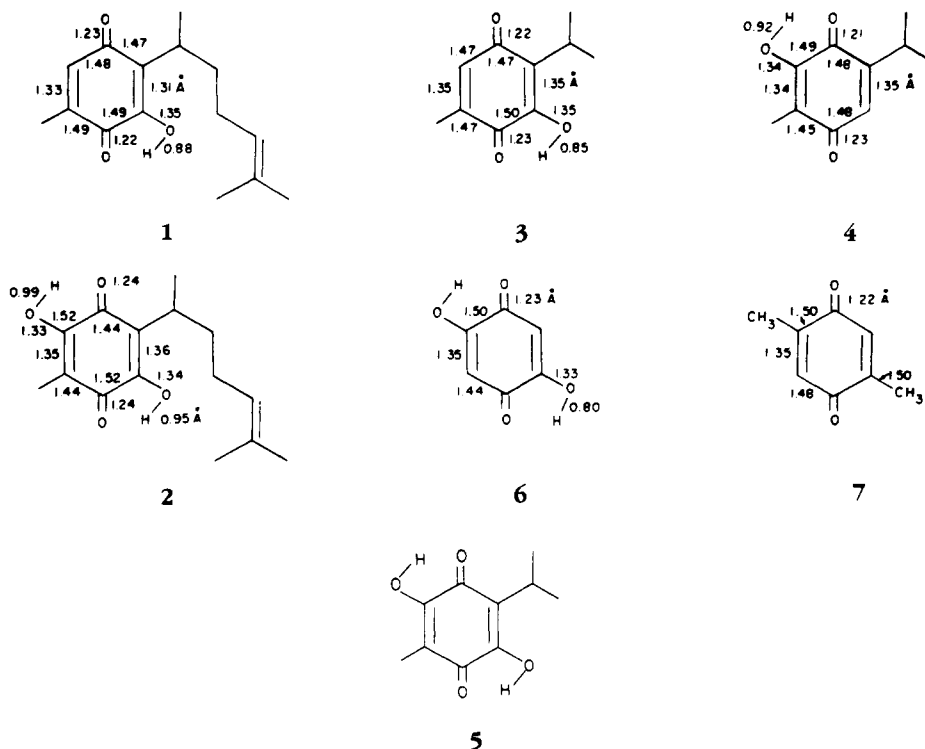


FIGURE 2. Bond lengths for the quinonoid ring of perezone [1], 6-hydroxyperezone [2], 3-hydroxythymoquinone [3], 6-hydroxythymoquinone [4], 2,5-dihydroxy-1,4-benzoquinone [6] (18), and 2,5-dimethyl-1,4-benzoquinone [7] (19).

It should also be mentioned that we were unable to obtain crystals of 3,6-dihydroxythymoquinone [5] suitable for X-ray analysis, since they were always found to be twinned.

EXPERIMENTAL

Naturally occurring perezone [1], crystals grown from hexane, and 6-hydroxyperezone [2], crystals obtained from CHCl_3 /hexane, were available from previous studies (20). 3-Hydroxy- [3] and 6-hydroxythymoquinone [4], crystals grown from a solvent mixture containing CHCl_3 -EtOAc-EtOH (50:40:10), were prepared by known procedures (21). The solid state ^{13}C -nmr data were obtained on a modified Nicolet TT-14 pulse-FT spectrometer operating at 15.089 MHz, by using high power proton decoupling (22-23) to eliminate the ^{13}C - ^1H dipolar broadening and high speed magic angle spinning (24-25) to eliminate broadening from the carbon chemical shift anisotropy. In addition, matched, spin-lock cross-polarization was used to enhance sensitivity (24-25). The cross-polarization conditions were 5 msec contact time, 2 sec delay; ^{13}C - ^1H RF fields matched at 31 KHz, and 900 scans were accumulated.

