

## Solid-State NMR Spectroscopy. Distinction of Diastereomers and Determination of Optical Purity

Sir:

Intermolecular interactions between molecules comprising optically pure and racemic crystals are, perforce, diastereomeric. The existence of diastereomeric interactions can generally be recognized in a variety of physical properties, e.g., melting points, solubilities, etc.<sup>1</sup> Although diastereomeric interactions must persist upon dissolution of such crystals in achiral solvents, solute-solute interactions are most frequently, though not always,<sup>2</sup> so weak that the solution NMR spectra of a racemate and of either constituent enantiomer appear identical. Diastereomers can generally be distinguished by solution NMR methods<sup>3,4</sup>; diastereomeric solvates<sup>5</sup> and complexes<sup>6</sup> are likewise distinguishable. Since solid optically pure and racemic samples constitute diastereomeric crystalline phases, they should exhibit unique properties by solid-state NMR methods; we report herein the observation of the anticipated differences in the solid-state NMR spectra of optically pure, racemic, and *meso*-tartaric acid (2,3-dihydroxy-1,4-butanedioic acid) and of the application of solid-state NMR methods to the determination of optical purities.

Optically pure (2*R*,3*R*)-tartaric acid<sup>7</sup> ((+)-**1**) crystallizes as a monoclinic anhydride (space group *P*2<sub>1</sub>); the unit cell contains two molecules.<sup>8,9</sup> Racemic tartaric acid ((±)-**1**) crystallizes as a triclinic hydrate (space group *P*1̄); the unit cell contains two molecules of acid and two of water.<sup>10</sup> *Meso*-Tartaric acid (**2**) crystallizes in four different modifications.<sup>11,12</sup> The modification employed in this work was the triclinic hydrate (space group *P*1̄); the unit cell contains two acid molecules and two water molecules.<sup>11</sup> In all three samples the carbonyl and α-carbon atoms within a single acid molecule are not symmetry related; a priori, it should be expected that two carbonyl and two α-carbon resonances should be observed in the <sup>13</sup>C NMR spectrum.

The <sup>13</sup>C chemical shift data for (+)-**1**, (±)-**1**, and **2** are collected in Table I and the spectra are presented in Figure 1.<sup>12</sup> For the sake of comparison, the chemical shifts of (+)-**1** in aqueous medium, relative to external Me<sub>4</sub>Si, are 175.3 and 72.8 ppm, respectively, for the carbonyl and α-carbon resonances.<sup>13</sup> First, the anticipated resonance multiplicities are observed; i.e., two carbonyl and two α-carbon absorptions occur in each compound's spectrum. Second, the classical diastereomers (+)-**1** or (±)-**1** and **2** display unique chemical shifts; i.e., classical diastereomers are readily distinguishable by solid-phase NMR techniques. Third, and probably most important, the crystalline diastereomers (+)-**1** and (±)-**1** are distinguishable.

The ability to distinguish (+)-**1** and (±)-**1** constitutes a new method for the determination of optical purity.<sup>14</sup> The anticipated and observed chemical-shift differences for corresponding resonances of (+)-**1** and (±)-**1** allow the simultaneous determination of the relative concentrations of the two species.<sup>15</sup> Provided that the chemical shift of only a single resonance of a complex molecule is sufficiently different for optically pure and racemic crystals,<sup>16</sup> the limit of detection of an optical impurity is directly related to the spectral signal to noise ratio; i.e., almost any degree of precision in the optical purity measurement is attainable. For the tartaric acid samples reported here it is estimated that a 5% impurity (either optical or diastereomeric) could be detected after 10 h of data acquisition.

