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^{13}C Cross-Polarization Magic Angle Spinning NMR Study on the Chain Packing in Anhydrous and Hydrated DL- and L-Dipalmitoylphosphatidylcholine

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With ^{13}C cross-polarization magic angle spinning (CP-MAS) NMR it is demonstrated that the anhydrous forms of DL- and L-DPPC show pronounced packing differences in both the headgroup region and the hydrocarbon part of the bilayer. In DL-DPPC the acyl chains and more specifically their end groups are more closely packed than in the L modification. The anhydrous L- and DL-DPPC structures show a completely different behavior toward the addition of 1 equiv of water. DL-DPPC is far less hygroscopic and forms small domains of dihydrated and anhydrous DPPC as was concluded from the combined results of the NMR and a DSC study. The dihydrated form of DL-DPPC is arranged according to a similar structure as is observed for anhydrous L-DPPC. On the other hand, L-DPPC did not show any packing changes in the acyl chains on going from the anhydrous state to the hydrated forms. These results reveal that stereospecific interactions can be responsible for different lipid packing modes and hence in their behavior toward the uptake of water.

Introduction

There is strong experimental evidence that various membrane processes are regulated by a controlled change in the fluidity of parts in the membrane with formation of domains.[1-4] The action of some anaesthetics on ion channels is supposed to occur via an alteration in the packing of the lipids which surround the channel.[5-7] A change in the lipid structure can already be induced by a local dehydration of phospholipids. It has been shown that for instance the transmembrane protein gramicidin can locally withdraw water from phosphatidylcholines.[8] The resulting change in the polar headgroup geometry can very well affect the packing of the lipid acyl chains, thus bringing about a (local) change in the membrane fluidity.

Previously it has been shown with Raman spectroscopy that the reverse process, i.e., the hydration of anhydrous bilayers, induces a marked change in the motional and conformational properties of the headgroup.[9] Moreover, the addition of about 4 equiv of water to dipalmitoylphosphatidylcholine (DPPC) results in a drastic increase in the intrachain (gauche/anti) and interchain (lattice) disorder. In contrast to these findings a recent ^{13}C CP-MAS NMR study revealed that no substantial changes in the conformational equilibria of the acyl chains take place upon hydrating anhydrous DPPC.[10] This discrepancy between the Raman and NMR results might very well originate from the difference in optical purities of the DPPC used in both studies. Whereas the Raman investigation was based on racemic DPPC, the NMR study was performed on the enantiomerically pure L form. In order to verify this supposition and to gain additional insight in the impact hydration may have on the acyl chain packing, we extended our previous ^{13}C CP-MAS NMR study to DL- and L-DPPC bilayers in the gel phase. It was recently demonstrated by De Weerd et al. that the ^{13}C chemical shift is very sensitive to packing differences arising from gauche/anti isomerizations and/or changes in van der Waals interactions. From the isotropic ^{13}C NMR chemical shifts it was possible to estimate the relative contributions of these effects in a number of mixed micellar, vesicular, or gel systems.[10,11] The present study shows that the CP-MAS NMR technique, in addition to its already well-known application in protein and carbohydrate research,[12] can be successfully used for monitoring packing changes in ordered phospholipids, even when relatively minor differences, like optical purities, are involved.

Experimental Section

Materials. DL- and L-dipalmitoylphosphatidylcholine were obtained from Sigma (99% pure) and treated with chloroform. Application of high vacuum ($<10^{-5}$ Torr) and elevated temperatures (about 40 °C) for 48 h yielded anhydrous DPPC, according to elemental analysis, DSC,[13] and our ^{13}C NMR results (one signal for NCH_3). Hydration of DPPC was accomplished either by controlled addition of double distilled water and centrifuging above the main phase transition temperature or by standing in a humid atmosphere until equilibrium was reached.[14] The amount of water absorbed was controlled by weighing accurately. In order to maintain the anhydrous and hydrated compounds in well-defined compositions, the samples were stored in Kel-F capsules[15] which were immediately sealed and subsequently used in aluminum oxide MAS rotors. By following this procedure moisture was kept out completely and any evaporation of water from the hydrated forms (due to electromagnetic heating) was prevented. This was established by weighing the samples before and after the measurements. Furthermore, no additional signals appeared in the NMR spectra after prolonged storage of the capsules containing anhydrous DPPC.

