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CORRELATION BETWEEN THE CIRCULAR DICHROISM SPECTRA OF *C*-NUCLEOSIDE 1,2,3-OSOTRIAZOLE ANALOGS AND THEIR ANOMERIC CONFIGURATION

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ABSTRACT

The circular dichroism spectra of a series of *C*-nucleoside 1,2,3-osotriazole analogs show a Cotton effect the reverse of that of the corresponding, acyclic polyhydroxyalkyl analogs having the same configuration at the carbon atom α to the osotriazole moiety. *C*-Nucleoside 1,2,3-osotriazoles having the α-D or β-L-configuration showed a positive Cotton effect, and those having the β-D- or α-L configuration showed a negative Cotton effect. This rule holds for D- and L-hexofuranosyl, D-heptofuranosyl, and D-heptopyranosyl *C*-nucleoside analogs. For anomeric assignment, it is more advantageous than n.m.r.-spectral methods, or optical rotation at the D line, as it does not require the use of both anomers for comparison.

INTRODUCTION

The correlation of optical rotation at the sodium D line with the stereochemistry of saccharide heterocyclic derivatives led to several rules that facilitate assignment of the configuration of the precursor sugars. One of the Hudson rules[1] states that the sign of the D-line rotation reflects the absolute configuration of the carbon atom α to the benzimidazole ring in such derivatives of sugars, thus permitting the configurational assignment of C-2 of the original sugar. This rule was extended by El Khadem[2] and Mills[3] to saccharide phenylosotriazoles. In their Fischer projection formulas, saccharide phenylosotriazoles possessing the D-*glycero* configuration [(*R*) chirality], with the hydroxyl group on the right at the α carbon, show a positive rotation. A negative rotation indicates the L-*glycero* configuration [(*S*) chirality], with OH on the left, thus permitting the assignment of the configuration of C-3 of the original sugar. El Khadem and El Shafei[4] suggested the general applicability of the rule to all aromatic systems; the sign of rotation of a heterocyclic or aromatic compound having more than one asymmetric carbon atom depends only on the configuration of the asymmetric carbon atom attached to the heterocyclic or benzene ring, provided that no other ring is present in the molecule. The asymmetric center at the α carbon atom has the major influence on the sign of

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rotation, owing to its proximity to the aromatic heterocycle. Chiroptical studies on saccharide pyrazolo[3,4-*b*]quinoxaline analogs[5] did not reveal a direct correlation between their optical rotation at the sodium D line and the absolute configuration of the α carbon atom, thus making difficult the assignment of the configuration at C-4 of the original sugar.

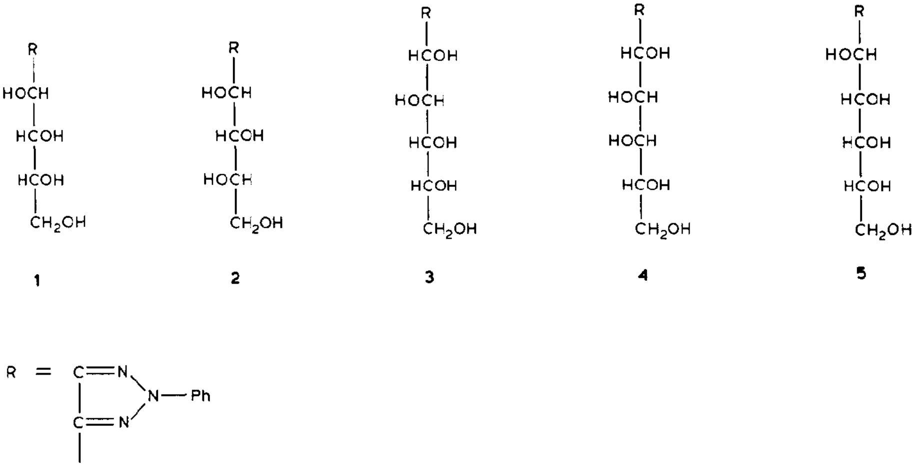
Optical rotatory dispersion and circular dichroism studies of polyhydroxyalkylated benzimidazoles, quinoxalines[6], and osotriazoles[7] provided identical potential rules that enable the assignment of the configuration of C-2 and C-3 of the original sugars. In addition, circular dichroism studies of saccharide pyrazolo[3,4-*b*]quinoxalines[5] enabled the assignment of the configuration of C-4 of the original sugar.

