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Substituent Effects in 2-Pyridone-Catalyzed Mutarotation

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Since 2-pysidone may be considered as a model of an active center of an enzyme, a series of substituted 2-pyridones has been used as catalysts for the mutarotation of 2,3,4,6-tetramethyl-α-D-glucose. The effect of position of the substituent on the rate has been studied by using 3-, 4-, 5-, and 6-methyl-2-pyridones. The effect of varying the electron density at a specific atom of 2-pyridone was studied by using 5-chloro-, 5-methyl-, and 5-nitro-2-pyridones. A methyl group in the 4 or 5 position enhances the catalysis; a 3-methyl group slows the rate; and a 6-methyl group has little net effect. A comparison of different substituents in the 5 position on the velocity of mutarotation gives the following order: methyl > hydrogen > chloro > nitro.

The mutarotation of 2,3,4,6-tetramethyl-α-D-glucose (TMG) is catalyzed by a mixture of pyridine and phenol in a concerted mechanism in which pyridine serves as a nucleophile and phenol serves as an electrophile (*1*). The mutarotation is even more rapid in the presence of catalytic amounts of 2-pyridone (2-pyridinol) in which both phenol and pyridine functions are combined in one molecule (*2*). In the sense that this molecule has enhanced catalytic activity because of the incorporation of two functional groups spaced an optimum distance apart, 2-pyridone may be considered to be a model of an active center of an enzyme. A study of the catalytic properties of substituted 2-pyridones thus provides information on possible inductive and steric effects to which such an active center might be subject.

In the present work we have had two specific objectives. One was to investigate the effect of using various 2-pyridones, each substituted in the 3-, 4-, 5-, or 6-position, on the rate of mutarotation of TMG. The second objective was to study how various electron withdrawing and releasing groups in the same position on 2-pyridone would alter the rate of mutarotation of TMG.

To achieve the first objective, 3-methyl-, 4-methyl-, 5-methyl, and 6-methyl-2-pyridones were used as catalysts for the mutarotation of TMG in benzene and the rate constants which were obtained were compared with the rate constant when 2-pyridone was used as the catalyst.

For investigating the effect of varying the electron density at a specific carbon atom of 2-pyridone, 5-methyl-, 5-nitro-, and 5-chloro-2-pyridone were selected. Because of the limited solubility of the latter two compounds in benzene it was necessary to use acetone as the solvent in the experiments involving these catalysts and TMG. For comparison purposes, 2-pyridone was also used as a catalyst in acetone as well as in benzene.

The results of the rate-constant determinations are given in Table 2. In runs 1–6, the ratio of catalyst to substrate is greater than one. At the concentrations used for the

catalysts, 5-methyl-2-pyridone was insoluble. However, the rates of 3-, 4-, and 6-methyl-2-pyridone relative to unsubstituted 2-pyridone show the same substituent effects as in subsequent experiments. That is, the rate of mutarotation of TMG was increased by 4-methyl-2-pyridone relative to that of 2-pyridone, decreased by 3-methyl-2-pyridone, and showed no notable difference with 6-methyl-2-pyridone.

The data in runs 7–16 are of greater significance than in runs 1–6, since the catalyst concentration was only one-third of the TMG concentration, and since each run was duplicated for the individual catalyst under the same conditions. The poor reproducibility in runs 12 and 14 may be largely due to the rotations found at completion of the mutarotation, since the infinity rotations were calculated rather than measured experimentally. It is, nevertheless, possible to draw the following conclusions. 4-Methyl- and 5-methyl-2-pyridones catalyze the mutarotation of TMG more efficiently than does 2-pyridone, while 3-methyl-2-pyridone is a poorer catalyst than 2-pyridone. The rate constant found for mutarotation using 6-methyl-2-pyridone was nearly the same as with 2-pyridone. These results are in agreement with those found in runs 1–6, in which an excess of catalyst was used.

Since neither 5-chloro- nor 5-nitro-2-pyridone was sufficiently soluble in benzene, acetone was used as the solvent for runs 17–24.

The rate constants for the mutarotation of TMG catalyzed by the substituted 2-pyridones in benzene imply that both steric effects and inductive effects are important in the reaction. A similar conclusion was drawn in a study of the mutarotation of TMG in water catalyzed by pyridine, 2-picoline, 4-picoline, and 2,6-lutidine (*3*).