^{13}C CP-MAS NMR Spectroscopy and Thermal Analysis. The ^{13}C CP-MAS spectra were recorded at 75.48 MHz on a Bruker CXP 300 NMR spectrometer equipped with a double air-bearing CP-MAS probe. The cross polarization measurements were carried out with flipback of the proton magnetization and spin temperature inversion. The sample amount was 0.1-0.2 g and the temperature was about 30 °C. The chemical shifts are related via adamantane to TMS. Typically 1000 scans of 1K data points were accumulated and zero-filled to 16K points prior to Fourier transformation. The spectral width was 16 kHz and the pulse

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TABLE I: Assignments for Anhydrous DL-DPPC and L-DPPC in the Solid State and in Solution ($CDCl_3/CD_3OD$ 3:2)[a]

	solid state		solution
	DL-DPPC	L-DPPC	DL-DPPC
headgroup			
CH_2N	66.5[b]	66.6	67.43
CH_2OP	60.3	60.4	59.90
$N(CH_3)_3$	53.25	53.50	55.17
backbone			
CHO	74.38	71.02	71.27
CH_2OP	66.5[b]	64.7	64.46
CH_2O	62.80	63.0	63.63
acyl chain			
C=O, *sn*-2	175.30	173.65	174.69
C=O, *sn*-1	172.55	172.77	174.33
α, *sn*-2	36.17	*c*	35.14
α, *sn*-1	35.55	*c*	34.99
β, *sn*-2	26.87	27.81	25.80
β, *sn*-1	26.10	27.33	25.76
internal	33.12	33.00	30.59
$\omega - 2$,[d] *sn*-2	34.54	*c*	32.80
$\omega - 2$, *sn*-1	34.02	*c*	32.80
$\omega - 1$,[d] *sn*-2	24.88	24.63	23.55
$\omega - 1$, *sn*-1	24.28	24.10	23.55
ω	15.03	14.50	14.12

[a] α and ω represent the first and terminal carbons of the hydrocarbon chain, respectively. [b] Coinciding signals. [c] Unresolved resonances. [d] Assignment is based on the well-documented finding that the ^{13}C nuclei of two approaching methyl(ene) groups become less shielded (van der Waals deshielding).[27-29] Crystallographic data show that the *sn*-2 chain has more van der Waals contacts compared with the *sn*-1 chain,[21] so we conclude that the downfield signal originates from the *sn*-2 $\omega - 1$ and $\omega - 2$ methylenes. The magnetic equivalence of the ultimate methyl groups of both chains is most likely due to a partial interdigitation of the opposed monolayers, resulting in similarly packed environments.

width employed was 6 μs (corresponding with a B_1 field of $\sim$10 G). The contact time was 2.5 ms. The pulse delay varied between 10 and 20 s. The acquisition time was 29 ms. The samples were rotated at 2.5–2.7 kHz. The reported chemical shifts are average values of at least two independently prepared samples (starting from chloroform evaporation) with a deviation of <0.05 ppm.

The solution spectrum was recorded on a Bruker CXP 300 NMR spectrometer at room temperature. The DPPC was dissolved in $CDCl_3/CD_3OD$ 2:1 v/v and the chemical shifts were related to TMS.

The DSC recordings (differential scanning calorimetry) were performed on a Perkin Elmer DSC-7 calorimeter at a scan rate of 10 K/min.

Results

Anhydrous DL- *and* L-*DPPC.* The anhydrous character of DL-DPPC was confirmed by elemental analysis and DSC, which showed a phase transition at 395 K. This is $\sim$20 K above the phase transition of pure L-DPPC.[13] The ^{13}C CP-MAS NMR spectrum of polycrystalline, anhydrous DL-DPPC is shown in Figure 1 along with the solution spectrum. In Table I the ^{13}C chemical shifts are collected and assigned according to the findings of De Haan et al.[10]

The following distinct features in the solid-state spectrum of DL-DPPC can be attributed to specific packing properties of the phospholipid. The carbonyl resonances are 2.7 ppm apart in the solid-state NMR spectra, versus 0.3 ppm when DPPC is solubilized in chloroform/methanol. This shift difference is due to the well-known bend in the *sn*-2 chain, situating the ester moiety at the interface between the polar headgroups and the nonpolar chains, whereas the *sn*-1 carbonyl is buried in the hydrophobic core. Based on this difference in dielectric constant of the surrounding medium of the carbonyls, combined with the well-known solvent polarity dependence of the chemical shift of ester groups,[16]

