CRYSTAL STRUCTURE OF THE MONO-LACTIM ETHER OF A BILATRIENE-*abc* DERIVATIVE AT 101 K

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Abstract —The crystal structure of (Z,Z,Z)-19, 24-dihydro-1-methoxy-19-oxo-2,7,13,18-tetramethyl-3,8,12,17-tetraethyl-22H-bilin was determined at 101 K by X-ray diffraction methods: space group P$\bar{1}$, $a = 9.532(2)$, $b = 12.189(4)$, $c = 13.984(4)$Å, $\alpha = 114.83(3)$, $\beta = 103.56(2)$, $\gamma = 90.55(1)°$, $Z = 2$ ($C_{32}H_{40}N_4O_2$), $D_x = 1.197$ g cm^{-3}. Intensity data were collected up to sin $\theta/\lambda = 0.765$, which permitted anisotropic refinement of all non-hydrogen atoms and isotropic refinement of all hydrogen atoms. The lactim ether exists as the 22H,24H tautomer in the crystal, and assumes a quasi-helical conformation with a C=O .. O—Me distance of 3.94Å. Molecular conformation and tautomeric form are discussed in terms of *intra*molecular hydrogen bonding between pyrrole hydrogen atoms and pyrrolenine nitrogen atoms. The molecular conformation in the crystal shows excellent agreement with the result of previous studies in solution.

CRYSTALLOGRAPHY on linear tetrapyrroles is a young science. More than 100 crystal structures of porphinoid compounds were known before the first structures of linear, metal-free tetrapyrroles were reported. In view of the potential biological relevance (phytochrome, haem metabolism, accessory pigments) and of the immense constitutional, configurational and conformational variability of this class of compounds, the number of structure determinations reported since then is surprisingly small.[1-10]

Experimental difficulties in obtaining and handling crystals suitable for single crystal diffraction seem to be the prime reason for the apparent restraint of crystallographers. Crystals of metal-free linear tetrapyrroles are hard to obtain, they are often unstable when exposed to light or X-rays and the resulting structures tend to be disordered.[11] Most structures are therefore not very accurate, and a detailed discussion of the bonding geometry (*e.g.* correlation of bond length *vs* dihedral angle about methine bonds) has to await future analyses. However, there is one result which is consistently observed in all relevant crystal structures, and which is now beyond reasonable doubt also from a chemical point of view:[12] whenever the possibility of lactam/lactim tautomerism exists, the lactam form predominates.

Keeping in mind that the available crystallographic

evidence constitutes only a minute and arbitrary sample, the molecular conformations observed in crystal structures of linear, metal-free tetrapyrroles can be summarized as follows (Fig. 1).

The conformation of compounds with a rubinoid chromophore is essentially the result of rotation about the two methylene single bonds C(9)–C(10) (ϕ_1) and C(10)–C(11) (ϕ_2). The "ridge-tile" conformation ($\phi_1 \sim \phi_2 \sim 60°$) observed in all known bilirubin crystal structures[1,3,4,6] is usually interpretable in terms of six intramolecular H-bonds between the pyrrole protons, the lactam CO groups and the carboxyl groups (in the case of di-isopropylammonium bilirubinate[4] also involving the isopropylammonium ions). A very similar conformation exists in the crystal structure of 1,19-di(ethoxycarbonyl)-octamethyl-biladiene-*ac* dihydrobromide,[2] where it appears to be the result of two *inter*molecular H-bonds between each protonated pyrromethene half and one bromide ion. We are only aware of one exception from the "ridge-tile" preference, which was observed in the crystal structure of diethoxybilirubin diethyl ester,[5] where the two pyrromethene halves (stabilized in a planar *syn* conformation by *intra*molecular H-bonding between pyrrole proton and pyrrolenine N) assume a "perpendicular" conformation ($\phi_1 \sim 0°$, $\phi_2 \sim 90°$).