Circular dichroism spectra of saccharide osazones and 3,6-anhydro-osazones[8] permitted the establishment of a general rule regarding the inversion occurring at C-3 during anhydro-osazone formation; this provided the anomeric configuration of the glycosyl group formed. Saccharide osazones and 3,6-anhydro-osazones having the same configuration at C-3 in their Fischer projection formula showed the same sign of Cotton effect in the high-wavelength region. Compounds in which the hydroxyl group at C-3 is on the right in the Fischer projection formula show a positive Cotton effect, and those having it on the left show a negative Cotton effect. These chiroptical results were confirmed by ^{1}H-n.m.r.-spectral studies[9] of the anomeric configuration of the glycosyl group of the anhydro-osazones.

In the present work, the circular dichroism spectra of a series of *C*-nucleoside phenylosotriazoles were studied, and compared with those of a series of saccharide phenylosotriazoles, in order to correlate the sign of the Cotton effect at the maximal ultraviolet absorption (265–267 nm) with the anomeric configuration of the *C*-nucleoside analogs, and to establish a chiroptical method for the anomeric assignment of these compounds, analogous to that obtained for osazones and 3,6-anhydro-osazones[8].

DISCUSSION

Optical rotatory dispersion[7] and circular dichroism spectra of saccharide phenylosotriazole derivatives of simple sugars (four to six carbon atoms per sugar molecule) indicated that the configuration of the carbon atom α to the phenylosotriazole ring is reflected by the sign of the Cotton effect at the maximal ultraviolet absorption (265–267 nm). The sign of the Cotton effect is positive if the hydroxyl group α to the phenylosotriazole ring is to the right [D-*glycero* or (*R*) configuration] in the Fischer projection formula, and conversely, it is negative if the OH is to the left [L-*glycero* or (*S*) configuration]. The circular dichroism spectra of heptulose phenylosotriazoles **3**–**5** showed a multiple Cotton effect (see Fig. 1). Compounds **3** and **4**, having the (*R*) configuration of the α carbon atom, showed a positive Cotton effect, and compound **5**, having the (*S*) configuration, showed a negative Cotton effect in the same wavelength-region, in agreement with the same



Scheme 1

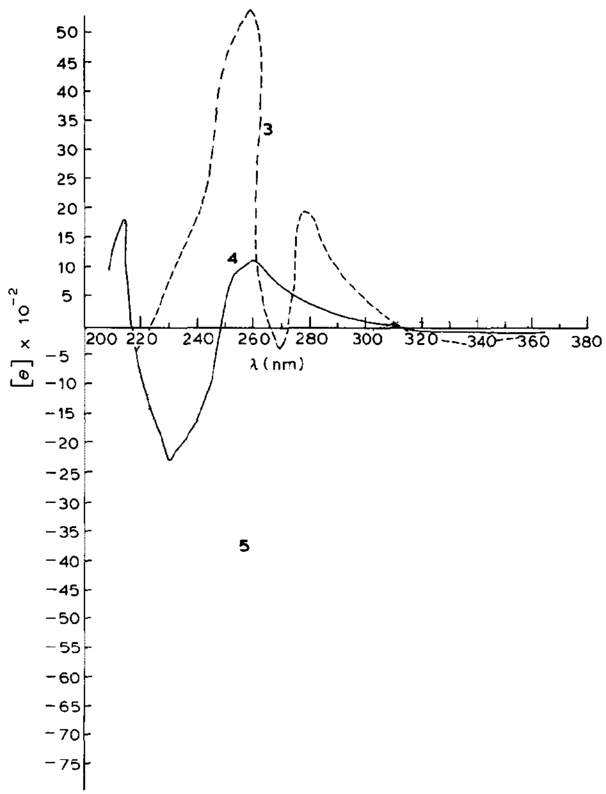


Fig. 1. C.d. spectra of 4-(D-*gluco*-pentitol-1-yl)-2-phenyl-1,2,3-osotriazole (**3**; -----); 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-1,2,3-osotriazole (**4**; ——); and 4-(D-*altro*-pentitol-1-yl)-2-phenyl-1,2,3-osotriazole (**5**; · · · · ·).

