Deuteration of simple α-dicarbonyl compounds and their quinoxaline derivatives

J. KÖNIGSTEIN, M. FEDOROŇKO, and J. ALFÖLDI

Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava

Received 14 November 1977

Incorporation of deuterium in acidic and basic media into glyoxal, methylglyoxal, diacetyl, and their quinoxaline derivatives, *viz.* quinoxaline, 2-methylquinoxaline, 2,3-dimethylquinoxaline has been studied by i.r. and mass spectrometry.

При помощи инфракрасной и масс-спектрометрии было изучено дейтерирование молекул глиоксала, метилглиоксала, диацетила и их хиноксалиновых производных, т.е. хиноксалина, 2-метилхиноксалина и 2,3-диметилхиноксалина, в кислой и щелочной средах.

Although important kinetic data were obtained by our previous studies on acid-base catalyzed reactions of the simplest monosaccharides [1, 2] and their products [3, 4], they have been insufficient to elucidate completely the reaction mechanisms. For these reasons the involved processes have been reinvestigated on selected model substances using deuterized acids and bases in deuterium oxide. The present study was undertaken to distinguish between the incorporation of deuterium into intermediates and final products of acid-base catalyzed reactions of monosaccharides. Glyoxal, methylglyoxal, and diacetyl can, under certain conditions, be the final products of these reactions. Since these substances are often isolated by means of quinoxaline derivatives [5] the information about the incorporation of deuterium into this class of substances is of great importance. It was also expected that the isotope-exchange study would provide data important to understand more fully the effect of the carbonyl and azomethine groups upon the tautomeric equilibria of the studied substances.

The known i.r. spectra of quinoxalines [6, 7], mechanisms of the mass spectral fragmentation [8, 9], polarographic properties [10, 11], and their separation by gas chromatography [12] were used as analytical tools. From the point of view of comparison of the results of i.r. spectroscopy 2,3-dihydroxyquinoxaline has also been studied.

Experimental

Instruments and methods

To keep the temperature constant (± 1.5°C) a KL 1 thermostat (Laboratorní přístroje, Prague), equipped with an incubating lid, has been used. The solutions were neutralized by way of an automatic titrator TTT 2 (Radiometer, Copenhagen). Polarographic measurements were performed using an OH 102 Polarograph (Radelkis, Budapest). The i.r. spectra were obtained with a Perkin—Elmer, Model 457 double-beam spectrometer. The mass spectra (23 eV, emission 30 μA) were taken with a JMS 100 D (Jeol) spectrometer coupled to a JGC-20 K gas chromatograph.

Chemicals

Glyoxal, methylglyoxal (40% aqueous solution), diacetyl and *o*-phenylenediamine were obtained from Fluka, A.G. (Buchs). The quinoxaline derivatives were prepared according to known procedures [13, 14]. 2,3-Dihydroxyquinoxaline was a product of Spolana (Neratovice). Deuterium oxide (99.75% D_2O), sodium hydroxide-d (40% solution in D_2O — degree of deuteration ≥99%), and hydrochloric acid-d (37% in D_2O — degree of deuteration ≥99%) were obtained from Merck, A.G. (Darmstadt).

Working procedures

Deuterium-exchange reactions were performed in test tubes or flasks equipped with ground-joint stoppers; prior to each experiment the reaction vessels were flushed with dry nitrogen. Deuterated chemicals were transferred from the containers in which they were delivered, under nitrogen, into rubber capped vials and closed immediately. The solutions were mixed with the aid of syringes by way of puncturing the rubber closures. Operations involving the ground-joint vials were done under dry nitrogen. The reactions were run at 50, 70, and 90°C using 0.1 M solutions of quinoxalines, except for 2,3-dihydroxyquinoxaline the concentration of which was 0.01 M. The reaction volume in D_2O, 0.1—1 M-NaOD, 1 M-CH_3COOD, and 0.1—4.5 M-DCl was 5—50 ml. For the reactions of dicarbonyl compounds under basic conditions 0.01 M solutions of the substances in 0.01 M-$NaHCO_3$ in D_2O were used. The reactions were terminated by cooling, dilution to at least 20 ml and fast neutralization to pH 7.5 and 6.5—7 for the reactions run under basic and acidic conditions, respectively. α-Dicarbonyl compounds were then allowed to react for 15—30 min with *o*-phenylenediamine. The formed quinoxaline derivatives were extracted with ether and the ethereal solutions were dried with anhydrous sodium sulfate. The distribution of quinoxaline derivatives between ether and water was checked by polarography [15]. After concentration of the ethereal solution quinoxaline and 2-methylquinoxaline were purified by distillation; 2,3-dimethyl- and 2,3-dihydroxyquinoxaline were crystallized.

