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NMR–spectroscopic investigation of o-nitrosobenzoic acid

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The synthesis of *o*-nitrosobenzoic acid 2 has been known for more than 100 years, and the photochemical preparation from *o*-nitrobenzaldehyde 1 became a textbook example for [1,5]-hydrogen shifts. However, neither the ^{1}H–NMR spectra nor the ^{13}C–{^{1}H}–NMR of this compound have been reported so far. This fact can most likely be attributed to the monomer–dimer equilibrium of the nitrosobenzoic acid, which leads to rather complex, concentration-dependent NMR spectra. In this paper, we report a thorough investigation of these spectra. In the ^{13}C-{^{1}H}-NMR spectra, all 21 lines could be assigned to the monomeric form, the *E*-dimer, and the *Z*-dimer. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; nitroso compounds; dissociation constant

Introduction

o-Nitrosobenzoic acid **2** had been already synthesized by Emil Fischer in 1895.[1] After five years, it was prepared photochemically from nitrobenzaldehyde **1** (Scheme 1).[2] This reaction became a common example for [1.5]-hydrogen shifts in current textbooks on photochemistry.[3–5] Therefore, it is really surprising that, since the introduction of the NMR–spectroscopy in the late 1940s,[6,7] neither the ^{1}H-NMR spectrum nor the ^{13}C–{^{1}H}–NMR spectrum has been published.

Since the last few years, it is known that nitroso compounds are in equilibrium with their azodioxy dimers (Scheme 2).[8–10] This could be the reason that nitrosobenzoic acid has not been studied so far using NMR–spectroscopy.

This is especially disturbing because *o*-nitrosobenzoic acid can be regarded as a model compound for other nitroso compounds. In the 1960s, Barltrop and Woodward extended the photochemistry of *o*-nitrobenzyl compounds, discovered by Silber, and designed photolabile-protecting groups (Scheme 1).[11–13] On the basis of this reaction, in the 1970s, Engels *et al*.[14,15] and Kaplan *et al*.[16] developed the concept of caged compounds **3**, which are photolabile-protected, inactive derivatives of biologically active molecules HX. The active species can be released from the caged compound by laser photolysis. Meanwhile, other photolabile-protecting groups have been introduced;[17,18] however, *o*-nitrobenzyl derivatives are by far the most important. It is remarkable that the nitroso side products are always postulated, but very rarely characterized.[19,20] Thus, it is of utmost importance to understand the NMR–spectra of nitrosobenzoic acid **1**. This should give the basics for the characterization of other nitroso compounds for a more detailed study of the *o*-nitrobenzyl photochemistry in general.

Results and Discussion

Owing to the equilibrium between the monomeric and dimeric form, it is not surprising that the ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of nitrosobenzoic acid **1** is by far more complicated than one would expect for a simple [ABCD] spin system[21] (Fig. 1). A thorough investigation shows a concentration dependence of the spectrum, as expected. In very dilute solutions (0.0061%, 0.469 mM) at high temperatures (100 °C), one can obtain the spectrum of the nearly pure monomeric form. At 6.87 ppm, a duplet with a coupling constant of 7.8 Hz can be detected, which is assigned to proton 6 by comparison with reference data.[22] At 7.61–7.67, a multiplet is observed, which can be assigned by COSY to proton 5. Line broadening and the bad signal-to-noise ratio due to the very dilute solution made it impossible to analyze this system further. A $^{4}J_{HH}$ coupling to proton 3 of about 3 Hz can be recognized. A second multiplet at 7.83–7.86 ppm with an integration of 2 can be assigned to the two isochronic protons 3 and 4. A coupling constant of 4.3 Hz can be obtained from this multiplet.