The relatively slow rate of mutarotation using 3-methyl-2-pyridone apparently indicates a steric interference involving the oxygen function of 2-pyridone. The increased rate of mutarotation relative to 2-pyridone when the catalyst is 4-methyl- or 5-methyl-2-pyridone could be due only to the electron-releasing nature of the methyl groups. The rate-accelerating effect of the 5-methyl substituent may be the result of an increase in the basicity of the oxygen, so that it is more nearly comparable to that of the nitrogen. When this is so, the α-pyridone and 2-hydroxypyridine forms of the catalyst are of more nearly equal energy. It appears that electronic and steric effects are of about the same, but opposite magnitudes in 6-methyl-2-pyridone.

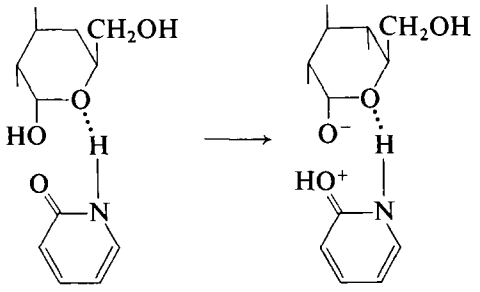
In measuring the rate constants for 5-chloro-, 5-methyl-, and 5-nitropyridone only inductive effects of the substituents should be observed. The results are consistent with those for the mutarotation catalyzed by the various methyl-substituted 2-pyridones.

It might be noted that mutarotation occurs much more slowly in acetone than in benzene when catalyzed by either 2-pyridone or 5-methyl-2-pyridone. This phenomenon can be attributed to a solvent effect.

5-Methyl-2-pyridone is a better catalyst than 2-pyridone in both benzene and acetone. If this difference is indeed due to inductive effects, then it might be expected that 5-chloro- and 5-nitro-2-pyridone would be poorer catalysts for the reaction than 2-pyridone. This is confirmed by the data. In addition, 5-chloro-2-pyridone is a better catalyst than 5-nitro-2-pyridone. Again, this fits in with the idea that groups in the 5-position exert an inductive effect, since the nitro group is more electronegative than the chloro group.

Since two groups (at the 1- and 2-position of the pyridine ring) are involved in the catalysis of mutarotation, the effect of substituent groups on the pyridine ring might

not be expected to be interpretable in terms of substituent constants. Thus, a substituent in the 5-position may be considered to be a *para* substituent with regard to the oxygen function at the 2-position, but at the same time the 5-substituent is a *meta* substituent with respect to the nitrogen of the pyridine ring. However, it is found that the substituents in the 5-position (CH_3, Cl, NO_2) fit the Hammett equation if *para* σ^+ values are used. This indicates that the oxygen at the 2-position develops a positive charge during the course of the reaction.



This can be interpreted to mean that the active catalyst for the ring opening is in the 2-pyridone form. The initial stage in the ring opening would then involve transfer of a proton from the 1-HO of the tetramethylglucose to the amide oxygen of the 2-pyridone, resulting in a positive charge on that oxygen, as would be predicted by the correlation with σ^+ values.

TABLE 1

RATE CONSTANT DATA FOR THE MUTAROTATION OF TMG IN BENZENE CATALYZED BY 2-PYRIDONE[a]

Time (sec)	Rotation (×.02667°)	$\log_{10}\left(\frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}\right)$	$K(\times 10^{-5}\ \text{sec}^{-1})$
0	4.85	—	—
50	4.72	0.0515	237
100	4.61	0.1004	231
150	4.50	0.1559	236
200	4.41	0.2071	238
250	4.35	0.2450	226
300	4.29	0.2863	219
350	4.22	0.3401	224
400	4.18	0.3742	215
450	4.12	0.4311	221
500	4.07	0.4846	223
550	4.02	0.5459	229
600	3.69	0.5874	226
∞	3.99	—	—

[a] k(average) = 227 × 10^{-5} sec^{-1}; k(least squares) = 222 × 10^{-5} sec^{-1} [2-pyridone] = 0.0096 M; [TMG] = 0.0303 M; temperature = 29°.

EXPERIMENTAL

2-Hydroxypyridine, 5-chloro-2-hydroxypyridine, and 5-nitro-2-hydroxypyridine were obtained from Aldrich Chemical Co. and were purified by vacuum sublimation. The 3-, 4-, 5-, and 6-methyl-2-hydroxypyridines were prepared by diazotization of the corresponding substituted 2-aminopyridines (*4*). 2,3,4,6-Tetramethylglucose (TMG) was prepared from methyl-α-D-glucoside (*5*).