The i.r. spectra for 5% solutions in chloroform were measured at 25°C in 0.1 mm sodium chloride cells. The spectra of 2,3-dihydroxyquinoxaline were measured in KBr or Nujol. The isotope-exchange reactions were monitored by following the shift of the absorption bands corresponding to —XH groups (X = C or O). The theoretical ratio of the wavenumbers for

the substituted and nonsubstituted —XH groups $\tilde{\nu}(X—D)/\tilde{\nu}(X—H) = 0.7$ [16]. Prior to taking the mass spectra the unreacted *o*-phenylenediamine was separated by gas chromatography using a column packed with OV-225 phase.

Results and discussion

The incorporation of deuterium into the methyl group of quinoxaline derivatives did not occur in basic media, although rather vigorous conditions had been applied (1 M-NaOD, 90°C, 24 h). When glyoxal, methylglyoxal, and diacetyl were treated with 0.01 M-$NaHCO_3$ at 50°C for 5 h no deuterium incorporation was observed either. The content of deuterium was determined after the conversion of the substances, under neutral conditions, to the corresponding quinoxaline derivatives. When treated with 0.1 M-NaOD (30 min, 50°C), a 0.01 M solution of methylglyoxal gave, by oxidation-reduction disproportionation, lactic acid. It was isolated, after acidification (pH 2.8), by extraction with ether. The substance contained no deuterium in its $\geqslant$CH groups. A total deuterium exchange occurred in the hydroxy groups of 2,3-dihydroxyquinoxaline, regardless of the reaction conditions applied.

Acidic hydrogens in the positions α to the carbonyl groups of α-dicarbonyl compounds treated with base are split off. The incorporation of deuterium does not occur, however, since the formed carbanions of the enol forms undergo further base-catalyzed reactions. When these reactions do not occur, or when they are sufficiently slow, the deuterium incorporation takes place. An example is the reaction of simple carbonyl compounds, acetone and acetaldehyde under alkaline conditions in D_2O [17]. In order to minimize the aldolization reactions and/or oxidation-reduction disproportionations milder basic reaction conditions were applied next.

When the dicarbonyl compounds studied, or their quinoxaline derivatives, were treated with D_2O at 50°C for 5 h under neutral conditions practically no deuterium incorporation was observed [18]. Similarly as in basic medium the hydrogen atoms of the hydroxy groups in 2,3-dihydroxyquinoxaline were fully exchanged under these conditions.

Under acidic conditions (3 M-DCl, 50°C, 8 h) complete incorporation of deuterium into the methyl groups was observed for α-dicarbonyl compounds (methylglyoxal and diacetyl). Glyoxal was not deuterated even when treated with 5 M-DCl at 90°C for 24 h. Under these conditions deuterium exchange was not observed for the hydrogen of the aldehyde group of methylglyoxal. Deuterium was incorporated into the methyl groups at the positions 2 and 3 on the heterocyclic ring of quinoxaline derivatives, *i.e.* in 2-methyl- and 2,3-dimethylquinoxaline. Quinoxaline itself was not deuterated even when treated with 5 M-DCl at 90°C for 24 h. These conditions were sufficient to cause a deuterium exchange of the hydrogen atoms of the heterocyclic ring in 2-methylquinoxaline. Deuterium was

fully incorporated at the positions 2 and 3 in both quinoxaline derivatives when they were treated with 3 M-DCl for 20 h at 50°C or with 4.5 M-DCl for 7 h at 70°C.