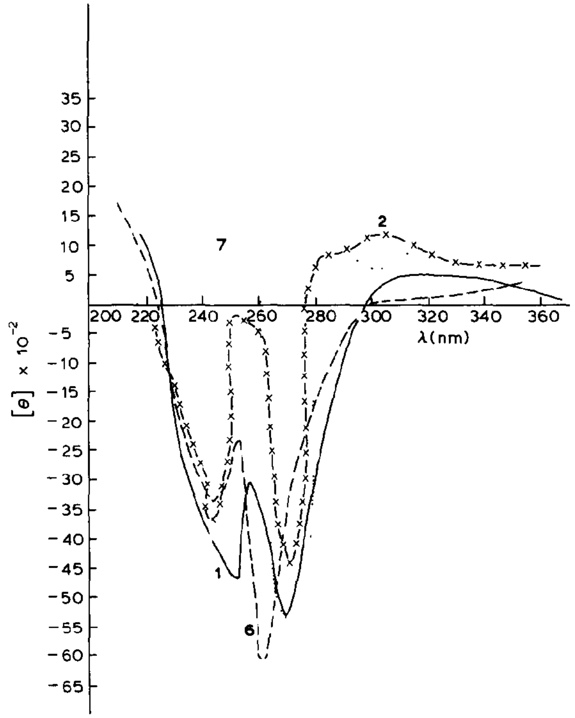


Fig. 2. C.d. spectra of 4-(D-*arabino*-tetritol-1-yl)-2-phenyl-1,2,3-osotriazole (**1**; ——); 4-(L-*lyxo*-tetritol-1-yl)-2-phenyl-1,2,3-osotriazole (**2**; -x-x-); 4-β-D-erythrofuranosyl-2-phenyl-1,2,3-osotriazole (**6**; -----); and 2-phenyl-4-α-L-threofuranosyl-1,2,3-osotriazole (**7**; · · · · ·).

correlation for the lower analogs. Changes in the stereochemistry other than at the α carbon atom change only the magnitude of the Cotton effect. Compounds **3** and **5**, respectively having the D-*gluco* and D-*altro* configuration, showed a higher amplitude than compound **4** (having the D-*galacto* configuration).

The circular dichroism spectra of both D-*arabino*-2-hexulose phenylosotriazole (**1**) and the corresponding *C*-nucleoside, namely, 4-β-D-erythrofuranosyl-2-phenyl-1,2,3-osotriazole[10] (**6**), showed a multiple Cotton effect having a negative sign, at 225–297 nm (see Fig. 2). However, the C-1′ atoms in the Fischer projection formula of compounds **1** and **6** have opposite configurations. The negative Cotton effect for compound **1** is in accord[7] with the L-*glycero* configuration for the asymmetric center C-1′. Accordingly, the negative Cotton effect observed for compound **6** would suggest the same configuration. However, circular dichroism[8] and ^{1}H-n.m.r.-spectral studies[10] confirmed the D-*glycero* configuration of C-1′ in the Fischer projection formula of compound **6** (the β-D configuration of the furanosyl group formed). Therefore, the negative Cotton effect for compound **6** reflects a correlation between the sign of the Cotton effect and the configuration at the asymmetric center (C-1′) that is the opposite of that for the acyclic polyhydroxyalkyl analogs[7]. This means that the negative Cotton effect observed for *C*-nuc-