A "helical" conformation with angles of 0–30°

Ridge tile   Perpendicular   Helical

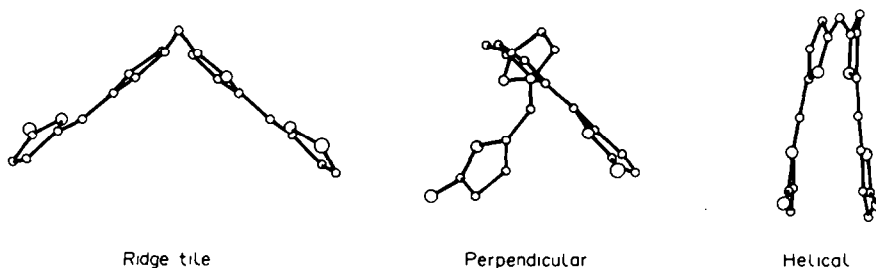Fig. 1. Three typical conformations observed in crystal structures of linear, metal-free tetrapyrroles.

between adjacent pyrrole rings and 3.5-4Å separation between rings A and D is typical for crystal structures of verdinoid compounds. This conformation is a compromise between good overall conjugation and *intra*-molecular N–H . . . N H-bonding on the one hand and steric repulsion between rings A and D on the other hand. In biliverdin dimethylester,[7] symmetry-equivalent helices are associated (by pairs of N–H . . . O=C hydrogen bonds) to form disordered dimers.[11] Other examples of a more or less helical conformation are the structures of 1,19-di(ethoxycarbonyl)-octamethylbilatriene-*abc* hydrobromide[9] and of 1,19-di(ethoxycarbonyl)octamethylbilatriene-*abc*,[10] the latter structure having the *anti-Z* configuration between rings A and B as a result of *inter*molecular H-bonding. Strong steric hindrance can lead to considerable distortion from the helical conformation, such as in the crystal structure of octaethyl-5-nitrobilin-1,19-dione,[8] where steric repulsion between *meso* and β substituents leads to a twist of nearly 90° between rings A and B.

^{1}H-NMR LIS and NOE measurements[13] for solutions in chloroform have established the configuration (*Z,Z,Z*) and the conformation (helical *syn,syn,syn*) of the lactim ether (1), with dihedral angles of roughly

1a   1b
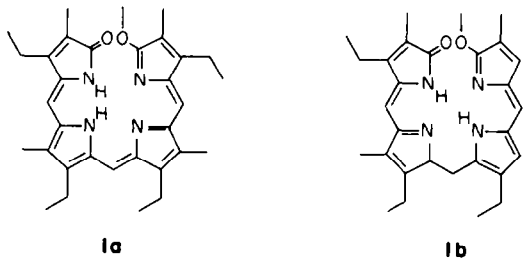
20° about each methine single bond and a helix "pitch" (C–O . . . O–CH$_3$ distance) of 5.6Å. These results could be reproduced with an appropriately parametrized force-field.[14] However, until recently[15] the solution experiments could not distinguish between the tautomeric forms (1a) and (1b). The only weak indication about the preference of one form over the other came from the electronic spectrum of 1, which fits the calculated (PPP-SCF-LCAO-MO-CI) band intensities of 1b slightly better than those of 1a.[16]

This situation called for a crystal structure analysis on compound 1 which is reported in the present communication. Apart from the relevance of this structure analysis in view of the well established solution behaviour and of the extensive theoretical work on compound 1 we intended to contribute to a better structural characterization of the verdinoid chromophore.

EXPERIMENTAL

The preparation of 1 has been described.[13] A few mg of microcrystalline material was dissolved in DMSO and placed in a desiccator containing a second open beaker with EtOH. Small but extremely well-formed dark-blue crystals slowly formed (cold room, several months). A specimen of approximately $0.24 \times 0.1 \times 0.06$ mm^3 was glued to a glass fibre and used for the structure determination, which was carried out on a locally modified STOE 4-circle diffractometer equipped with a Nonius low-temp attachment (graphite-monochromatized MoK$_\alpha$ radiation, $\lambda = 0.71069$Å). To prevent formation of ice on the crystal, the diffractometer was placed inside a glove box. Before the onset of the X-ray work,

the crystal was cooled (cold-stream temperature: 101 ± 1 K) and kept at low temperature for the whole five weeks used for the X-ray investigation. Visual inspection through the diffractometer microscope showed that the crystal remained essentially free of ice deposits during this time.