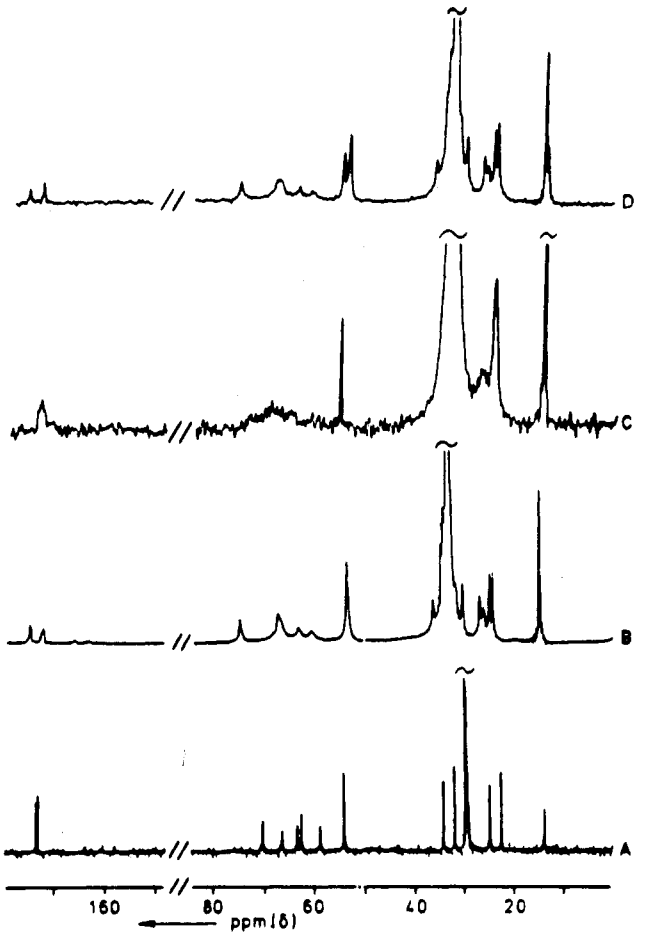

Figure 1. ^{13}C spectrum of DL-DPPC in $CDCl_3/CD_3OD$ (A) and the CP-MAS spectra of anhydrous DL-DPPC (B) and DL-DPPC with 2 equiv of water (C) and with 1 equiv of water (D). The experimental conditions used to record the spectra are described in the Experimental Section.

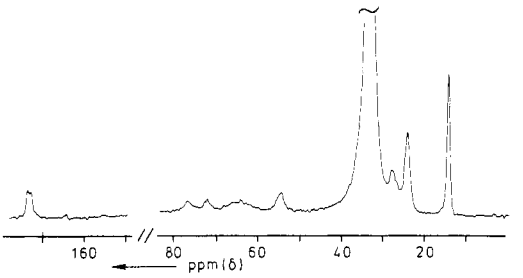

Figure 2. ^{13}C CP-MAS spectrum of anhydrous L-DPPC. The same experimental conditions were applied as for the CP-MAS spectra in Figure 1.

the assignment is made that the downfield signal originates from the *sn*-2 carbonyl moiety. According to a similar way of reasoning, such assignment has been made for the different carbonyl signals in a ^{13}C CP-MAS spectrum of a triglyceride.[17]

Furthermore, the resonances of the penultimate ($\omega - 1$) as well as the $\omega - 2$ methylene groups in the two chains can clearly be distinguished, whereas only one resonance for the ω-methyl groups is observed. Apparently, both terminal methyl groups experience the same environment, in contrast to the $\omega - 1$ and $\omega - 2$ groups of the *sn*-1 and *sn*-2 chains which are differently packed.

