

## The Anomalous Deuterium Isotope Effect on the Chemical Shift of the Bridge Hydrogen in the Enol Tautomer of 2,4-Pentanedione

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**Abstract.** The nature of the intramolecular hydrogen bond in the enol tautomer of 2,4-pentanedione has been investigated by high resolution proton and deutron magnetic resonance spectroscopy. An unusually large deuterium isotope effect on the chemical shift of the bridge hydrogen has been observed. This unexpected result, together with the observation of a pronounced temperature dependence for both the proton and deutron resonances, suggests that two states with different chemical shifts for the bridge hydrogen are involved in rapid equilibrium and that the anomalous deuterium isotope effect has its origin in the effect of deuterium substitution on the energy separation between these states. It is proposed that these states correspond to the symmetrical and asymmetrical structures of the intramolecular hydrogen bond.

It is well known that 2,4-pentanedione (acetylacetone) exists in both the enol and keto tautomers and that the interconversion between these species is slow.<sup>1</sup> The nature of the intramolecular hydrogen bond in the enol tautomer has received considerable interest. There is little question that the hydrogen bonding is strong, since the O—H...O antisymmetric stretching vibration appears near 2700 cm<sup>-1</sup> in the infrared spectrum<sup>2</sup> and the proton chemical shift of the bridge hydrogen is found to be approximately 15 ppm downfield from TMS.<sup>1</sup> Reeves has also noted that the chemical shift of the hydroxyl proton is independent of concentration and the solvent system provided the solvent is not too basic.<sup>1</sup> Thus, the enol tautomer exists primarily as the intramolecular hydrogen-bonded monomer.

In this work, the effect of deuterium substitution on the chemical shift of the bridge hydrogen has been investigated. A pronounced deuterium isotope effect has been observed. In Table 1, we have summarized the effect of deuterium substitution on the chemical shift between the bridge hydrogen and the methyl hydrogens of the enol tautomer in the pure liquid and upon dilution in cyclohexane and *n*-butyl ether. For comparison, we have also included the corresponding isotope effect on the chemical shift between the hydroxyl and methyl hydrogens in neat methanol and acetic acid. Whereas the isotope effects observed for the latter two hydrogen-bonded systems are comparable to those normally noted between hydrogens bonded to oxygen and carbon,<sup>3</sup> the effect observed in the case of acetylacetone is an order of magnitude larger. Insofar

TABLE 1. Observed proton and deuteron chemical shifts of hydroxyl groups in several hydrogen-bonded systems at 27°C.

| System                                      | $\delta_{\text{OH}}^a$ (ppm) | $\delta_{\text{OD}}$ (ppm) | $\delta_{\text{OD}} - \delta_{\text{OH}}$ (ppm) |
|---|------------------------------|----------------------------|---|
| Acetylacetone <sup>d</sup>                  |                              |                            |   |
| Pure (anhydrous)                            | -13.640                      | -13.06 <sup>b</sup>        | +0.58   |
| 0.16 mole fraction in cyclohexane           | -13.641                      | -13.09 <sup>b</sup>        | +0.55   |
| 0.12 mole fraction in <i>n</i> -butyl ether | -13.585                      | -13.01 <sup>b</sup>        | +0.58   |
| 3-Methyl-2,4-pentanedione <sup>c</sup>      |                              |                            |   |
| 0.5 mole fraction in cyclohexane            | -15.020                      | -14.57 <sup>c</sup>        | +0.45   |
| 1,3-Diphenyl-1,3-propanedione <sup>c</sup>  |                              |                            |   |
| 0.15 mole fraction in carbon tetrachloride  | -15.524                      | -15.07 <sup>c</sup>        | +0.45   |
| 1-Phenyl-1,3-butanedione <sup>c</sup>       |                              |                            |   |
| 0.3 mole fraction in carbon tetrachloride   | -14.812                      | -14.39 <sup>c</sup>        | +0.42   |
| Ethyl acetoacetate <sup>c</sup>             |                              |                            |   |
| 0.2 mole fraction in carbon tetrachloride   | -10.639                      | -10.66 <sup>c</sup>        | -0.02   |
| Methanol <sup>d</sup> (neat)                | -1.540                       | -1.54 <sup>c</sup>         | 0.00  |
| Acetic acid <sup>d</sup> (neat)             | -9.238                       | -9.17 <sup>c</sup>         | +0.07   |

<sup>a</sup> Measured at 100 MHz; experimental error  $\pm 0.005$  ppm.