In addition to providing stereochemical information comparable with the currently employed solutions techniques (diastereomer distinction and optical purities),<sup>4-6</sup> the solid-phase NMR technique is potentially capable of providing other, unique information, viz., the crystalline modification type for racemic mixtures (racemates or conglomerates),<sup>16</sup>

Table I. <sup>13</sup>C Solid-State Chemical Shifts of Tartaric Acids

| tartaric acid                            | chemical shifts, ppm <sup>a</sup> |        |          |       |
|--|-----------------------------------|--------|----------|-------|
|  | carbonyl                          |        | α carbon |       |
| optically pure (2 <i>R</i> ,3 <i>R</i> ) | 175.98                            | 171.16 | 74.11    | 71.78 |
| <i>dl</i>                                | 179.24                            | 177.45 | 74.26    | 73.10 |
| <i>meso</i>                              | 176.99                            | 174.58 | 76.82    | 74.81 |

<sup>a</sup> Referenced to the methyl chemical shift of solid hexamethylbenzene which was assigned the solution chemical shift of 16.70 ppm relative to Me<sub>4</sub>Si.

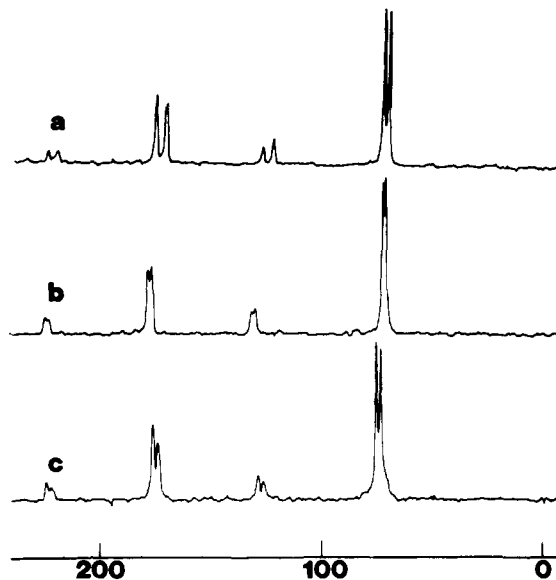


Figure 1. The <sup>13</sup>C solid-state spectra of (a) (+)-**1**; (b) (±)-**1**; and (c) **2**.

thermodynamic data on thermal solid-phase transitions, the existence and nature of inclusion complexes, etc.<sup>17</sup> Experiments of these types are currently in progress.

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## References and Notes

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- (12) The spectra were determined at 50.308 MHz on a Varian XL-200 superconducting NMR spectrometer equipped with a magic angle solid-state accessory. Dipolar decoupling and magic angle spinning were employed. The sample spinning rate was ~2.5 kHz. Employing cross polarization and ~25-s delay times, ~1700 transients were collected on each sample.
- (13) Johnson, L. F.; Jankowski, W. C. "Carbon-13 NMR Spectra"; Wiley: New York, 1972; p 64.
- (14) The optical purity of tartaric acid has been determined in chiral solvents: Kaehler, H.; Rehse, K. *Tetrahedron Lett.* **1968**, 5019.
- (15) It is assumed that the pertinent resonances exhibit comparable relaxation rates, i.e., peak heights can be employed, or that sufficient spectral resolution is attainable for peak integration. A priori, there is no reason to believe that similar functionalities residing in diastereomeric environments could possess identical relaxation times; to the contrary, such diastereomerically disposed functionalities must possess different relaxation rates. The carbonyl resonances of *meso*-tartaric acid are a case in point; the low-field-high-field resonances appear in a 55:45 ratio (peak heights) while the α-methylene resonances are of equal intensity.
- (16) This distinction is mandatory. In those instances in which crystallization

produces conglomerates, as opposed to racemates, spectral distinctions are not expected.

- (17) The ammonium sodium tartrates exhibit spectra similar to those obtained for tartaric acid. The ammonium sodium salts of (+)-**1** and of the racemate of (±)-**1** exhibit double carbonyl absorptions which are chemically shifted relative to each other; the salt of (+)-**1** exhibits an  $\alpha$ -carbon doublet, while that of (±)-**1** exhibits a broad single absorption. Both resonances for the ammonium sodium salt of **2** are narrow, single signals indicating that a crystalline modification is adopted in which the carbonyls and  $\alpha$ -carbon atoms are symmetry equivalent. (An alternate explanation of the observed spectrum is possible: symmetry nonequivalent groups can exhibit accidental isochrony.<sup>3,4</sup>) To our knowledge the crystal structure of meso-ammonium sodium tartrate is unknown.