Despite pronounced differences in the hydrocarbon chain, backbone, and *sn*-2 carbonyl resonances between anhydrous L- and DL-DPPC (compare Figure 1 with Figure 2), the shifts of the headgroup carbons in both forms are almost identical. The NCH_3 resonance at 53.4 ppm found in L- and DL-DPPC is an additional

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TABLE II: ^{13}C Chemical Shifts of the Resolvable Resonances in Anhydrous and Hydrated DPPC[a]

	DL-DPPC			L-DPPC	
	anhyd	2-H_2O	4-H_2O	anhyd	1-H_2O[b]
C=O, *sn*-2	175.30	172.0	172.7	173.65	173.3
C=O, *sn*-1	172.55	172.0	172.7	172.77	173.3
CHO	74.38	<70	<70	71.0	71.0
$N(CH_3)_3$	53.25	54.32	54.41	53.50	54.25
internal	33.12	33.01	32.97	33.00	33.01
$\omega - 1$,[c] *sn*-2	24.88	24.14	24.15	24.63	24.37
$\omega - 1$, *sn*-1	24.28	24.14	24.12	24.10	24.37
ω	15.03	14.40	14.40	14.50	14.40

[a] Experimental parameters are given in the Experimental Section. α and ω represent the first and terminal carbons of the hydrocarbon chain, respectively. [b] Similar shifts are found for 2-H_2O and 4-H_2O. [c] For assignment see legend for Table I.

indication of their anhydrous character. The other resonances in L-DPPC show a remarkable resemblance with those for the dihydrated DL-DPPC form (vide infra). The chemical shifts for L-DPPC agree well with those found previously.[10]

Addition of Water to Anhydrous DL-*DPPC.* The controlled addition of 2 equiv of water to anhydrous DL-DPPC causes the spectrum to change clearly (see Figure 1). The *sn*-2 carbonyl resonance has shifted upfield and has collapsed with the *sn*-1 carbonyl group resulting in a broad featureless signal in the hydrated form. We also observed a downfield shift of ~1 ppm for the choline methyl carbons and a considerable upfield shift of 3–4 ppm for the CHO-glyceryl carbon. The internal methylene groups of the chains and, more pronounced, the chain–methyl resonances move upfield on the addition of 2 equiv of water, which indicates an increased gauche contribution and/or a larger intermolecular distance between the hydrocarbon chains in the matrix. The *sn*-1 and *sn*-2 $\omega - 1$ methylene groups can no longer be distinguished and resonate at approximately the same frequency as the upfield signal in the anhydrous state. Furthermore, the glyceryl backbone and headgroup resonances are considerably broadened, probably as a consequence of molecules experiencing different, noninterchangeable environments.[18]

An interesting phenomenon occurred when anhydrous DL-DPPC was exposed to a humid atmosphere until 1 equiv of water was absorbed. The ^{13}C NMR spectrum of this phase turned out to be a superposition of resonances of the anhydrous and dihydrated forms of DPPC (within the experimental error) (see Figure 1). To check whether the monohydrated phase was homogeneous, a DSC analysis was performed. In the temperature range from 305 to 410 K only one phase transition was observed at 350 K. Furthermore, a monohydrated sample of DPPC, prepared by slow solvent crystallization from chloroform/methanol according to Chapman,[13] yielded similar ^{13}C NMR and DSC results as above. Moreover, when an anhydrous sample was exposed to an atmosphere of ~60% humidity and aliquots were taken in regular time intervals, a decrease in intensity was observed of the $\delta = 53.25$ and 15.03 signals (originating from the choline and chain methyl groups, respectively) in favor of the 54.32 and 14.40 intensities, respectively. This observation would indicate the formation of the dihydrated phase along with the anhydrous material (vide infra).

Addition of Water to Anhydrous L-*DPPC.* The hydration of L-DPPC has been studied previously with ^{13}C CP-MAS NMR by De Haan et al.[10] For a proper evaluation of the packing changes between both forms of DPPC it is essential that the samples are prepared according to exactly the same procedure; otherwise the preparation technique itself might impose a distinct crystallographic form on the phospholipids.[19] Therefore, the effects of water addition to L-DPPC were reinvestigated in the present study.

On hydrating L-DPPC in a humid atmosphere it is observed that L-DPPC is much more hygroscopic than the racemic modification. However, the data in Table II reveal that, apart from a deshielding of the choline methyl carbons, no pronounced changes in chemical shifts are detected between the anhydrous and the monohydrated form of L-DPPC. Thus, in contrast to the situation in DL-DPPC, only one signal each for the choline and chain methyl groups is found on the addition of 1 equiv of water. The present findings confirm the previous results.[10] Increasing the water content, to four water molecules per lipid, does not further affect the chemical shift significantly (data not shown).