<sup>b</sup> Measured at 15 MHz; experimental error  $\pm 0.03$  ppm.

<sup>c</sup> Measured at 6.5 MHz; experimental error  $\pm 0.1$  ppm.

<sup>d</sup>  $\delta_{\text{OH}}$  and  $\delta_{\text{OD}}$  are measured relative to the chemical shifts of the methyl group(s) ( $-\text{CH}_3$  and  $-\text{CD}_3$ , respectively) in the same molecule.

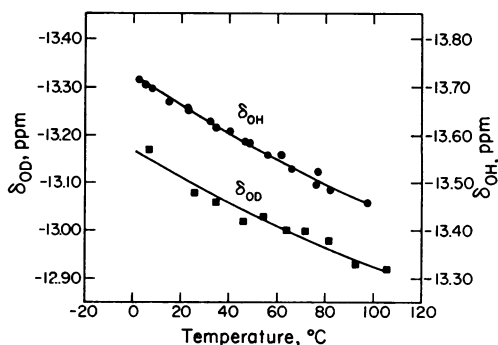
<sup>e</sup> Chemical shifts are measured relative to cyclohexane.

as it was possible to ascertain, the pronounced isotope effect is independent of concentration and the solvent system.

It is reasonable to attribute the large isotope effect observed in acetylacetone primarily to the effect of deuterium substitution on the average magnetic shielding of the bridge hydrogen. Deuterium isotope effects on the magnetic shielding of hydrogen bonded to carbon and oxygen are generally thought to be small (certainly  $< 0.1$  ppm) and are usually interpreted in terms of modifications in zero-point vibrational amplitudes upon isotopic substitution.<sup>4</sup> Thus, the pronounced isotope effect observed here suggests either an unusual anharmonicity in the vibrational motion of the bridge hydrogen in the intramolecular hydrogen bond or an alternate interpretation.

It is known that the proton chemical shift of the bridge hydrogen in acetylacetone is temperature dependent.<sup>5</sup> We have repeated these measurements using anhydrous materials, and, in addition, have examined the temperature dependence of the deuteron chemical shift. The results for acetylacetone in cyclohexane are shown in Figure 1. We note that a temperature dependence is

FIG. 1.—Temperature dependence of the proton and deuteron chemical shifts observed for the bridge hydrogen in the enol tautomer of acetylacetone in cyclohexane.  $\delta_{\text{OH}}$  and  $\delta_{\text{OD}}$  are measured relative to chemical shifts of enol methyl groups ( $-\text{CH}_3$  and  $-\text{CD}_3$ , respectively). Concentration of acetylacetone is 0.086 mole fraction in proton magnetic resonance experiments and 0.16 mole fraction in deuteron magnetic resonance experiments.



also observed for the deuterium resonance. The observation of a temperature dependence for both the proton and deuterium resonances would seem to indicate that two or more states with different chemical shifts for the bridge hydrogen are involved in rapid equilibrium<sup>6</sup> and suggests that the large deuterium isotope effect observed might well have its origin in the effect of deuterium substitution on the energy spacings between these states. In fact, both the temperature data and the observed deuterium isotope effect can be shown to be consistent with a two-state system, in which the effect of deuteration of the bridge hydrogen has resulted in a decrease in the energy separation between the two states by  $\sim 200$   $\text{cm}^{-1}$ . The results of a least-squares analysis of the OH temperature data in terms of a two-state model indicate an energy separation of  $405$   $\text{cm}^{-1}$  between the two states, and chemical shifts of  $-14.15$  and  $-10.10$  ppm (relative to the methyl resonance of the enol tautomer) for the OH proton in the lower and upper states, respectively. A similar analysis of the OD temperature data yields an energy separation of  $200$   $\text{cm}^{-1}$  between the corresponding states in the deuterated system, but essentially identical chemical shifts for the OD deuterium as for the OH proton in each state. It is a matter of simple algebra then to show that the above effect of deuteration on the energy spacing between the two states does indeed lead to the deuterium isotope effect observed.