When 2-methyl- and 2,3-dimethylquinoxaline was treated with 1 M-CH_3COOD for 8 h at 90°C the methyl groups in the substituents were fully deuterized, but the hydrogen atom at the position 3 remained unexchanged. No deuteration was observed for glyoxal and quinoxaline, and in methylglyoxal and diacetyl only partial deuterium exchange (1 D = 79%, 2 D = 21% and 2 D = 62%, 4 D = 38%, respectively) occurred. The hydrogen atom of the aldehyde group in methylglyoxal remained unchanged.

The i.r. spectra of quinoxaline and the derivatives under investigation were identical with those in the literature [6, 7]. The alterations of the wavenumbers resulting from the isotopic substitution (XH→XD) are in Table 1.

Table 1

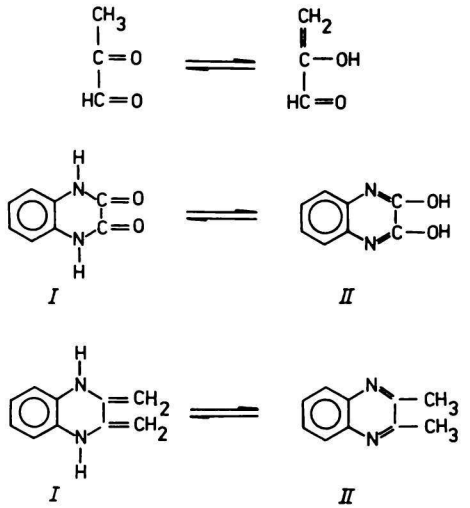
ν(X—H) and ν(X—D)* vibrations for quinoxaline derivatives

Compound	cm^{-1}						$\frac{\nu(X—D)}{\nu(X—H)}$
	ν(C—H)	$\delta(CH_3)$	ν(OH)	ν(CD)	$\delta(CD_3)$	ν(OD)	
Quinoxaline	2985	1470	—	—	—	—	—
2-Methylquinoxaline	2980	1380	—	2250	1175	—	0.76
2,3-Dimethylquinoxaline	2965	1380	—	2210 2250	1185	—	0.76
2,3-Dihydroxyquinoxaline	—	—	3100 3160	—	—	2280 2220	0.72

* X = C or O.

The deuterations observed result from the tautomeric equilibria showing themselves in acidic media. With the dicarbonyl compounds it is the keto-enol tautomery, whereas with the quinoxaline derivatives it is the enamine-imine tautomery (the formation and the disproportionation of structures containing $CH_2=$ or O= substituents at the positions 2 and 3 in the hexadiazine ring) (Scheme 1).

In the i.r. spectra (measured in $CHCl_3$) of 2-methylquinoxaline and 2,3-dimethylquinoxaline the absorption band characteristic of the NH group was not observed; the band for CH_2 group could not be unequivocally determined either, because of the presence of the aromatic ring. The predominance of the structures *II* was confirmed by the presence of the absorption bands at 1440 and 1380 cm^{-1} [$\nu(CH_3)$] and at 1565 cm^{-1} [ν(CN)]. The spectra of 2,3-dihydroxyquinoxaline



Scheme 1

show characteristic bands at 1695—1700 [ν(CO)], 3125 [ν(NH)], and 3400 cm^{-1} [ν(OH)]. The ν(CN) assignment could not be made definitely because of the presence of a broad absorption band at 1800—1550 cm^{-1} of the carbonyl groups and of the aromatic ring. Following the incorporation of deuterium two bands at 2280 and 2180 cm^{-1} were observed [ν(OD) and ν(ND)], suggesting that the forms *I* and *II* are present in a comparable amount.

The results obtained by i.r. spectrometry were checked by mass spectrometry. The quinoxaline derivatives show fragmentation characteristics in agreement with published data [8, 9], by means of which the amount and the sites of deuteration could be unequivocally determined.