Cell dimensions were calculated by a least-squares fit to the setting angles of 14 reflections obtained from a random peak search. Intensity data were subsequently collected in the ω-scan mode (scan width $\Delta\omega = 1.0$ 1.2°), using a double-scan algorithm with a fast pre-scan and an optional second scan whose speed depended on the result of the pre-scan. All symmetry-independent reflections with $2\theta \leqslant 65°$ ($\sin\theta/\lambda \leqslant 0.765$) were measured at least once.

During data collection, three standard reflections were periodically remeasured. These standard intensities continuously decreased to about 55% of their initial intensity during the 5 weeks of data collection. The decay affected the three standard reflections by nearly the same factor, and it also affected the backgrounds of the standard reflections by a factor of 0.64. The orientation matrix was redetermined during and after data collection and found to be unchanged within experimental error. The mosaic spread of the crystal (as judged by the line width of several reflections) did not change during data collection. We attribute the decay in standard intensities to a drop in primary intensity, but we cannot exclude other reasons, such as decomposition of the crystal.

The 12548 intensity values were scaled to equal standard intensity. After merging of multiply measured reflections ($R = 0.0052$), the usual data processing of the 10328 independent reflections (LP-correction, but no absorption correction, μ(MoK$_\alpha$) = 0.82 cm^{-1}) yielded 4613 significant structure factors ($|F_0| > 3\sigma(|F_0|)$).

The structure was solved with direct methods and refined by least-squares techniques.[17] Hydrogen atoms were included at observed positions and refined with isotropic temp factors, while all other atoms were refined anisotropically. Computer limitations forced us to carry out the least-squares refinement in a "blocked" mode, where each cycle involved a full-matrix refinement of approximately one quarter of the molecule. The refinement (whose results are given in Fig. 5 and Table 1) converged at $R = 0.0678$, $R_w = 0.0559$ ($1/\sigma^2$ weights, 503 parameters, 3994 observations). A final difference Fourier synthesis showed peaks up to 0.4eÅ^{-3}, most of them approximately centred on C–C, C–N and C–O bonds.*

RESULTS AND DISCUSSION

In spite of difficulties during data collection (drop in standard intensities—see experimental section), the high crystal quality and the experimental conditions of data collection (low temperature) permitted the acquisition of a large data set. Compared to other crystal structures of linear tetrapyrroles, the present structure is therefore of unusual accuracy. This is manifested in the low estimated standard deviations for positional and thermal parameters and in the good agreement between the bond lengths of chemically equivalent groups. All H atoms were observed experimentally and behaved well during least-squares refinement. At no stage of structure determination and refinement did we observe any indication of disorder, which has been a frequent problem in the structure analysis of related compounds.[1-11] We believe that some of the merit for the good quality of our crystals may be attributed to the experimental conditions of crystallization (slow vapour diffusion at cold room temperature).

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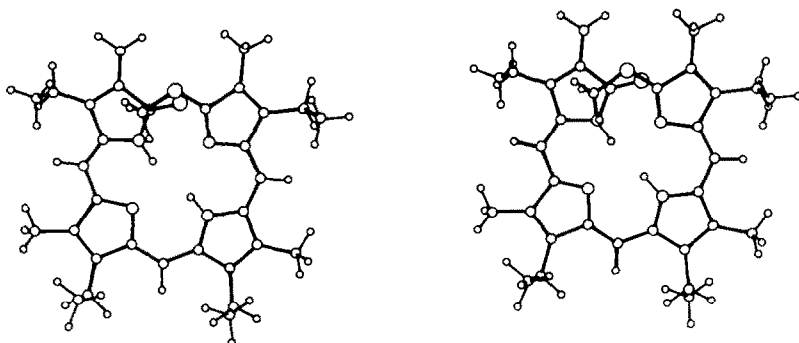*Tabulated observed and calculated structure factors have been deposited with the Cambridge Crystallographic Data Centre.

Fig. 2. Stereoscopic drawing of the asymmetric unit in the crystal structure of 1. Projection approximately into the mean plane through the tetrapyrrole moiety.

The result of the crystal structure analysis is presented in Figs. 2–5 and in Table 1. The structure analysis leaves no doubt about the exclusive occurrence of tautomeric form (1b) in the crystal. This assignment is revealed by the successful refinement of the two imino H atoms and it is supported by the observed distribution of bond lengths (Fig. 5), which indicates the importance of the resonance structure shown in 1b.