As further indication that the observed deuterium isotope effect probably has the same origin as the temperature dependence of the chemical shift observed for both the OH and OD resonances, we have undertaken a similar study of the  $\beta$ -keto esters, for which the chemical shift of the bridge hydrogen is known to be essentially temperature independent on the basis of previous work.<sup>5</sup> Our measurements with neat ethyl acetoacetate reveal essentially no temperature effect, and as anticipated, no significant deuterium isotope effect on the chemical shift of the bridge hydrogen was observed (see Table 1). By contrast, we have observed an anomalous deuterium isotope effect on the chemical shift of the bridge hydrogen in several other  $\beta$ -diketones: 3-methyl-2,4-pentanedione, 1,3-diphenyl-1,3-propanedione, and 1-phenyl-1,3-butanedione; and a temperature dependence of the chemical shift of the bridge hydrogen has also been noted in each case (Table 2).

TABLE 2. *Temperature dependence of the chemical shifts of the bridge hydrogen in several  $\beta$ -diketones and  $\beta$ -keto esters.*

| Compound                      | Temperature range ( $^{\circ}\text{C}$ ) | Temperature shift (ppm upfield) |
|-------------------------------|--|---------------------------------|
| Acetylacetone, anhydrous      | 5–82                                     | 0.22                            |
| 3-Methyl-2,4-pentanedione     | 18–80                                    | 0.27                            |
| 1,3-Diphenyl-1,3-propanedione | –17–64                                   | 0.38                            |
| 1-Phenyl-1,3-butanedione      | –14–76                                   | 0.20                            |
| Ethyl acetoacetate            | 30–92                                    | 0.06                            |

In principle, the states in question could either be close-lying vibrational levels of the  $\text{O}—\text{H}\cdots\text{O}$  antisymmetric stretching vibration in the ground electronic state, or those of different molecular or electronic structures including tautomeric forms as well as low-lying electronic states. In view of the small energy differ-

ence between the two states and the pronounced effect of deuteration on their energy separation, it is clear that in the case of the first possibility, the potential energy function associated with the motion of the hydrogen in the  $\text{O}-\text{H}\cdots\text{O}$  antisymmetric stretch must be double minimum in nature with a moderately high central barrier. While a double-minimum potential function for the  $\text{O}-\text{H}\cdots\text{O}$  antisymmetric stretching vibration is not unexpected, it is, however, difficult to reconcile all our observations on the basis of this simple interpretation, since for any reasonable potential function and any reasonable dependence of the magnetic shielding on the vibrational motion of the bridge hydrogen, the thermal population of the higher vibrational levels, and the modification of the vibrational amplitudes by deuterium substitution are expected to have opposite effects on the observed average magnetic shielding of the bridge hydrogen. Contrary to this expectation, both deuterium substitution and raising the temperature increase the observed shielding of the bridge hydrogen. We are therefore more inclined to believe that the states are associated with different tautomeric or electronic structures, and that the large deuterium isotope effect reflects differences in the effects of deuteration on the *zero-point energies* of these structures. Needless to say, the potential functions associated with the motion of the bridge hydrogen in the two structures must possess quite different anharmonicities if the effect is to manifest itself. Considerations of deuterium isotope effects on zero-point vibrational energies for a wide variety of potential wells<sup>7</sup> indicate that at least the lower energy tautomeric or electronic structure must have a potential function for the  $\text{O}-\text{H}\cdots\text{O}$  antisymmetric stretch which is double minimum. In fact, if the potential function is symmetrically double minimum with the height of the central barrier of the order of  $\sim 2000\text{ cm}^{-1}$ , the presence of this barrier will result in a deuterium isotope shift of the zero-point vibrational energy which is some  $150\text{--}200\text{ cm}^{-1}$  smaller than that expected for a more normal potential well, such as that which might be representative of the upper state. This scheme would readily account for our nuclear magnetic resonance (nmr) observations.