X-RAY DATA.¹—Data collection for perezone [1], 6-hydroxyperezone [2], 3-hydroxythymoquinone [3], and 6-hydroxythymoquinone [4] were done in the $\theta:2\theta$ scanning mode on a Nicolet R3m four circle diffractometer using $\text{CuK}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). The crystal data for compounds 1 to 4 are summarized in Table 2. The collected reflections were corrected for background, Lorentz, and polarization effects, while crystal decay and absorption were negligible. The structures were solved by direct methods using the software provided by the manufacturer and refined by full-matrix least-squares based on F, using data for which $I \geq 2.5\sigma(I)$. The least-squares weighing scheme used is $w = 1/\sigma^2(F_0) + G(F_0)^2$, where σ is the standard deviation of observed amplitudes based on counting statistics, and G is a variable adjusted after each cycle to minimize the function $\sum w(\Delta F)^2$. Final G values are given in Table 2.

¹Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

TABLE 2. Crystal Data of Perezone [1], 6-Hydroxyperezone [2], 3-Hydroxythymoquinone [3], and 6-Hydroxythymoquinone [4]

| | Compounds | | | |
|---|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| | 1 | 2 | 3 | 4 |
| Crystal parameters | | | | |
| chemical formula | $C_{15}H_{20}O_3$ | $C_{15}H_{20}O_4$ | $C_{10}H_{12}O_3$ | $C_{10}H_{12}O_3$ |
| molecular weight | 248.3 | 264.3 | 180.3 | 180.2 |
| crystal system | orthorhombic | orthorhombic | orthorhombic | monoclinic |
| space group | $P2_12_12_1$ | $P2_12_12_1$ | $Cmc2_1$ | $P2_1$ |
| crystal size, mm | $0.49 \times 0.20 \times 0.12$ | $0.45 \times 0.18 \times 0.04$ | $0.10 \times 0.10 \times 0.10$ | $0.30 \times 0.26 \times 0.28$ |
| crystal color | orange | red | orange | orange |
| cell constants | | | | |
| a, Å | 6.581(2) | 6.474(3) | 6.588(3) | 7.302(3) |
| b, Å | 7.346(2) | 7.390(2) | 19.960(3) | 6.398(3) |
| c, Å | 29.323(10) | 31.189(14) | 7.329(4) | 10.546(4) |
| β , deg | | | | 91.39(3) |
| cell volume, Å ³ | 1417.3 | 1492.1 | 963.81 | 492.6 |
| ρ (calc), g/cm ³ | 1.163 | 1.176 | 1.242 | 1.215 |
| Z | 4 | 4 | 4 | 2 |
| F(000), e ⁻ | 536 | 568 | 384 | 192 |
| Data Collection Parameters | | | | |
| μ , cm ⁻¹ | 6.08 | 6.56 | 7.17 | 7.02 |
| scan width, below $K_{\alpha 1}$, above $K_{\alpha 2}$, deg | 1.0, 1.0 | 1.0, 1.0 | 0.9, 1.1 | 0.9, 1.5 |
| 2 θ limits, deg | 3-110 | 3-110 | 3-110 | 3-110 |
| scan speed, deg min ⁻¹ | variable, 3-29 | variable, 4-29 | variable, 4-29 | variable, 4-29 |
| exposure time, h | 27.4 | 23.2 | 15.8 | 30.4 |
| total no. reflections collected | 1097 | 1159 | 794 | 755 |
| no. unique reflections | 944 | 996 | 332 | 640 |
| Structure Refinement | | | | |
| reflections for final refinement | 941 | 980 | 326 | 629 |
| parameters refined | 177 | 189 | 89 | 127 |
| R(F), % | 4.56 | 5.65 | 3.34 | 7.08 |
| R _w (F), % | 4.77 | 7.05 | 3.80 | 10.04 |
| goodness of fit for the last cycle | 1.288 | 1.137 | 1.228 | 1.246 |
| final G | 0.00182 | 0.0055 | 0.000964 | 0.01111 |

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