

## Isomerization of Phenylhydrazones of Dehydroascorbic Acid

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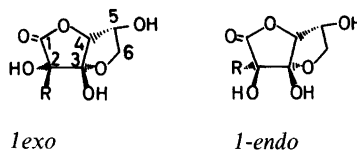
The structure and dynamics of some *para* substituted dehydroascorbic acid (DHA) phenylhydrazones in solution have been studied by  $^{13}\text{C}$  NMR spectroscopy. Two isomers are observed in *N,N*-dimethylformamide solution. The standard free energy difference ( $\Delta G$ ) between the two isomers is found to be  $0.7 \pm 0.2$  kJ/mol and the free energy barrier ( $\Delta G^\ddagger$ )  $62 \pm 2$  kJ/mol. The phenylhydrazine group is coplanar with the DHA lactone ring and the N–H group is engaged in a weak hydrogen bond to one of the  $\alpha$  carbonyl groups in both isomers. The most stable isomer has the same structure as observed previously for the molecule in the crystalline state. The phenylhydrazones of some simple aldoses (mannose, arabinose, xylose and glycolaldehyde) have been studied for comparison. Only one isomer was detected. The hydrazones were made by adding a phenylhydrazone to a solution of DHA or an aldose. Hydrazides were detected as intermediates.

In a recent study of the structure of dehydroascorbic acid (DHA) in solution the *p*-bromophenylhydrazone of monomeric DHA (*2b*) was used as a model compound.<sup>1</sup> The  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts could be interpreted on the basis of the structure of the molecule as found in the crystalline state, *2A*.<sup>2</sup> The peaks from C4 and C1, however, were markedly broader than the other peaks. Low temperature  $^{13}\text{C}$  NMR spectra, to be discussed below, show that this broadening is due to a dynamic process.

In the  $^{13}\text{C}$  spectrum of *2b* the peak from C2 was covered by another peak. Therefore also the *p*-nitro and the unsubstituted phenylhydrazones of DHA have been studied.

**Hydrazide intermediates.** The compounds were made by adding a stoichiometric amount of the appropriate phenylhydrazine to a solution of DHA in *N,N*-dimethylformamide. The  $^{13}\text{C}$  spectra

showed that the phenylhydrazide *1* was formed within a minute after the addition of the phenylhydrazine. Two isomers, *1-exo* and *1-endo*, are formed, but not in equal amounts (see Table 1). The structure of the hydrazides are probably similar to the corresponding isomers found by adding an alcohol to the DHA solution.<sup>3</sup>



*1a*, R = C<sub>6</sub>H<sub>5</sub>NHNH–

*1b*, R = *p*-BrC<sub>6</sub>H<sub>4</sub>NHNH–

*1c*, R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NHNH–

**The structure of the DHA phenylhydrazones.** *1* slowly transformed to the phenylhydrazones *2* and after a week at room temperature *2* was the dominating species in solution. The  $^{13}\text{C}$  chemical shifts are given in Table 1. (The assignments have been made by comparison with other compounds, analyses of uncoupled spectra and by looking for internal consistency.)

In *2c* all peaks are separated and in Fig. 1 three representative spectra of this compound are given. At 62 °C each carbon atom in the molecule gives rise to a single peak in the spectrum. At –50 °C, on the other hand, the four peaks assigned to the carbon atoms in the lactone ring have each split into an asymmetric doublet.

In crystalline *2b* the structure of the molecule is as in *2A*. The  $\gamma$ -lactone ring and the phenylhydrazone part are almost coplanar. N–H is engaged in a weak hydrogen bond to O1.

Table 1. Observed  $^{13}\text{C}$  NMR chemical shifts of some phenylhydrazine derivatives of dehydroascorbic acid (DHA) in dimethylformamide (at 28 °C except when noted. Digital resolution 0.03 ppm).

