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Kinetic Studies of Fast Equilibrium by Means of High-Performance Liquid Chromatography. XVII. Separation of Tautomers of 1,3-Cyclohexanediones

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Synopsis. Tautomers of 1,3-cyclohexanediones have been separated by means of low-temperature high-performance liquid chromatography (HPLC). The ratios of keto- and enol-forms have been found to be highly solvent dependent, which is explained in terms of solute-solvent and solute-solute hydrogen bonding.

We have already separated keto- and enol-forms of various β-dicarbonyl compounds[1–3] by means of low-temperature HPLC. However, the separation of tautomers of cyclic β-diketones has been unsuccessful, even though various column packings including narrow-pore silica gel, wide-pore silica gel, and narrow-pore diol-silica (chemically bonded silica-gel packings which contain alcoholic hydroxyl-groups) have been tried under various conditions. In the course of this study, we found that only wide-pore diol-silica achieved the separation. The nature of the keto-enol tautomerism of 1,3-cyclohexanediones was found to differ markedly from other β-dicarbonyl compounds, which is explained in terms of ring dimer formation of the enol-form in nonpolar media.

Experimental

1,3-Cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) were obtained commercially. These were used without further purification because no peak attributable to the impurity appeared on the chromatograms.

The HPLC apparatus for low-temperature measurements have been detailed elsewhere.[1,2] In the present work it was necessary to cool the column to about −60 °C.

Wide-pore diol-silica (Nucleosil 4000-OH, 7 µm, from M. Nagel) was slurry packed into a stainless steel column (4.6 mm×10 cm). Various other column packings of different types were also tried, but no satisfactory results were obtained.

Results and Discussion

Among various column packings tested, only wide-pore diol-silica seems to separate tautomers. As shown in Fig. 1, the separation was attained on Nucleosil 4000-OH under the solvent system composed of hexane and ethyl acetate. For the complete separation in which the interconversion between tautomers during chromatography is negligible, a low column temperature (−60 °C) was necessary. The interconversion of 1,3-cyclohexanediones seems to be highly sensitive to the solvent. The solvent system composed of hexane and 1-propanol, which had given satisfactory separations of tautomers of various β-dicarbonyl compounds, did not give any separation even at −60 to −70 °C. Furthermore, addition of a minute amount of alcohols to the eluent (hexane–ethyl acetate) seriously depressed the separation. It seems that the interconversion was very fast in alcohols. The interconversion seems to be somewhat slower in less polar solvents, but still too fast to measure the rate constants at 0 °C or lower. The interconversion also seems to be activated on the surface of the adsorbent. On both narrow-pore and wide-pore silica gel, the interconversion seems to be fast, since no separation was attained. Acidic silanol group seems to drastically accelerate the interconversion. Although narrow-pore diol-silica did not, wide-pore diol-silica gave the separation, probably due to its low concentration of residual silanol group and less content of alcoholic -OH groups. In addition to 1,3-cyclohexanediones, separation of tautomers of 1,3-cycloheptanedione was also tried, but no separation was attained, even at −70 °C.

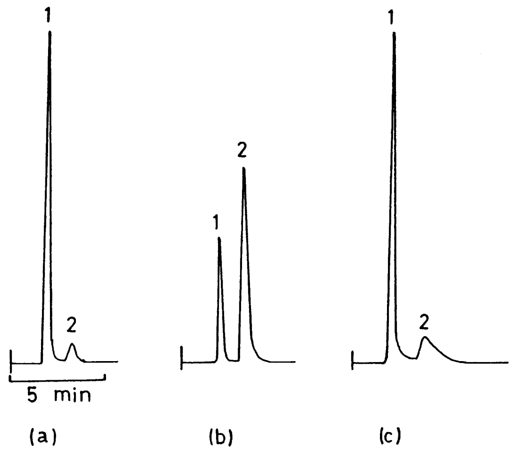


Fig. 1. HPLC separation of tautomers of 1,3-cyclohexanediones. Column: Nucleosil 4000-DIOL, 7 µm (4.6 mm×10 cm). Eluent: hexane:ethyl acetate=100:50. Flow rate: 2.5 cm^3 min^{-1}. Detector: UV 254 nm. Column temperature: −60 °C. Sample: (a) 10 mM dimedone in chloroform, (b) 10 mM dimedone in ethyl acetate, (c) 10 mM 1,3-cyclohexanedione in chloroform. 1: keto-form, 2: enol-form.

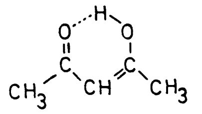
Table 1. Percentages of Enol-Form of 1,3-Cyclohexanedione and Dimedone in Different Solvents

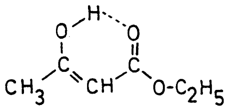
Solvent	Enol-form/%	
	1,3-Cyclohexanedione	Dimedone
Carbon tetrachloride[a]	28	5
Chloroform	30	12
Dichloromethane	26	10
Diethyl ether	72	70
Ethyl acetate	78	69
Tetrahydrofuran	48	54
Acetonitrile	60	50
1-Propanol	92	95
Ethanol	93	97

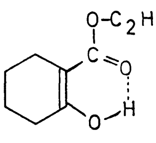
10 mM solution, 25 °C. a) 1 mM solution.