We now comment on the nature of the two states. The possibility of an equilibrium between the intramolecularly hydrogen-bonded cyclic structure and the "open" structure immediately suggests itself. However, this does not appear to be likely, in view of the lack of any noticeable dependence of the chemical shift of the bridge hydrogen as well as the isotope effect on the basicity of the solvent. Moreover, if the deuterium isotope effect and the temperature dependence of the chemical shift of the bridge hydrogen observed for the  $\beta$ -diketones are to be interpreted in terms of this equilibrium, it is difficult to understand why this equilibrium is not also established in the case of the  $\beta$ -keto esters, where the strength of the intramolecular hydrogen bond is presumably weaker, at least on the basis of the proton chemical shift of the bridge hydrogen. Additional evidence in support of this conclusion is provided by the broadening of the OH resonance observed in *anhydrous n*-butyl ether, a phenomenon which is not observed in cyclohexane or carbon tetrachloride. We have examined this line broadening as a function of temperature and at two different radiofrequencies. The observed dependence on temperature and frequency that is depicted

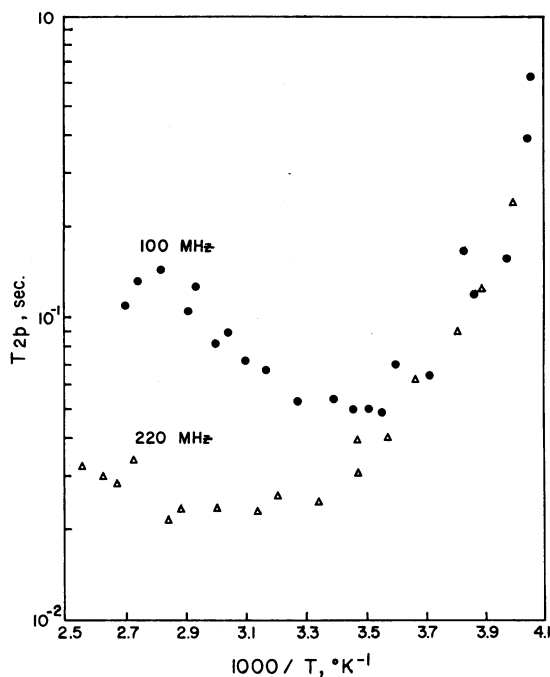


FIG. 2.—Temperature dependence and frequency dependence of the reciprocal linewidth due to chemical exchange ( $T_{2p}$ ) for the proton resonance of the bridge hydrogen in the enol tautomer of acetylacetone in *n*-butyl ether. Concentration of acetylacetone: 0.12 mole fraction.

in Figure 2 suggests the interpretation of chemical exchange broadening. Consistent with this interpretation is the observation of an inflection point in the variation of the OH proton chemical shift with temperature (Fig. 3), a feature which is expected with the transition from slow to rapid chemical exchange. As expected, the temperature corresponding to this inflection point is radio-frequency dependent and is found at a higher temperature at the higher magnetic field. It is also interesting to note that the chemical shift of the bridge hydrogen is essentially the same within experimental error in both cyclohexane and *n*-butyl ether at temperatures below this transition temperature ( $10^{\circ}\text{C}$  at