Substance	DHA						Phenyl				Fractional population $\pm 0.03$
	1	2	3	4	5	6	1'	2'	3'	4'	
Phenylhydrazine							153.14	112.28	129.01	117.73	
<i>p</i> -Bromophenylhydrazine							152.72	114.03	131.70	108.02	
<i>p</i> -Nitrophenylhydrazine							158.17	110.06	126.42	137.0	
1a	171.59	85.88	106.88	74.33	88.23	76.15	150.86	112.92	129.03	118.38	
1b	171.56	85.60	106.82	74.4	88.27	76.2	150.41	114.71	131.70	108.93	0.86
	172.75	84.86	107.63	74.4	89.83	76.2	150.93	115.65	131.34	108.47	0.14
1c	171.28	85.45	106.75	74.4	88.24	76.3	156.87	110.96	126.3	138.0	0.80
	172.58	84.80	107.53	74.4	89.86	76.3	157.45	111.81	126.3	138.0	0.20
2a	166.22	121.81	193.75	81.23	71.62	62.46	141.68	117.52	130.18	127.52	
2b	165.90	122.42	193.75	82.56	71.65	62.43	141.32	119.54	133.07	119.76	
−40 °C 2A	166.55	122.46	193.49	81.10	71.49	62.14	141.42	119.66	133.04	118.95	0.70
−40 °C 2B	165.44	121.87	194.53	84.15	71.49	62.14	141.42	119.66	133.04	118.95	0.30
2c	165.11	124.67	194.08	82.00	71.86	62.40	147.33	117.91	125.97	145.51	
−50 °C 2A	166.20	124.81	193.88	81.73	71.80	62.44	147.75	118.12	126.37	145.34	0.59
−50 °C 2B	164.32	124.42	195.37	84.92	71.80	62.44	147.75	118.12	126.37	145.34	0.41

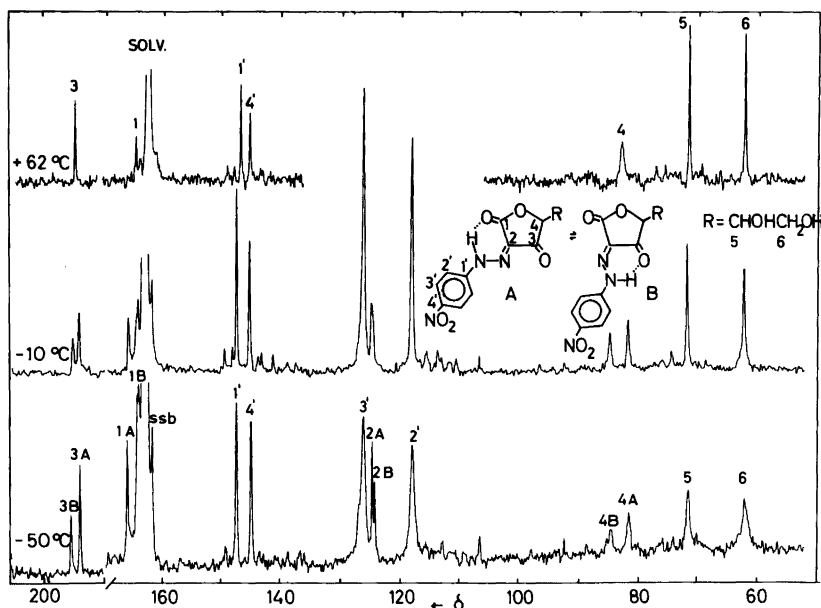
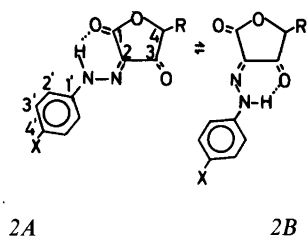


Fig. 1. 15 MHz proton decoupled  $^{13}\text{C}$  NMR spectra of 0.5 M *p*-nitrophenylhydrazone of dehydroascorbic acid (2c) in dimethylformamide solution. (The spectra were recorded on an FX-60 JEOL spectrometer. 500 pulses, repetition time 3 s, 8  $\mu\text{s}$  pulse width (45°), 1.0 Hz digital resolution.)



2A

2B

- 1a, X=H            R=CH(OH)CH<sub>2</sub>OH  
 2b, X=p-Br        5            6  
 2c, X=p-NO<sub>2</sub>

However, a similar structure is obtained by reorienting the hydrazine group as in 2B. The changes observed in the spectra are very likely induced by the molecule interconverting between the two isomers 2A and 2B. At temperatures below about  $-10^{\circ}\text{C}$  the rate of interconversion is slower than the chemical shift differences and at higher temperatures the rate is sufficiently fast to average out the differences in chemical shifts between the two isomers.