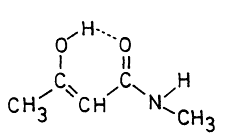
Peak identification in Fig. 1 was done by comparing the present HPLC data with other data obtained by UV or NMR.[4] It is established that 1,3-cyclohexanediones are highly ketonic in dilute nonpolar media such as chloroform and cyclohexane[4] or in the gaseous phase.[5] With increasing concentration, the ratios of keto-form decrease. Since in chloroform the peak area with shorter retention time in Fig. 1 decreases with increasing concentration, the peak should be attributed to the keto-form. The percentages of enol-form were determined from peak area measurements for 1,3-cyclohexanedione in chloroform as follows: 89% (750 mM, 1 M=1 mol dm^{-3}), 85% (500 mM), 77% (250 mM), 58% (100 mM), 53% (70 mH), 33% (20 mM), 24% (5 mM), and 20% (2 mM). The reported values by means of NMR and UV[4] are as follows: 89% (770 mM, NMR), 82% (510 mM, NMR), 71% (240 mM, NMR), 52% (103 mM, NMR), 46% (68 mM, NMR), 25% (19 mM, UV), and 15% (4.2 mM, UV). Both results agree rather well. With similar procedures the percentages of enol-form of dimedone in chloroform were also determined, the results being as follows: Our results; 33% (100 mM), 23% (60 mM), 21% (40 mM), 15% (20 mM), and 10% (6 mM). NMR or UV data;[4] 28% (94 mM, NMR), 18% (63 mM, NMR), 5% (42 mM, NMR), 14% (39 mM, UV), and 4% (6.2 mM, UV). The ratios of keto- and enol-forms in different solvents at dilute concentration (10 mM) at 25 °C were also measured, and the results are summarized in Table 1.

The chromatographic behavior and the nature of the tautomerism of 1,3-cyclohexanediones differ markedly from other various β-dicarbonyl compounds

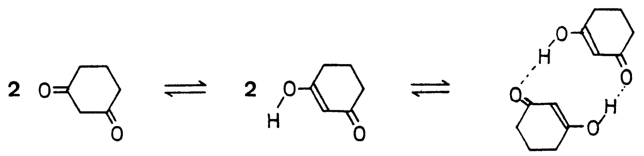








we investigated previously.[1–3] (1) For the separation of tautomers of 1,3-cyclohexanediones, a lower column temperature than for other β-dicarbonyl compounds is necessary. This suggests a faster interconversion of 1,3-cyclohexanediones. (2) The keto form is eluted faster than the enol-form for 1,3-cyclohexanediones on adsorption chromatography, which is the reverse to other β-dicarbonyl compounds. (3) For 1,3-cyclohexanediones, the percentages of enol-form are higher in polar solvents such as alcohols, which is also opposite in the case of other β-dicarbonyl compounds. These characteristic features can be explained in terms of the difference of structure between enol-forms of 1,3-cyclohexanediones and others. As shown above, enol-forms of most β-dicarbonyl compounds such as β-diketones, β-keto esters including cyclic ones, and β-keto amides form chelated intramolecular hydrogen bonds. Consequently, enol-forms are less polar chemically than keto-forms.[6] Since adsorption on silica gel (or diol-silica) surface will occur by intermolecular hydrogen bonding between polar groups of substances and -OH group of the stationary phase, strongly chelated enol-forms may not be easily adsorbed. Thus, the enol-forms are eluted faster than the keto-forms, although alcohols are usually more polar than ketones. Strongly chelated enol-forms also might be somewhat resistant to hydrogen abstraction by a solute molecule which is one of the fast steps of keto-enol conversion. The situation differs for 1,3-cyclohexanediones. The equilibrium of 1,3-cyclohexanediones is explained in terms of the following three labile species, ketone monomer, enol monomer, and enol dimer.[4,7] Due to geometrical restrictions, intramolecular hydrogen bonds cannot be formed for enol-forms. Thus, enol-forms should be more polar and eluted later than keto-forms. As shown above, in non-polar solvents such as cyclohexane and chloroform or in gaseous phase, the ketone monomer is predominant. With increasing concentration, the intermolecular hydrogen-bonded enol dimer begins to be formed. In protic solvents such as alcohols, enol monomer may be predominant due to strong solute-solvent intermolecular hydrogen bonds. Thus, the ratios of keto- and enol-forms of 1,3-cyclohexanediones differ markedly from other β-dicarbonyl compounds. The behavior rather resembles the case for the separation of rotamers of formanilide[8] in which the (*E*)-rotamer forms an intramolecular hydrogen-bonded ring dimer.



References

1) M. Moriyasu, A. Kato, and Y. Hashimoto, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 515.

2) M. Moriyasu, A. Kato, and Y. Hashimoto, *J. Chromatogr.*, **400**, 143 (1987).

3) M. Moriyasu, A. Kato, and Y. Hashimoto, *J. Chromatogr.*, **411**, 466 (1987).

4) A. Yogev and Y. Mazur, *J. Org. Chem.*, **32**, 2162 (1967).

5) K. N. Houk, L. P. Davis, G. R. Newkome, R. E. Duke, Jr., and R. V. Nauman, *J. Am. Chem. Soc.*, **95**, 8364 (1973).

6) K. H. Meyer and V. Schoeller, *Chem. Ber.*, **53**, 1410 (1920).

7) N. Cyr and L. W. Reeves, *Can. J. Chem.*, **43**, 3057 (1965).

8) M. Moriyasu, K. Kawanishi, A. Kato, and Y. Hashimoto, *Bull. Chem. Soc. Jpn.*, **57**, 1766 (1984).