Mutarotation rate measurements. A Cary Model 60 Recording Spectropolarimeter was set at 589.1 nm, slit 2.4 mm, chart speed either 50 or 100 sec/division, internal temperature control at 29°. A 1-dm cell was used. The catalyst, 2-pyridone or one of its derivatives, and the TMG were weighed into 10-ml and 5-ml volumetric flasks, respectively. A flask, containing spectrograde benzene or acetone was kept in a 30°C, constant-temperature bath. The volumetric flask containing the catalyst was filled to the mark with the appropriate solvent which was at 30°C. While the catalyst was dissolving, the catalyst solution along with the volumetric flask containing the TMG and the sample cell were stored in the sample chamber of the polarimeter; thus equilibrating the system

TABLE 2

RATE CONSTANTS FOR MUTAROTATION OF TMG CATALYZED BY SUBSTITUTED 2-PYRIDONES[a]

Run no.	Catalyst R =	Concentration of catalyst (*M*)	Concentration of TMG (*M*)	$k_{average}$ $\times 10^{-5}$ sec^{-1}	$k_{least\ squares}$ $\times 10^{-5}$ sec^{-1}
1	H	0.1004	0.0397	447	486
2	3-Methyl	0.0970	0.0400	361	401
3	4-Methyl	0.0970	0.0400	753	852
4	6-Methyl	0.0962	0.0404	464	481
5	4-Methyl	0.0962	0.0400	540	747
6	H	0.1106	0.0276	782	1140
7	H	0.0098	0.0302	224	215
8	H	0.0096	0.0303	227	222
9	3-Methyl	0.0100	0.0299	182	175
10	3-Methyl	0.0099	0.0298	162	172
11	4-Methyl	0.0102	0.0302	299	280
12	4-Methyl	0.0098	0.0302	380	377
13	5-Methyl	0.0101	0.0303	319	317
14	5-Methyl	0.0101	0.0302	279	274
15	6-Methyl	0.0102	0.0299	223	222
16	6-Methyl	0.0100	0.0300	194	199
17	5-Methyl	0.0098	0.0258	18.7	18.2
18	5-Methyl	0.0099	0.0257	19.7	20.5
19	5-Nitro	0.0104	0.0253	1.3	1.9
20	5-Nitro	0.0102	0.0254	1.8	1.9
21	5-Chloro	0.0100	0.0251	7.0	7.3
22	5-Chloro	0.0098	0.0258	7.2	7.6
23	H	0.0100	0.0255	10.1	9.8
24	H	0.0101	0.0251	10.4	10.2

[a] T = 29°. Solvent was benzene in runs 1–16 and acetone in runs 17–24.

to 29°C. After equilibration, the catalyst solution and the TMG were quickly removed from the sample compartment and the 5-ml volumetric flask was filled to the appropriate level with the catalyst solution. The reaction mixture was inverted twice for mixing and then the sample cell was filled and placed in position. The recorder was turned on and the rotation was recorded until reaction appeared to be near completion. When possible, the rotation was followed until the mutarotation reached equilibrium; otherwise infinity readings were taken several hours or days later.

Calculation of rate constants. The first-order rate constants were determined by noting the rotation at various times during the course of the reaction and also after the reaction had reached completion; this was only a matter of reading the Cary spectropolarimeter chart for a given run. These data were tabulated as illustrated by Table 1. The rate constants were calculated at various time intervals using

$$k = \frac{2.303 \log\left(\frac{\alpha_0 - \alpha_\infty}{a_t - \alpha_\infty}\right)}{t}$$

The average of these calculated rate constants were taken for each run.

The method of least squares was used in determining the rate constant for each run. Data for the various runs are listed in Table 2.

REFERENCES

1. C. G. SWAIN AND J. F. BROWN, JR., *J. Amer. Chem. Soc.* **74**, 2534 (1952).
2. C. G. SWAIN AND J. F. BROWN, JR., *J. Amer. Chem. Soc.* **74**, 2538 (1952).
3. H. H. HUANG, A. N. H. YEO AND L. H. L. CHIA, *J. Chem. Soc. B* **1969**, 836.
4. R. ADAMS AND A. W. SHRECKER, *J. Amer. Chem. Soc.* **71**, 1186 (1949).
5. E. S. WEST AND R. F. HOLDEN, *Org. Syn. Coll. vol. 3*, 800 (1955).