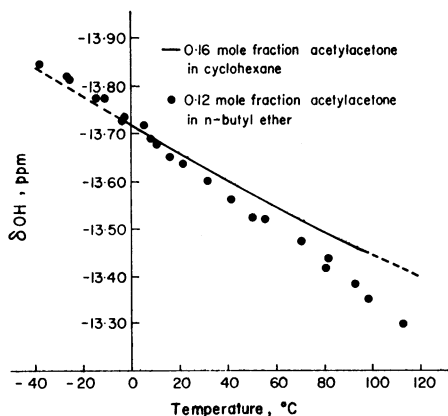


FIG. 3.—Comparison of the temperature dependences of the proton chemical shifts observed for the bridge hydrogen in the enol tautomer of acetylacetone in *n*-butyl ether and cyclohexane.  $\delta_{\text{OH}}$  is measured relative to chemical shifts of enol methyl groups.

100 MHz), where the chemical exchange is slow, whereas in the region of rapid chemical exchange, the resonance in *n*-butyl ether is shifted progressively upfield with increasing temperature from its spectral position in cyclohexane. These observations clearly indicate the presence of a third species in this solvent system, and that it undergoes intermediate chemical exchange at room temperature with the principal species. Analysis of the results within the framework of this interpretation indicates that this third species is present to the extent of 1 per cent in *n*-butyl ether. From the chemical shift deduced for the OH proton in this minor tautomer (5 ppm downfield from enol methyl), the deduced enthalpy and entropy of formation of 3.7 kcal/mole and  $\sim 2$  entropy units, respectively, and the kinetic activation enthalpy of 5.5 kcal/mole for the conversion of the principal species to the minor tautomer, it appears that the open structure is the most reasonable candidate for the minor species, and we can also conclude that it is hydrogen bonded to the solvent. Since the deuterium isotope effect on the chemical shift of the bridge hydrogen is the same in cyclohexane and *n*-butyl ether, even at low temperatures where the equilibrium between the intramolecularly hydrogen-bonded cyclic structure and the open structure is slow in *n*-butyl ether, we must conclude that this equilibrium is not important in cyclohexane and that the observed isotope effect as well as the temperature dependences observed for both the proton and deuterium resonances are inherent in the strong intramolecular hydrogen bond.

TABLE 3. *Correlation of the proton chemical shifts of the bridge hydrogen in the enol tautomer of several pure  $\beta$ -diketones and  $\beta$ -keto esters with the effects of temperature and deuterium substitution.*

| Compound                                     | Chemical shift<br>(enol OH) <sup>a</sup> | Temperature effect  | Anomalous deuterium isotope effect |
|--|--|---------------------|------------------------------------|
| Acetylacetone                                | -15.57                                   | Yes <sup>b, c</sup> | Yes <sup>c</sup>                   |
| $\alpha$ -Chloroacetylacetone                | -15.37                                   | Yes <sup>b</sup>    |                                    |
| 1,3-Diphenyl-1,3-propanedione                | -17.00                                   | Yes <sup>c</sup>    | Yes <sup>c</sup>                   |
| Hexafluoroacetylacetone                      | -13.00                                   | No <sup>b</sup>     |                                    |
| 1-Phenyl-1,3-butanedione                     | -16.33                                   | Yes <sup>c</sup>    | Yes <sup>c</sup>                   |
| 3-Methyl-1,4-pentanedione                    | -16.50                                   | Yes <sup>b, c</sup> | Yes <sup>c</sup>                   |
| Trifluoroacetylacetone                       | -14.12                                   | Yes <sup>b</sup>    |                                    |
| Butyl acetoacetate                           | -12.17                                   | No <sup>b</sup>     |                                    |
| <i>t</i> -Butyl acetoacetate                 | -12.22                                   | No <sup>b</sup>     |                                    |
| <i>t</i> -Butyl $\alpha$ -chloroacetoacetate | -12.45                                   | Small <sup>b</sup>  |                                    |
| Ethyl acetoacetate                           | -12.17                                   | No <sup>b, c</sup>  | No <sup>c</sup>                    |
| Ethyl benzoylacetoacetate                    | -12.83                                   | Small <sup>b</sup>  |                                    |
| Ethyl $\alpha$ -bromoacetoacetate            | -12.73                                   | No <sup>b</sup>     |                                    |
| Ethyl $\alpha$ - <i>n</i> -butylacetoacetate | -12.85                                   | No <sup>b</sup>     |                                    |
| Ethyl $\alpha$ -chloroacetoacetate           | -12.28                                   | Small <sup>b</sup>  |                                    |
| Ethyl $\alpha$ -cyanoacetoacetate            | -13.45                                   | Small <sup>b</sup>  |                                    |
| Ethyl $\alpha$ -ethylacetoacetate            | -12.73                                   | No <sup>b</sup>     |                                    |
| Ethyl trifluoroacetoacetate                  | -12.00                                   | Small <sup>b</sup>  |                                    |
| Ethyl $\alpha$ -methylacetoacetate           | -12.63                                   | No <sup>b</sup>     |                                    |