The low temperature spectra shown in Fig. 1 is a superposition of the spectra from each isomer. The asymmetry in the doublets shows that the concentrations of the two isomers are not equal. The largest peak in each doublet can be assigned to the isomer of highest concentration. The chemical shift differences between this most stable isomer and the less stable isomer at  $-50^{\circ}\text{C}$  are: C1 +1.88; C2 +0.39; C3 -1.49; -3.19. It is known that the chemical shift of a carbonyl group shifts downfield when the carbonyl group acts as a hydrogen bond acceptor. The approximately equal magnitude, and opposite sign, of the C1 and C3 chemical shift differences therefore shows that 2A - the crystal isomer - is the most stable isomer in dimethylformamide solution.

The relative area of one of the peaks in a doublet is equal to the mol fraction of the isomer contributing to that peak. The C3 and the C4 doublets are the only doublets that are well-separated and isolated in the spectrum. From the  $-50^{\circ}\text{C}$  spectrum the relative area of the smallest peak is found to be C3 0.382; C4 0.411. The C4 peaks are expected to be less influenced by differences in  $T_1$  and NOE between the two isomers. We therefore expect the mol fraction  $x$  of 2B to be  $0.411 \pm 0.016$ . From this value of  $x$  we can calculate the difference between the molar standard free energy of 2A and 2B:  $\Delta G = RT \ln [(1-x)/x]$ . We find  $\Delta G = 0.7 \pm 0.2$  kJ/mol.

**Barrier for isomerization.** At temperatures above  $-10^{\circ}\text{C}$  the rate of interconversion between the two isomers 2A and 2B is sufficiently fast to partly average out differences in chemical shifts between the two isomers. The C4 doublet is close to coalescence at room temperature. Ignoring the small difference in concentration between the two isomers we can from this observation calculate the free energy barrier for isomerization  $\Delta G^{\ddagger}$ . As  $\Delta G^{\ddagger}/RT_c = 22.96 + \ln(T_c/\delta)$ ,  $T_c = 300 \pm 10$  K,  $\delta = 48.0 \pm 0.1$  Hz, we find  $\Delta G^{\ddagger} = 62 \pm 2$  kJ/mol.

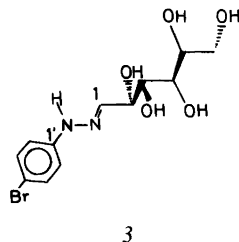
**Phenylhydrazones of some aldoses.** For comparison the  $^{13}\text{C}$  NMR spectra of phenylhydrazones of some simple sugars have also been recorded. The sugars listed in Table 2 react in a similar way as DHA with the phenylhydrazines. Minor peaks, probably from hydrazides, were detected but have not been analyzed in detail.

The crystal structure of sugar phenylhydrazones have been determined by Furberg and coworkers.<sup>4,5</sup> The most accurately determined structure is of mannose *p*-Br-phenylhydrazone<sup>4</sup> shown schematically in 3.

Table 2. Observed  $^{13}\text{C}$  NMR chemical shifts of some sugar phenylhydrazones in dimethylformamide at room temperature (digital resolution 0.06 ppm).<sup>a</sup>

Substance	1	2	3	4	5	6	1'	2'	3'	4'
Mannose <i>p</i> -BrP <sup>b</sup>	143.7	72.2*	71.9*	71.0	72.4	65.0	146.2	114.2	132.2	109.6
Arabinose P <sup>b</sup>	142.1	71.7*	72.4*	74.8*	64.7		146.9	112.4	129.5	118.8
Arabinose <i>p</i> -BrP	143.1	71.6*	72.3*	74.6*	64.6		146.0	114.2	132.1	109.7
Xylose <i>p</i> -BrP	142.2	72.5*	73.1*	73.3*	63.8		145.9	114.2	132.1	109.7
Glycolaldehyde <i>p</i> -BrP	141.0	62.3					146.0	114.2	132.1	109.8

<sup>a</sup> P, phenylhydrazone; \*, Assignments may be interchanged. <sup>b</sup> The samples used were synthesized by Furberg and Solbakk (Ref. 4).



3

3 is the isomer where the phenyl group and the sugar are *trans* relative to the C1=N bond. The group C1'-N-N-C1-C2-H is planar. The sugar carbons form a nearly planar zigzag chain making an angle of 56° with the plane of the hydrazine group.<sup>4</sup>

The <sup>13</sup>C spectra can be assigned on the basis of this structure, and the spectrum of mannitol dissolved in *N,N*-dimethylformamide (C1,C6 65.1; C2,C5 72.7; C3,C4 71.3). Using the mannitol peaks as reference for the corresponding peaks from 3 the C1 peak is shifted 78.6 ppm to low field, the three terminal carbons C4, C5 and C6 are, as expected, unshifted and C2 and C3 are remarkably little shifted. <sup>1</sup>J(C1-H) is found to be about 165 Hz in all five hydrazones.