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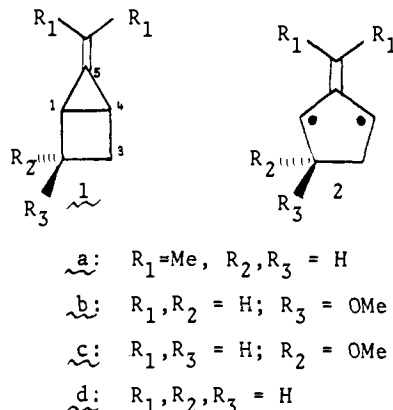
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### 5-Alkylidenebicyclo[2.1.0]pentanes. On the Question of a Negative Bond Dissociation Energy

Sir:

The 5-alkylidenebicyclo[2.1.0]pentanes (general structure **1**) are of special interest because their large ring strain and their relationship to relatively stable trimethylenemethanes (TMMs) of structure **2**<sup>1-6</sup> may conspire to produce a carbon-carbon bond (C-1-C-4) with a negative dissociation energy. In this paper, we report the preparation and properties of four members of the class, **1a-d**.



The first of two synthetic approaches (Scheme 1) modifies the previously reported<sup>6</sup> addition of dimethylvinylidene (**3**) to cyclobutene (**4**), which under the earlier conditions (isolation of the products above room temperature) gave low yields of dimers of the TMM **2a**. We now find that addition of cyclobutene to **3** generated by thermal decomposition of ethereal 1-lithio-1-bromo-2-methylpropene (**5**)<sup>18</sup> at  $-78^\circ\text{C}$  forms a solution, which, when treated with methyl acrylate and allowed to warm to room temperature, gives the characteristic adducts<sup>1,2</sup> **6** and **7**. This suggests that the species produced in the **3** + **4** reaction persists at  $-78^\circ\text{C}$  for at least several minutes, a property expected of the bicyclopentane **1a** but not of its biradical counterpart **2a**.

Compound **1a** is formed in virtually quantitative yield by photolysis ( $>350\text{ nm}$ ) of the diazene **8a** in  $\text{CD}_2\text{Cl}_2$ ,  $\text{CDCl}_3$ - $\text{CFCl}_3$ , or toluene- $d_8$  solutions at  $-78^\circ\text{C}$ . The 270-MHz nuclear magnetic resonance (NMR) spectrum, observed at  $-80^\circ\text{C}$ , shows six equivalent allylic  $\text{CH}_3$  protons ( $\delta$  1.74), two equivalent bridgehead protons (1.99), and two pairs of

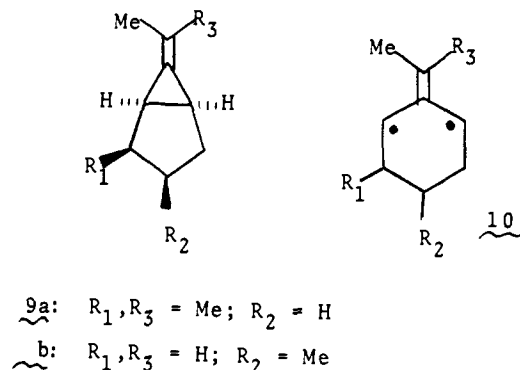
equivalent methylene protons (1.46 and 2.17). These features require a structure of  $C_s$  rather than  $C_{2v}$  symmetry and demonstrate that **1a** is not in rapid equilibrium (NMR time scale) with the biradical **2a** at  $-80^\circ\text{C}$ .