In the crystal, the molecule assumes an all-*syn* conformation (Fig. 2), with an O(1)–O(19) distance of 3.94Å. Following the established terminology,[5] this conformation could be described as "helical". However, inspection of Fig. 3 and of the methine dihedral angles (Fig. 5) suggests that the conformation is more appropriately termed "sharp ridge tile", with an angle
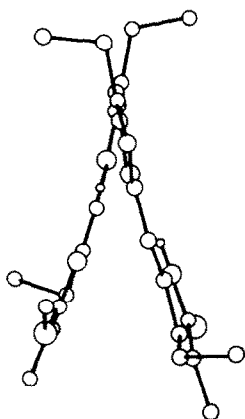

Fig. 3. Crystal structure of 1. Projection approximately along the C(9) C(11) vector.

of 33° between the least-squares planes through the pyrromethenone (rings C, D) and the azafulvene (rings A, B) moieties.

We note the dihedral angle of 7.1° about the C(15)–C(16) bond which, according to the structure shown at 1b, is formally a double bond. Dihedral angles of the same order of magnitude were previously observed in the crystal structures of biliverdin dimethyl ester (6.5°),[7] of 1,19-di-(ethoxycarbonyl)-octamethyl-bilatriene-*abc* (5.7°)[10] and of bilirubin[1] (observed values between 5 and 10.7°, but of questionable significance due to constraints during least-squares refinement). These observations indicate that deviations can occur from planarity about formal methine double bonds.

Judging from the distribution of bond lengths at the methine bridges (Fig. 5), the π-conjugation extends over the whole of the chromophore. Values up to 1.48Å for methine "single" and values down to 1.32Å for methine "double"[3] bonds have been observed in other metal-free linear di-, tri- and tetrapyrroles, which again puts the above C(15)–C(16) dihedral angle into perspective. We believe that the intramolecular H-bonds (see below) are an important factor for the conjugation.

As usual in crystal structures of tetrapyrroles, individual pyrrole and pyrrolenine rings are planar to within 0.01Å. If α-substituent atoms are included in the calculation of least-squares planes, deviations from planarity still do not exceed 0.06Å.

Inspection of Fig. 5 reveals that both the preference for tautomeric form (1b) over (1a) and the overall molecular conformation can be interpreted in terms of the intramolecular H-bonds between the pyrrole H atoms and the pyrrolenine nitrogens. There are three intramolecular H-bonds in this crystal structure
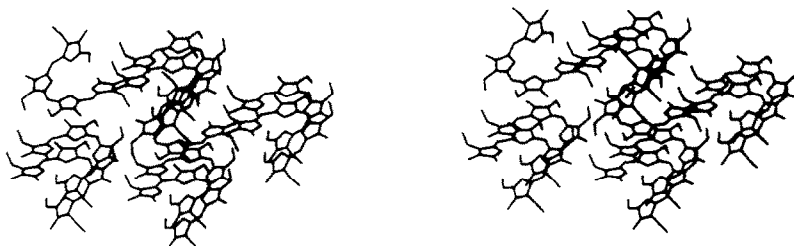

Fig. 4. Packing in the crystal structure of 1. Projection into the crystallographic y · z plane

Table 1. Fractional atomic coordinates and isotropic tensor components ($\times 10^4$ for C, N and O; $\times 10^3$ for H; U-values in Å^2). E.s.d.'s are in units of the last figure. The isotropic temperature factor has the form:

$$T = \exp[-(8\pi^2 U \sin^2 \theta / \lambda^2)].$$

Non-hydrogen atoms (left column) were refined anisotropically; equivalent isotropic tensor components Ueq were calculated as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	X/a	Y/b	Z/c	Ueq	Atom	X/a	Y/b	Z/c	Uiso
N21	1985 3	287 2	−300 2	175 11	H-N22	142 3	−89 3	−209 2	29 9
N22	1825 3	−1577 2	−2394 2	160 11	N-N24	180 4	134 3	−197 3	44 11
N23	123 3	−101 2	−3325 2	167 11					
N24	1807 3	2115 2	−1726 2	181 11	H−C5	433 3	−170 2	−40 2	15 8
					H-C10	−11 3	−301 2	−489 2	3 7
O1	898 2	1935 2	762 2	249 10	H−C15	−126 3	236 2	−315 2	13 7
O19	3940 2	2882 2	−329 2	275 11					
					H1−C100	−113 4	207 3	2 3	33 10
C1	1872 3	1135 3	630 2	193 13	H2−C100	−44 3	99 3	−70 3	29 9
C2	2881 3	1157 3	1604 2	216 13	H3−C100	10 4	236 3	−43 3	43 11
C3	3672 3	234 3	1218 2	192 13	H1−C21	379 5	207 4	327 4	68 15
C4	3121 3	−330 2	22 2	163 13	H2−C21	221 5	172 4	304 4	89 17
C5	3548 3	−1344 3	−685 2	168 13	H3−C21	284 5	284 4	287 4	73 15
C6	2930 3	−1966 2	−1836 2	162 13	H1-C31	536 3	45 3	253 3	22 9
C7	3236 3	−3080 2	−2589 2	163 12	H2-C31	552 4	−59 3	141 3	42 11
C8	2262 3	−3367 2	−3604 2	162 13	H1−C32	482 3	−154 3	252 3	27 9
C9	1397 3	−2405 2	−3470 2	153 12	H2-C32	350 4	−185 3	146 3	49 12
C10	252 3	−2281 3	−4261 2	166 12	H3−C32	342 3	−79 3	261 3	26 9
C11	−391 3	−1266 2	−4194 2	155 12					
C12	−1632 3	−1201 2	−4997 2	157 13	H1−C71	474 4	−426 3	−290 3	39 11
C13	−1853 3	−7 3	−4618 2	170 13	H2−C71	394 4	−445 3	−220 3	34 10
C14	−734 3	640 2	−3591 2	160 12	H3-C71	523 4	−333 3	−172 3	42 10
C15	−549 3	1938 3	−2955 3	177 13	H1-C81	249 3	−515 2	−458 2	14 7
C16	614 3	2597 2	−2112 2	167 13	H2−C81	113 3	−470 3	−515 2	24 8
C17	878 3	3921 2	−1436 2	182 13	H1-C82	314 4	−490 4	−597 3	55 13
C18	2172 3	4181 3	−690 3	197 13	H2−C82	418 5	−395 3	−479 3	70 14
C19	2799 3	3020 3	−851 3	194 14	H3−C82	278 4	−354 3	−552 3	40 10
C100	−216 4	1777 3	−197 3	238 16	H1−C121	−288 3	−204 3	−664 3	27 9
C21	2901 5	1993 3	2752 3	336 18	H2−C121	−201 3	−292 3	−625 2	22 8
C31	4794 3	−229 3	1859 3	232 14	H1-C122	−455 3	−334 3	−652 3	31 9
C32	4096 4	−1172 3	2111 3	316 18	H2−C122	−446 3	−201 3	−557 2	17 8
C71	4359 4	−3836 3	−2328 3	241 15	H3−C122	−369 4	−304 3	−529 3	36 10
C81	2196 3	−4453 3	−4667 2	205 14	H1−C131	−262 5	99 4	−545 4	85 17
C82	3152 4	−4223 3	−5307 3	353 19	H2−C131	−331 5	115 4	−461 4	80 16
C121	−2530 3	−2251 3	−6004 2	184 13	H3−C131	−383 5	7 4	−553 3	62 13
C122	−3901 4	−2692 3	−5822 3	246 15					
C131	−2980 4	560 3	−5148 3	234 15	H1−C171	−121 3	439 3	−196 3	20 8
C171	−135 3	4794 3	−1611 3	210 14	H2−C171	−12 3	545 2	−91 2	5 7
C172	310 5	5356 4	−2299 3	333 20	H1-C172	−30 4	591 3	−240 3	42 12
C181	2952 4	5382 3	181 3	297 17	H2−C172	34 4	476 3	−299 3	36 10
					H3−C172	128 4	583 3	−197 3	23 9
					H1-C181	233 4	599 3	30 3	41 11
					H2−C181	378 4	571 3	1 3	40 11
					H3−C181	339 4	534 3	85 3	46 12

(H(N22)...N(21), H(N24)...N(23), H(N22)...N(23)), while there could be only one such intramolecular H-bond in tautometic form (**1a**) (between H(N23) and N(22)). This apparently favours tautomeric form (**1b**) in the absence of intermolecular hydrogen bonding. Moreover, it is plausible that the two short intramolecular H-bonds (H(N22) . . . N(21) and H(N24) . . . N(23)) are energetically favoured by the roughly planar conformation of the two halves of the molecule.