The spectra of the sugar phenylhydrazones did not change significantly down to -50 °C. Only the peaks from C2', C3' and the sugar carbons broadened somewhat as observed for 2 at the same temperature (see Fig. 1).

*The nature of the barrier for isomerization.* Activation barriers observable by dynamic <sup>13</sup>C NMR are in the range from about 20 to 100 kJ/mol.<sup>6</sup> In the phenylhydrazones there are three bonds with partial double bond character: C1=N, N-N and N-C1'. Generally the rotational barrier for double bonds are too high to be detected by dynamic NMR and the rotational barrier for single bonds too low. However, electronic effects like conjugation lower the double bond barrier and lift the single bond barrier to within the range observable by dynamic NMR. Also steric effects may contribute to the barrier. Furthermore, for C=N bonds the nitrogen inversion barrier may be lower than the rotational barrier.<sup>6</sup>

In 2A the C1-N distance is 131 pm, the N-N distance is 131 pm and the N-C1' distance is 142 pm.<sup>1</sup> In 3 the corresponding distances are 125, 137 and 137 pm.<sup>4</sup> Hence, we see that the C1-N bond distance is close to a double bond in 3, but significantly longer in 2A. In both compounds the N-N bond is shorter than a single bond, but it is

shortest in 2A. The π electrons are therefore more delocalized in 2A than in 3. Another characteristic difference between 2 and 3 is the presence of an intramolecular hydrogen bond in 2 and the two α carbonyl groups stabilizing two structurally very similar isomers in 2, but not in 3. The basic reasons that isomerization is observed in 2 and not in 3 are therefore partly because the C=N barrier is lower for 2, and partly because the two C=N isomers have approximately equal energy in 2 and probably markedly different energies in 3.

In 2A the phenyl group is making an angle of 5° with the hydrazine moiety<sup>1</sup> and in 3 the angle is 21°.<sup>4</sup> It is, therefore, likely that the phenyl group in 2 is more engaged in π electron delocalization than in 3. Also the chemical shifts observed for the phenyl carbons in 2 (Table 1) and 3 (Table 2) reflect this. The chemical shifts observed for 3 are more similar to the values observed for 1 and markedly different from the values observed for 2.

The broadening observed for the C2' and C3' peaks at about -50 °C in both 2 and 3 indicates that the rate of isomerization about the C1'-N bond is close to the critical rate. Unfortunately, dimethylformamide freezes at -60 °C, so it was not possible to study this process at lower temperatures.

The structure of sugar phenylhydrazones in the crystalline state has been ascertained by the X-ray diffraction work by Furberg and coworkers.<sup>4,5</sup> In solution, observed mutarotation indicates that more than one species are present as reviewed by Mester.<sup>7</sup> Our observation of only one hydrazone isomer in solution is, therefore, significant. Very recently Takeda<sup>8</sup> has reported a <sup>1</sup>H and <sup>13</sup>C NMR study of sugar hydrazide and hydrazone structures in solution. Some of the compounds studied here have also been investigated by Takeda,<sup>8</sup> but he gives no interpretation of the spectra.

## REFERENCES

1. Hvoslef, J. and Pedersen, B. *Acta Chem. Scand. B* 33 (1979) 503.
2. Hvoslef, J. and Nordenson, S. *Acta Crystallogr. B* 32 (1976) 448.
3. Hvoslef, J. and Pedersen, B. *Acta Chem. Scand. B* 34 (1980) 285.
4. Furberg, S. and Solbakk, J. *Acta Chem. Scand. B* 23 (1969) 3248.
5. Furberg, S. and Petersen, C. S. In Andersen, P., Bastiansen, O. and Furberg, S., Eds., *Selected Topics in Structure Chemistry*, Universitetsforlaget, Oslo 1967, p. 183.

6. Jackman, L. M. and Cotton, F. A. *Dynamic Nuclear Magnetic Resonance Spectroscopy*, Academic, New York 1975.
7. Mester, L. In Lederer, E., Ed., *Chimie des Substances Naturelles, VII, Derivés hydraziniques des glucides*, Hermann, Paris 1967.
8. Takeda, Y. *Carbohydr. Res.* 77 (1979) 9.

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