With these data, one can deduct from the spectra at room temperature that at high concentrations of nitrosobenzoic acid **1** (13.0%, 1020 mM), there is only a minute portion of the compound in the monomeric form. Yet, the NMR spectrum is too complicated to represent only one species. Therefore, one has to assume that the dimeric form can exist as *E*-isomer **5** and as *Z*-isomer **6** (Scheme 2). The alternate explanation for the contribution of oligomers can be ruled out by the examination of the ^{13}C–{^{1}H}–NMR spectra (see below). At 8.08 ppm, a dd ($^{3}J_{HH}$ = 7.8 Hz, $^{2}J_{HH}$ = 1.2 Hz) can be observed. On the basis of the following two reasons, we assign this signal to the *E*-isomer: (i) By intuition and according to *ab initio* calculations on the STO 6-31G**/B3LYP[23–31] level, the *E*-isomer should be more stable. According to the integration, the species with the signal at 8.08 ppm is the major component (ratio about 7 : 4). (ii) This signal exhibits a very high low-field shift. Owing to geometric considerations, one would expect a high-field shift for all signals based on anisotropic effects for the *Z*-isomer.

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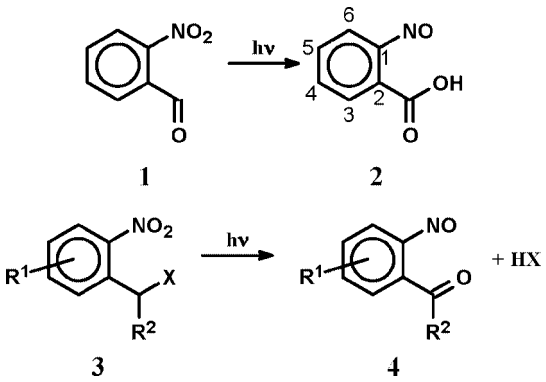
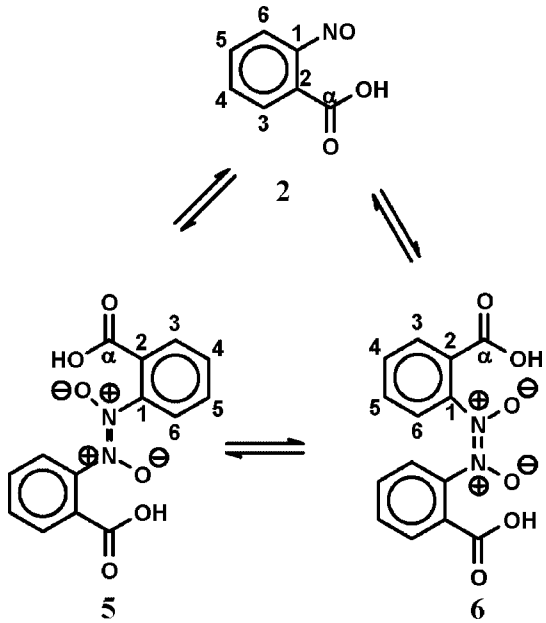


Scheme 1. Photochemical formation of 2-nitrosobenzoic acid form 2-nitrobenzaldehyde and photochemical cleavage of caged compounds of the 2-nitrobenzyl type.



Scheme 2. Equilibrium between the monomeric form and the dimeric forms of 2-nitrosobenzoic acid.

The remaining three signals represent the missing seven lines. The multiplets are too complicated to be analyzed in detail. However, from the integration, the multiplets can be assigned to the two species: **5** and **6**. The multiplet at 7.91–7.84 ppm represents one proton of the *E*-isomer and one of the *Z*-isomer, the multiplet at 7.75–7.65 ppm represents two protons of the *E*-isomer and one of the *Z*-isomer, and the multiplet at 7.54–7.49 ppm represents two protons of the *Z*-isomer. There are no increments available for azodioxy compounds **5** and **6**. However, an assignment of the signals is possible using increments[32] for quaternary amines instead of the azodioxy group (Table 1). All signals for the *Z*-isomer exhibit a high-field shift of 0.14–0.19 ppm compared to the *E*-isomer in agreement with our suggestion above. From the intensity of the ^{1}H–NMR signal at about 6.87 ppm in relation to the overall intensity, we estimated an overall dissociation constant of 2.2×10^{-3} mol l^{-1}.