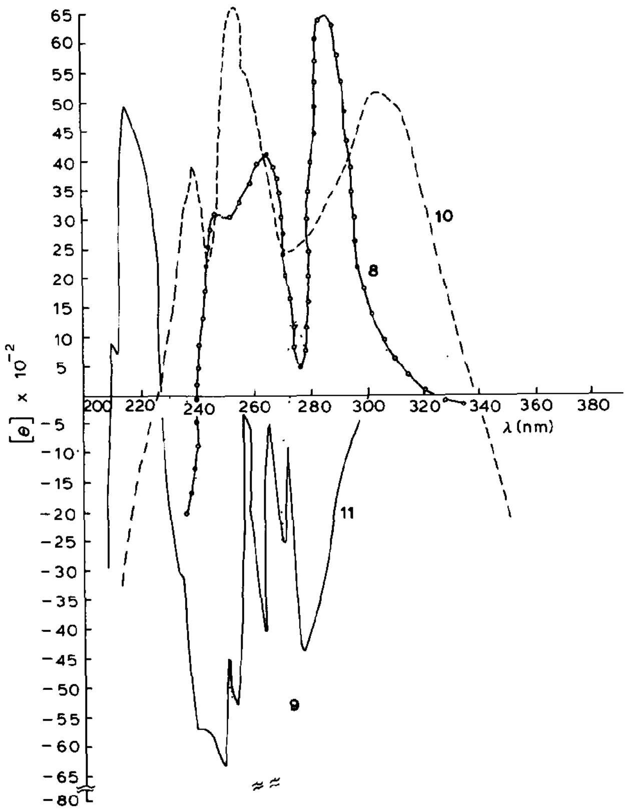
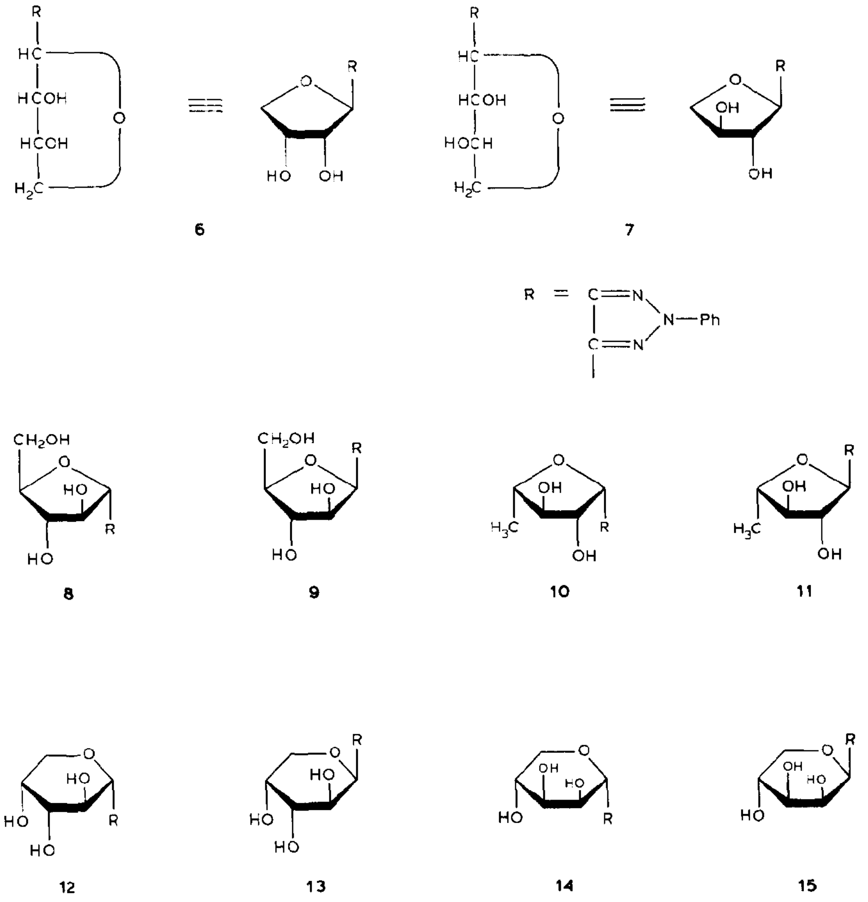


Fig. 3. C.d. spectra of 4-α-D-arabinofuranosyl-2-phenyl-1,2,3-osotriazole (**8**; -O-O-O); 4-β-D-arabinofuranosyl-2-phenyl-1,2,3-osotriazole (**9**; · · · · · ·); 4-(5-deoxy-β-L-arabinofuranosyl)-2-phenyl-1,2,3-osotriazole (**10**; -----); and 4-(5-deoxy-α-L-arabinofuranosyl)-1,2,3-osotriazole (**11**; ——).

leoside osotriazoles indicates the D-*glycero* configuration of C-1′ (β-D configuration of the furanosyl group) and not the L-*glycero* configuration that would be suggested from the criterion for the acyclic analogs[7].