<sup>a</sup> Data taken from Burdett, J. L., and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2105 (1964). Chemical shifts are room temperature values and are in ppm from internal TMS.

<sup>b</sup> Burdett, J. L., and M. T. Rogers, *J. Phys. Chem.*, **70**, 939 (1966).

<sup>c</sup> This work.

What then are the two states? A reasonable speculation is that they correspond to the symmetrical (I) and asymmetrical (II) structures of the intramolecular hydrogen bond. Presumably the structure of the hydrogen bond as



well as the electronic charge distribution in the  $\pi$ -system are different in these structures. If this interpretation is correct, the nmr results which we have presented here would indicate that the symmetrical structure is the lower energy form, and that the chemical shifts of the bridge hydrogen in the symmetrical and asymmetrical structures are  $-16$  ppm and  $-12$  ppm from TMS, respectively. In this connection, we note that there is an apparent correlation between the chemical shifts of the bridge hydrogen in the pure  $\beta$ -diketones and  $\beta$ -keto esters with their temperature dependences and deuterium isotope effects (Table 3). It is perhaps no coincidence that in the  $\beta$ -keto esters, where the enol tautomer is expected to exist predominantly in the asymmetrical structure, the chemical shift of the bridge hydrogen does not exhibit any significant temperature dependence or isotope effect on deuterium substitution and that it is also invariably found to be  $-12$  ppm (from TMS), consistently 3 to 4 ppm upfield from that observed in the  $\beta$ -diketones.<sup>5</sup>

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<sup>1</sup> Reeves, L. W., *Can. J. Chem.*, **35**, 1351 (1957).

<sup>2</sup> Mecke, R., and E. Funck, *Zeit. Electrochemie*, **60**, 1124 (1956).

<sup>3</sup> Diehl, P., and T. Leipert, *Helv. Chim. Acta*, **47**, 545 (1964).

<sup>4</sup> Batiz-Hernandez, H., and R. A. Bernheim, in *Progress in Nuclear Magnetic Resonance Spectroscopy* (Oxford: Pergamon Press, 1967), vol. 3, pp. 63-85.

<sup>5</sup> Burdett, J. L., and M. T. Rogers, *J. Phys. Chem.*, **70**, 939 (1966).

<sup>6</sup> Since the time scales of observation are somewhat different in the proton and deuteron magnetic resonance experiments, subtle dynamic effects can also lead to *apparent* isotope effects if the kinetics of exchange between these states fall in between the two time-scales of measurement. However, this possibility can be eliminated by a detailed investigation of the chemical shifts and the linewidths of both the proton and the deuteron resonances as a function of temperature and nmr frequency. The proton magnetic resonance measurements were undertaken at 60, 100, and 220 MHz, and the deuteron magnetic resonance studies were taken at 6.5 and 15.35 MHz.

<sup>7</sup> Chan, S. I., unpublished results.