Additionally, we investigated the system by means of ^{13}C–{^{1}H}–NMR spectroscopy. Spectra at different concentrations are shown in Fig. 2. In these spectra, a total of 21 signals has been found. This is in agreement with three different species: the monomeric form **2**, the *E*-dimer **5**, and the *Z*-dimer **6**. In order to assign the signals to the three species, we did the integration for each line. Line 1 (Fig. 2) was normalized to 1 for each spectra, all lines in the spectrum at 13% (1020 mM) nitrosobenzoic acid were normalized to 1, and the relative changes of the integration in the spectra of the more diluted samples were plotted as a function of concentration for each signal (Fig. 3). By definition, line 1 gives a straight line. Six additional signals gave straight lines as a function of concentration within experimental error (Fig. 3, red bars). The remaining 14 signals showed a decrease in intensity with

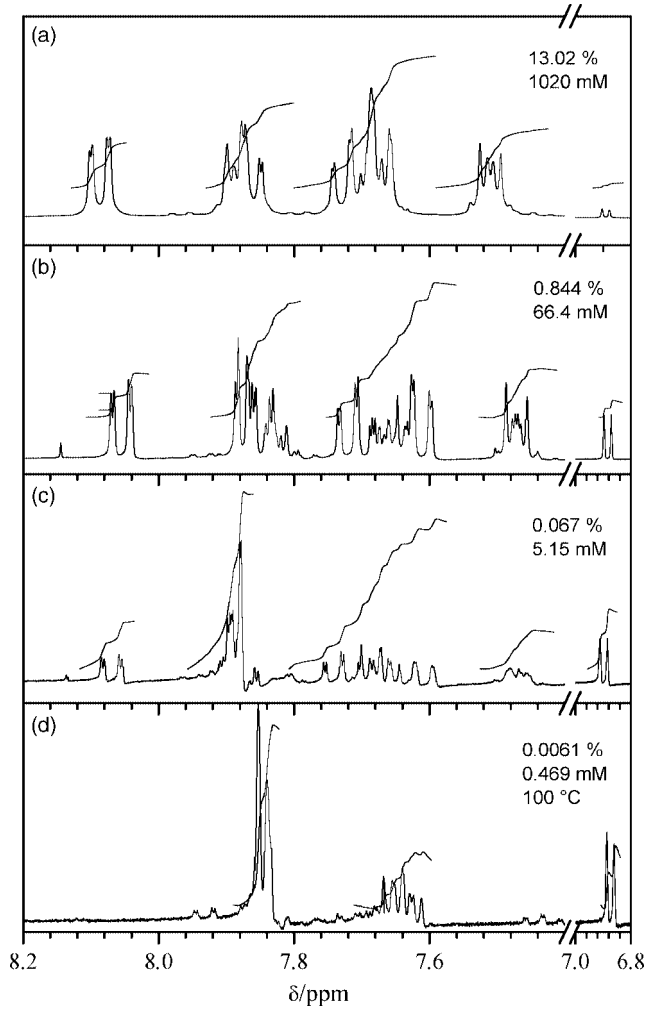


Figure 1. The 300 MHz ^{1}H–NMR spectra of nitrosobenzoic acid **1** in DMSO-d_6 at different concentrations and temperatures are shown.

Table 1. The protons of the two azodioxy-isomers **5** and **6** are assigned to the NMR-spectroscopic data. The calculated chemical shifts are based on increment systems

Proton	δ_{exp}/ppm for **5**	δ_{calc}/ppm	δ_{exp}/ppm for **6**
3	8.08	8.47	7.91–7.84
4	7.75–7.65	7.75	7.54–7.49
5	7.75–7.65	7.87	7.54–7.49
6	7.91–7.84	8.13	7.76–7.65