Similarly, the c.d. spectra of both L-*xylo*-2-hexulose 2-phenyl-1,2,3-osotriazole (**2**) and the corresponding *C*-nucleoside, namely, 2-phenyl-4-α-L-threofuranosyl-1,2,3-osotriazole[11] (**7**), showed a negative Cotton effect (see Fig. 2), although having opposite configurations at C-1′. The negative Cotton effect for compound **2** is in accord[7] with the L-*glycero* configuration of C-1′. However, the D-*glycero* configuration of C-1′ in the Fischer projection formula of compound **7** (α-L configuration of the glycosyl group) was confirmed by ^{1}H-n.m.r.-spectral studies[11].

The circular dichroism spectra (see Fig. 3) of a series of heptosyl *C*-nucleosides, 1,2,3-osotriazole analogs having the furanoid ring-structure **8**–**11**, showed multiple Cotton effects. 4-α-D-Arabinofuranosyl-2-phenyl-1,2,3-osotriazole (**8**) showed a positive Cotton effect (λ 240–320), in agreement with the L-*glycero* configuration of C-1′ in the Fischer projection formula. 4-β-D-Arabinofuranosyl-2-



Scheme 2

phenyl-1,2,3-osotriazole (**9**) showed a negative Cotton effect (λ 236–270), in agreement with the D-*glycero* configuration of C-1′ in the Fischer projection formula. The anomeric configuration of compounds **8** and **9** was confirmed by n.m.r. spectroscopy[9].

4-(5-Deoxy-β-L-arabinofuranosyl)-2-phenyl-1,2,3-osotriazole (**10**), having the L-*glycero* configuration of C-1′ in the Fischer projection formula, showed a positive Cotton effect (λ 225–340), and its anomer, 4-(5-deoxy-α-L-arabinofuranosyl)-2-phenyl-1,2,3-osotriazole (**11**), having the D-*glycero* configuration of C-1′ in the Fischer projection formula, showed a negative Cotton effect (λ 225–300). The anomeric configuration of compounds **10** and **11** was ascertained[12] by ^{1}H-n.m.r.-spectral studies.

The assignment of the anomeric configuration of pyranosyl *C*-nucleoside analogs by n.m.r. spectroscopy is sometimes difficult, owing to the conformational

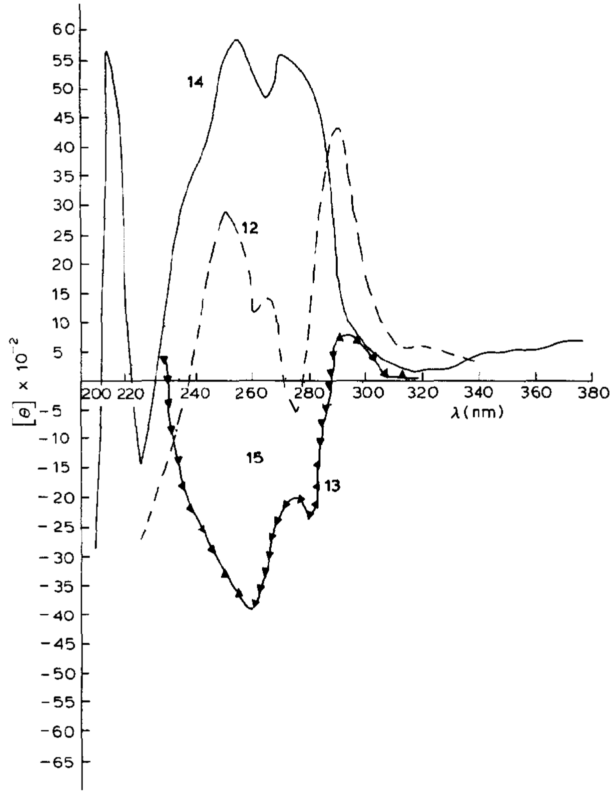


Fig. 4. C.d. spectra of 4-α-D-arabinopyranosyl-2-phenyl-1,2,3-osotriazole (**12**; ------) 4-β-D-arabinopyranosyl-2-phenyl-1,2,3-osotriazole (**13**; -▲-▲-▲-); 4-α-D-lyxopyranosyl-2-phenyl-1,2,3-osotriazole (**14**; ——); and 4-β-D-lyxopyranosyl-2-phenyl-1,2,3-osotriazole (**15**; · · · · ·).

mobility of the pyranoid ring. However, study of their circular dichroism spectra at the maximal ultraviolet absorption region permits ready establishment of their anomeric configuration. 4-α-D-Arabinopyranosyl-2-phenyl-1,2,3-osotriazole (**12**) showed a positive Cotton effect, whereas its anomer, 4-β-D-arabinopyranosyl-2-phenyl-1,2,3-osotriazole (**13**), showed a negative Cotton effect (see Fig. 4).