Figure 4 shows a stereoscopic packing diagram, projected down the crystallographic x-axis. The figure includes one molecule with its nine nearest neighbours. Molecules pack in a seemingly irregular fashion, with no evidence for intermolecular H-bonding in the crystal. It is quite possible, that it is this "irregularity", i.e. the complete absence of any pseudosymmetry, which prevents the occurrence of disorder in these crystals.

The crystal structure accords with the results of solution studies on compound (**1**):[13] the configuration (Z,Z,Z) and overall conformation (*syn,syn,syn*) are found to be the same in the crystal and in chloroform solution; and the tautomeric form observed in the crystal is identical to that recently determined for the species in solution.[15] In the crystal, tautomeric form (**1b**) is stabilized by intramolecular H-bonding between pyrrole N atoms. Depending on the polarity of the solvent, competition between intramolecular and intermolecular H-bonding will come into effect, which may
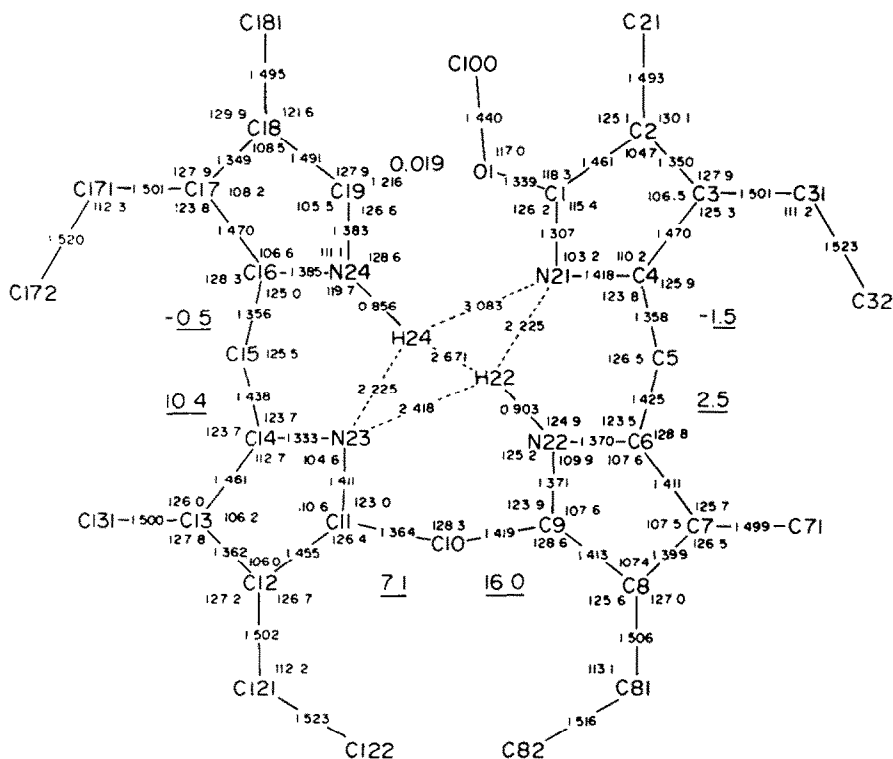
Fig. 5. Bond lengths, bond angles and dihedral angles (underlined) in the crystal structure of **1**. Estimated standard deviations: for bond lengths between non-hydrogen atoms 0.003–0.006Å, N–H 0.03 0.04Å; for bond angles between non-hydrogen atoms 0.2–0.3°, C–N–H 1.9–2.4°; for dihedral angles 0.3–0.6°.

well stabilize other tautomers in sufficiently polar solvents.

Possible differences which appear between the conformation in the crystal and that in solution (the latter one being deduced to be more "open", with a C=O . . . O Me distance of 5.6Å) are at the limits of significance of the LIS technique. Force-field results suggest[18] that the two conformations (solution and crystal) differ by no more than 20 kJ mol⁻¹, which is well within the range accessible by solvation.

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