Efficient photochemical formation of **1a** is the fortunate consequence of a "thermal window". The species is unstable at higher temperatures (see below), and product studies<sup>2</sup> have suggested that photolysis of **8a** at much lower temperatures in immobilized media gives not **1a** but rather the triplet ground state of the biradical **2a**, which is known<sup>7</sup> to dimerize rapidly in fluid solution. In qualitative confirmation, we now find that photolysis of **8a** in toluene- $d_8$  (mp  $-95^\circ\text{C}$ ) at  $-196^\circ\text{C}$  and NMR examination of the solution carefully warmed to  $-80^\circ\text{C}$  shows the alkylidenebicyclopentane **1a** to be only a minor component, the major products ( $\sim 80\%$ ) being the TMM dimers of **2a**.

At higher temperatures, **1a** is converted into dimers of the TMM **2a** with a half-life at  $-40^\circ\text{C}$  of  $\sim 20$  min. Qualitatively, the unsubstituted 5-methylenebicyclo[2.1.0]pentane (**1d**), prepared by photolysis of **8d**<sup>4</sup> in  $\text{CDCl}_3$ - $\text{CFCl}_3$  at  $-78^\circ\text{C}$ , is less stable than **1a**, since conversion of **1d** into the corresponding TMM dimers has a comparable rate at  $-65^\circ\text{C}$ . On the other hand, one of the two stereoisomers of the methoxy compound (**1b** or **1c**<sup>8,9</sup>) decomposes to dimers at an appreciable rate only above  $0^\circ\text{C}$ . The origin of these apparent substituent effects remains to be elucidated.

Compounds **1a** and **1b** (or **1c**<sup>8,9</sup>) decompose to dimers in  $\text{CDCl}_3$  or  $\text{CD}_2\text{Cl}_2$ - $\text{CFCl}_3$  solutions with strict first-order kinetics. The products are the same as those produced when the corresponding diazenes **8a**<sup>6</sup> and **8c** are pyrolyzed ( $>60^\circ\text{C}$ ). The disappearance of the bicyclic monomer is followed by NMR spectroscopic observation at 270 MHz of the strong allylic  $\text{CH}_3$  signals (**1a**) or of the  $=\text{CH}_2$  signals (**1b**). Practical considerations prevent the study of a wide temperature range, but the Arrhenius parameters  $E_a = 13.2\text{ kcal/mol}$ ,  $\log A = 9.2$  ( $A$  in seconds) for **1a**, and  $E_a = 16.9\text{ kcal/mol}$ ,  $\log A = 9.8$  for **1b** (or **1c**<sup>9</sup>) are based upon measurements at four temperatures each, spanning  $-50$  to  $-30^\circ\text{C}$  for **1a** and  $+5$  to  $+25^\circ\text{C}$  for **1b** (or **1c**). Statistical analysis suggests error limits of  $\pm 1\text{ kcal/mol}$  in  $E_a$  and  $\pm 1$  unit in  $\log A$ .<sup>10</sup>

The observed  $A$  factors (corresponding to about  $-16\text{ eu}$  in  $\Delta S^\ddagger$ ) are extremely low for a thermal unimolecular methylenecyclopropane pyrolysis. By contrast, the thermal stereomutations of the ring-homologous 6-alkylidenebicyclo[3.1.0]hexanes **9a**<sup>11</sup> and **9b**,<sup>12</sup> which occur in the tem-



perature range  $160$ – $200^\circ\text{C}$  and are believed to involve TMM intermediates **10**, have  $\log A$  values of 14.5 and 13.5, respectively.

The low  $A$  factors observed in the 5-alkylidenebicyclo[2.1.0]pentane pyrolyses may signify a spin-forbidden transition state, either (i) in a direct bicyclopentane  $\rightarrow$  triplet reaction, presumably involving a crossing of energy surfaces, or (ii) in the second, rate-determining step of a sequential mechanism bicyclopentane **1**  $\rightarrow$  singlet **2**  $\rightarrow$  triplet