Similarly, 4-α-D-lyxopyranosyl-2-phenyl-1,2,3-osotriazole[13] (**14**) showed a positive Cotton effect (λ 225–300), in accord with the α-D configuration, and its anomer, 4-β-D-lyxopyranosyl-2-phenyl-1,2,3-osotriazole (**15**), showed a negative Cotton effect, in agreement with the β-D configuration.

This chiroptical assignment for the anomeric configuration of *C*-nucleosides of 1,2,3-osotriazoles is in agreement with the H-5 chemical-shift criterion[14] for the osotriazole moiety.

Pyranosyl nucleosides differ from furanosyl nucleosides in two ways[15]: firstly, the conformation of the pyranosyl part differs from that of the furanosyl part, and the conformation of the α anomer differs from that of the β anomer, and these factors complicate the interpretation of their c.d. spectra. Secondly, as a whole, the molecule is more flexible than that of the furanosyl nucleoside, rotation about the nucleoside bond is less restricted, and, consequently, Cotton effects tend to be smaller. Despite these considerations, the pyranosyl osotriazole *C*-nucleosides **12–15** obey the rule formulated for the furanosyl analogs.

The discrepancy between the sign of the Cotton effect of the *C*-nucleoside 1,2,3-triazoles and that of the polyhydroxyalkyl analogs having the same configuration of the α carbon atom may be attributed to the difference in the conformation of the glycosyl ring and that of the polyhydroxyalkyl chain. In addition, the difference in the angle between the chromophoric base and the chiral center of the sugar moiety, *i.e.*, the direction of the dipole moment, controls[16] the sign of the Cotton effect. For anomeric nucleosides having the same base moiety, the difference in the Cotton effect is obviously due to the glycosyl moiety, and the anomeric center, which is closest to the chromophore group, has the largest effect. Changes in the stereochemistry, other than at the anomeric center (C-1′ of the glycosyl group), merely changes the magnitude, but not the sign, of the Cotton effect.

This chiroptical assignment of the anomeric configuration of *C*-nucleoside 2-phenyl-1,2,3-osotriazole analogs, having a furanosyl or pyranosyl group, from the sign of the Cotton effect at the maximal ultraviolet absorption is in agreement with the Hudson isorotation rules[1] at the sodium D line; α-D-*C*-nucleoside osotriazole analogs having a positive Cotton effect are more dextrorotatory than the corresponding β anomers displaying a negative Cotton effect.

The observed sign of the Cotton effect of the 2-phenyl-1,2,3-osotriazole *C*-nucleoside analogs **6–15** is similar to that of azopyrimidine and purine *N*-nucleosides, whereas pyrimidine *N*-nucleosides exhibit an opposite relationship[17].

This chiroptical method for assignment of the anomeric configuration of *C*-nucleosides is more advantageous than that obtained from the rotation at the sodium D line, or from ^{1}H-n.m.r. spectroscopy, as it does not require the presence of both anomers for comparison. It offers a simple approach, and should find application in determining the anomeric configuration of *C*-nucleoside 1,2,3-osotriazole analogs having a furanosyl or pyranosyl group.

EXPERIMENTAL

The polyhydroxyalkylated 2-phenyl-1,2,3-osotriazole analogs **1–5** were prepared by previously described methods[7,18]. The *C*-nucleoside 2-phenyl-1,2,3-osotriazole analogs **6–15** were prepared from their precursor 3,6- or 3,7-anhydro-osazones by standard procedures[9–12]. Circular dichroism spectra of solutions (0.04 mg/mL) in methanol were recorded with a Cary 60 spectropolarimeter at a dynode voltage $\leq$0.75 kV.

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