The incorporation of deuterium into the molecules of α-dicarbonyl compounds occurs obviously as a result of a reversible reaction in the course of which the enol forms of the substances isomerize to ketones. With quinoxalines, the form *I* containing a protonized atom of nitrogen gives the form *II* during this process. Since glyoxal or an unsubstituted quinoxaline cannot isomerize to these forms no exchange reaction of this type is observed. The ease of isotope exchange in α-dicarbonyl and heterocyclic compounds studied herein is governed by the basicity of the carbonyl oxygen and nitrogen in the heterocycle, respectively. The results of the exchange reactions as well as those of i.r. spectroscopy suggest that the keto-enol tautomeric equilibria for methylglyoxal and diacetyl are shifted strongly to the keto forms; the same holds for the shift of the equilibria of quinoxaline methyl derivatives in favour of the forms *II*. As a result of ketimine-amine tautomery 2,3-dihydroxyquinoxaline contains comparable quantities of both forms. With this substance complete and instantaneous deuteration of OH groups occurs even without any isomerization.

It follows from the present study that methylglyoxal, diacetyl, 2-methylquinoxaline, and 2,3-dimethylquinoxaline incorporate deuterium only in acidic medium. Under these conditions no exchange reaction occurs with glyoxal and quinoxaline. The obtained information about the deuteration of α-dicarbonyl compounds and quinoxaline derivatives under investigation under various conditions is important in the elucidation of the reaction mechanism of the acid-base catalyzed transformation of simplest substances of the sugar series. During this process compounds of this class play an important role as intermediates or stable derivatives thereof.

Acknowledgements. The authors are indebted to Dr. V. Kováčik for mass spectrometry and valuable suggestions, and R. Justhová and M. Salíniová for exceptionally skillful technical assistance.

References

1. Fedoroňko, M. and Königstein, J., *Collect. Czech. Chem. Commun.* ***34,*** 3881 (1969).
2. Königstein, J. and Fedoroňko, M., *Collect. Czech. Chem. Commun.* ***40,*** 1183 (1975).
3. Fedoroňko, M. and Königstein, J., *Collect. Czech. Chem. Commun.* ***36,*** 3424 (1971).
4. Königstein, J. and Fedoroňko, M., *Collect. Czech. Chem. Commun.* ***38,*** 3801 (1973).
5. *Chemistry of Carbon Compounds,* Vol. *IVA.* (Rodd, E. H., Editor.) P. 1345—1374. Elsevier, Amsterdam, 1957.
6. *The Aldrich Library of Infrared Spectra,* 2nd Ed. (Pouchert, Ch. J., Editor.) P. 1227—1228. Aldrich Chem. Company, Wisconsin, 1975.
7. *Infrared Structural Correlation Tables.* (Miller, R. G. J. and Villis, H. A., Editors.) Heyden and Son, London, 1969.
8. Karjalainen, A. and Krieger, H., *Suom. Kemistilehti* ***B43,*** 273 (1970).
9. Kováčik, V., Fedoroňko, M., and Ježo, I., *Org. Mass Spectrom.* ***7,*** 449 (1973).
10. Musha, S., Wasa, T., and Naito, T., *Bull. Chem. Soc. Jap.* ***39,*** 1902 (1966).
11. Wasa, T. and Musha, S., *Bull. Chem. Soc. Jap.* ***40,*** 1617 (1967).
12. Medonos, V., Růžička, V., Kalina, J., and Marhoul, A., *Collect. Czech. Chem. Commun.* ***33,*** 4393 (1968).
13. Johnes, R. G. and Laughlin, K. G., *Org. Syn.* ***30,*** 86 (1950).
14. Landquist, J. K. and Stacey, G. J., *J. Chem. Soc.* ***1953,*** 2822.
15. Königstein, J. and Fedoroňko, M., *Proceedings of the 3rd Analytical Conference,* Vol. *2,* p. 113. Budapest, 1970.
16. Horák, M. and Papoušek, D., *Infračervená spektra a struktura molekul.* (Infrared Spectra and Structure of Molecules.) P. 100. Academia, Prague, 1976.
17. Miklukhin, G. P., *Izotopy v organicheskoi khimii,* p. 234. Izd. Akad. Nauk Ukr. SSR, Kiev, 1961.
18. Walters, W. D., *J. Amer. Chem. Soc.* ***63,*** 2850 (1941).

Translated by P. Kováč