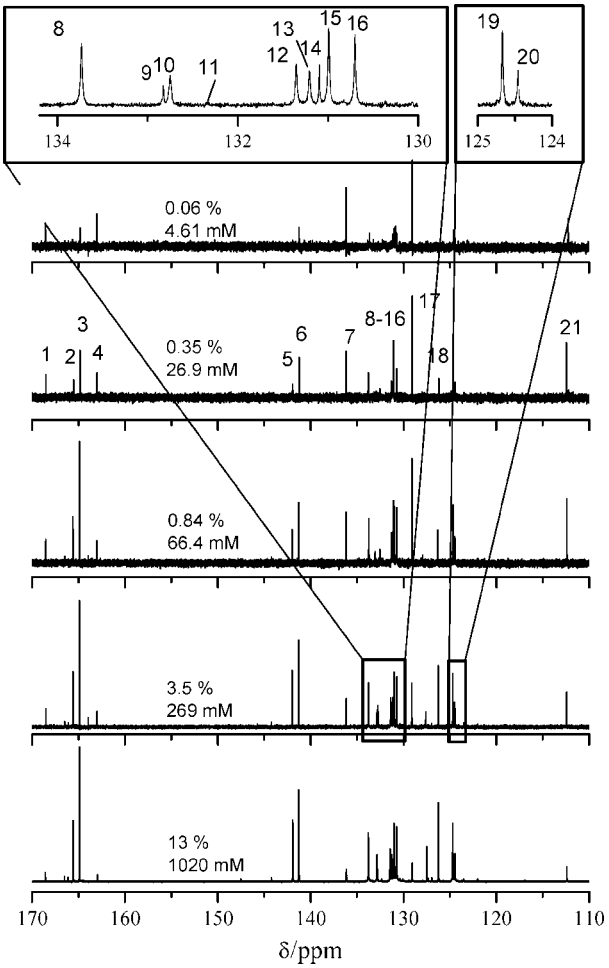


Figure 2. The 75 MHz $^{13}C-\{^1H\}$–NMR spectra of nitrosobenzoic acid **1** in $[D_6]$DMSO at different concentrations and temperatures are shown.

increasing concentration (Fig. 3, blue and green bars). Therefore, these 14 signals were assigned to the two dimeric species **5** and **6**, while the remaining seven lines were assigned to the monomeric form **2**.

All 14 lines for the dimeric forms show the same concentration dependence. This proves that the two species are indeed two different dimeric forms and not one dimer and one oligomeric form. In Fig. 4, the absolute intensities of these 14 lines are shown. They were assigned to CH–carbons and quaternary carbons by DEPT-GL. For the quaternary carbons, there are three signals with high intensity and three signals with low intensity. For the CH–carbons, there are four signals with high intensity and four carbons with low intensity. Even if the integration in $^{13}C-\{^1H\}$–NMR is due to polarization transfer, which is not proportional to the number of carbons (as in ^1H–NMR), this allows the assignment to the two isomeric dimers. Again, the isomer with the higher intensity is assigned to the *E*-form (Fig. 3, green bars, D2), and the one with the lower intensity is assigned to the *Z*-form (Fig. 3, blue bars, D1, also see Fig. 4). From this data, one can estimate a ratio of the two isomers of 5 : 3, which is in reasonable agreement with the ratio 7 : 4 taken from the ^1H–NMR spectra.

After the signals were assigned to the three species, it was possible to understand the spectra (Table 2). On the basis of the data for *p*-nitrosoanilines,[33] we computed chemical shifts for the *o*-nitrosobenzoic acid **2** by subtracting the dialkylamino increment and adding the appropriate carboxy increment.[32] For the α–carbon, a typical shift for aromatic carboxylic acids was assumed. There are no increments available for azodioxy substituents. Therefore, we used the increment for an azooxy substituent from a review article by Ewing[34] and a standard increment[32] for the carboxy group. Apart from carbons 4 and 5, which are shown by our calculations and by the experimental data, to have very similar shifts in **5** and **6** we were able to assign all signals. Attempts to calculate the chemical shifts by the gauge-including atomic orbitals (GIAO) method[35–38] based on STO 6-31 G**/B3LYP,[23–31] geometry optimization did not produce decent results. This is most likely due to problems determining the correct conformation in solution. According to our calculations for the monomeric form **2,** the nitroso group is pointing toward the carboxy group (Fig. 5). However, the chemical shift of 112.3 ppm for carbon 6 strongly indicates a conformation where the nitroso group is pointing toward carbon 6.

Five hundred megahertz ^1H–NMR studies reveal an even more complex situation (Fig. 6). One can detect six more small, but distinct signals, which vanish when the sample is diluted. This leads to two more different species or to one species with molecules in two nonequivalent positions. These signals can be attributed to oligomeric forms, which are most likely aggregates of the dimeric form. As not all of these signals can be detected, we did not analyze the problem further.

Table 2. The 21 signals in the $^{13}C-\{^1H\}$–NMR spectra for nitrosobenzoic acid **2** and its two dimeric forms **5** and **6** are assigned by comparison with calculated values

		2		**5**	**5** and **6**	**6**
Proton		δ_{exp}/ppm	δ_{theor}/ppm	δ_{exp}/ppm	δ_{theor}/ppm	δ_{exp}/ppm
1	q	162.9	168.5	141.2	145.6	141.8
2	q	132.7	143.5	126.1	127.8	127.4
3	–	129.0	128.6	130.9/130.6[a]	130.1	131.3/131.2[a]
4	–	136.1	142.9		129.3	
5	–	131.0	131.8	133.7	133.3	132.7
6	–	112.3	110.2	124.6	125.2	124.4
α	q	168.5	172.0	164.8	172.0	165.5

[a] An unambiguous assignment is not possible.

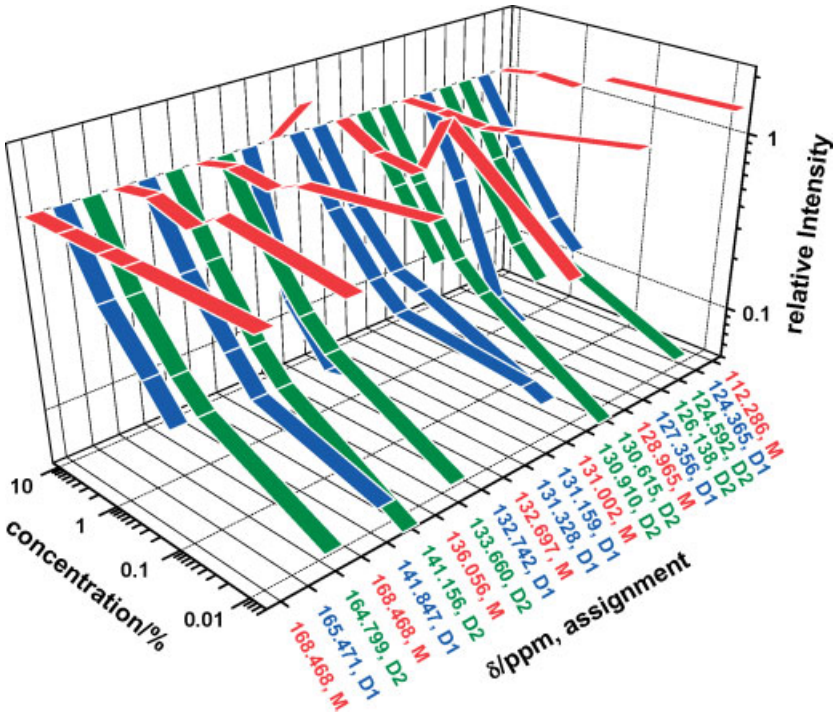


Figure 3. The relative intensities for all 21 lines of $^{13}C-\{^1H\}-NMR$ spectra (75 MHz/[D_6]DMSO) of nitrosobenzoic acid are plotted as a function of concentration.

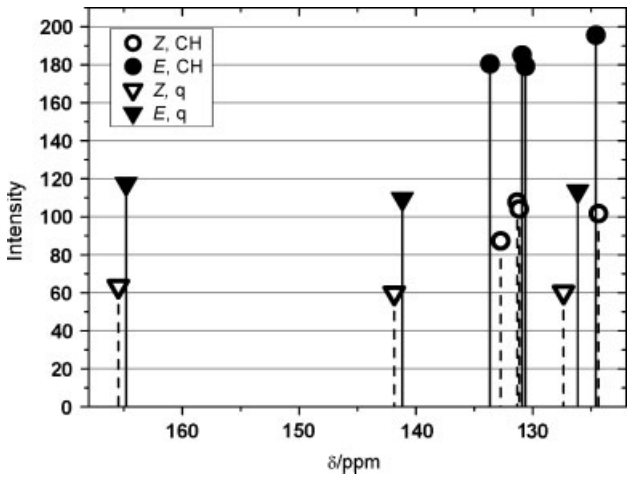


Figure 4. The absolute intensities in relative units of the two dimeric forms of *o*-nitrosobenzoic acid **5** and **6** for the 14 signals in the $^{13}C-\{^1H\}-NMR$ spectra (75 MHz/[D_6]DMSO) for a concentration of 13% (1020 mM) are plotted as a function of chemical shift.

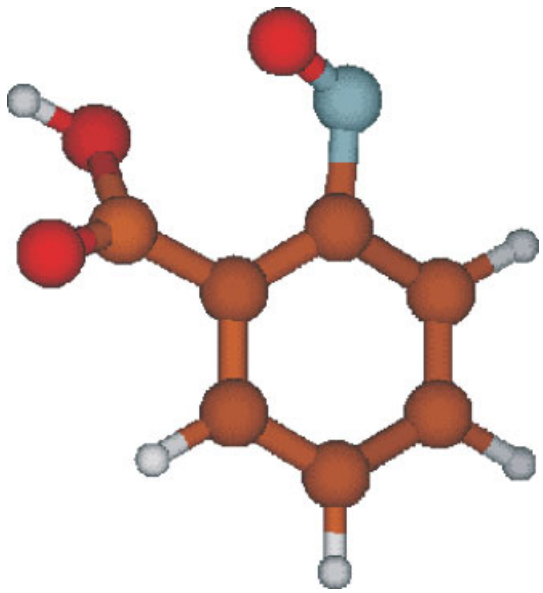


Figure 5. The geometry of nitrosobenzoic acid **2** based on *ab initio* STO 6-31 G**/B3LYP calculations is shown.

Conclusion

The proton and carbon NMR spectra of nitrosobenzoic acid **2** are complex and strongly concentration dependent. This behavior can be attributed to the fact that there are three major species, namely, the monomeric form **2**, the *E*-dimer **5,** and the *Z*-dimer **6**, and two minor species, which are most likely oligomers, in equilibrium. It was possible to assign all 21 signals in the $^{13}C-\{^1H\}-NMR$ to these three major species. The ^1H-NMR is also fully understood. However, owing to an overlap of the lines, it was not possible to determine the chemical shifts and coupling constants of the dimeric species. Hopefully, these results will provide the necessary information for understanding the NMR–spectra of other nitroso compounds like **4**, which are side products in caged compound chemistry.

Experimental Section

All ^1H-NMR spectra and $^{13}C-NMR$ spectra were recorded in dimethyl sulfoxide (DMSO), and chemical shifts are given relative to tetramethylsilan.

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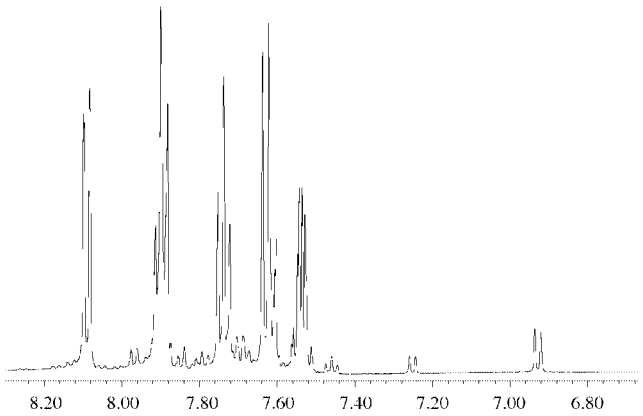

Figure 6. The ^{1}H–NMR spectrum (500 MHz/[D_6]DMSO of nitrosobenzoic acid **2** (13.0%, 1020 mM)).

Three hundred megahertz ^{1}H–NMR spectra and 75 MHz ^{13}C–NMR spectra were measured on a Varian VXR 300. For 300 MHz ^{1}H–NMR spectra, a pulse width of 5998.5 Hz and a spectral resolution of 0.2 Hz were used. For 75 MHz ^{13}C–NMR, a pulse width of 18 587 Hz and a spectral resolution of 0.56 Hz were used.

Five hundred megahertz ^{1}H–NMR spectra and 125 MHz ^{13}C–NMR spectra were measured on a Bruker AM-500. For 500 MHz ^{1}H–NMR spectra, a pulse width of 10 330 Hz and a spectral resolution of 0.16 Hz were used. For 75 MHz ^{13}C–NMR, a pulse width of 39 682 Hz and a spectral resolution of 0.61 Hz were used.

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