Discussion

On addition of 2 equiv of water to anhydrous DL-DPPC, changes are observed in the headgroup and acyl chain regions. The upfield shifts of the ^{13}C NMR resonances of the internal methylenes, the *sn*-2 $\omega - 1$ methylene, and the methyl groups upon hydration is ascribed to an increase in the effective headgroup area as the result of a weakening of intermolecular electrostatic $PO^-\cdots N^+CH_3$ interactions. Due to the resulting mismatch in the cross-sectional area between the headgroups and the chains, a rearrangement of the chains will occur either by changing the interchain interactions or by increasing the number of gauche conformers or both. The results indicate that it is mainly the former mechanism which is operative in filling up the resulting space. The introduction of gauche conformers would shift the internal methylene groups more upfield than the methyl groups as can be deduced from simple statistical considerations.[11b,20] Since this is clearly not supported by our results, the changes in the end group chemical shifts are predominantly attributed to a change in the interchain interactions. From the chemical shift data, it is difficult to depict the exact arrangement of the chains that causes the (near) NMR equivalence of both chains and the pronounced upfield shift of the chain end region compared to the anhydrous state. Nevertheless, the chemical shifts indicate a less densely packed environment.

The appearance of the subspectrum of the dihydrated form of DL-DPPC as soon as anhydrous DL-DPPC is exposed to a humid atmosphere indicates that the monohydrate phase of DPPC is not homogeneous with respect to the water distribution. To the best of our knowledge this behavior has not been described earlier. Apparently, the monohydrate phase of DL-DPPC as prepared in this study consists of an immiscible combination of anhydrous and dihydrated forms of DPPC, which can be distinguished by ^{13}C NMR. This observation, combined with the single-phase transition in the DSC spectrum, demonstrates that domains are formed which are too small to be detected separately with DSC. The possibility of a dihydrated phase homogeneously mixed with anhydrous DL-DPPC at a molecular level, can be ruled out, since cooperativity in packing properties to a very large extent is needed to bring about *exactly* the same chemical shifts in a mixed phase as in the separate phases. Thus, it is postulated that the monohydrate phase of DL-DPPC prepared under the conditions described here does not exist on a molecular level. Further investigations are needed for a more detailed description of this finding in terms of packing differences.

The observation that the domains postulated above are clearly visible with ^{13}C NMR but not with DSC enables us to estimate the domain dimensions. We assume a hexagonal chain packing, which is most commonly encountered for DPPC,[21,22] and a single boundary layer. In view of the demonstrated sensitivities of the ^{13}C NMR chemical shifts of the methyl groups (choline and chain terminus) toward the presence of water and the resulting packings (see Table II) it would be very improbable that the resonances of boundary lipids would coincide completely with those of the two domains. Since no other signals were detected besides those of the domains, the total amount of boundary lipids must be less

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than the detection limit (estimated at ~10%). Simplifying the domain geometry to a cubic structure and using the known values for the lipid cross-sectional area and bilayer thickness (42 Å^2 and 24 Å, respectively, for anhydrous DL-DPPC[22]), one can calculate in a straightforward manner that the domains must have a minimum size of ~700 Å, corresponding to 10^5 lipids. This result compares favorably with the domain size in DSPC/DMPC hydrated bilayers for which a cooperative length of ~500 Å was found with neutron diffraction.[4] It is possible in principle that domains of this order of magnitude cannot be detected separately with DSC. It has been shown for polymer blends that the detection limit may very well be greater than 1000 Å.[23] Therefore, we surmise that the domain sizes in "monohydrated" DL-DPPC are about 1000 Å.

The packing of anhydrous L-DPPC differs significantly from that in the anhydrous DL modification as is revealed by comparing the chemical shifts of specifically the *sn*-2 C=O, CHO, and ω-methyl carbons. Given the fact that exactly the same sample preparation and drying techniques were used, it is concluded that the discrepancy in packing properties is caused partially by stereospecific interactions. Apparently, these interactions allow a more tightly packed arrangement for DL-DPPC than for the L form as is demonstrated by the downfield shift of the internal methylene groups and the ω-methyl groups of DL-DPPC compared with the L form. This finding is supported by the DSC measurements showing a phase transition for the DL form some 20 °C higher than for the L enantiomer.[13] Furthermore, additional evidence is found in a previous electron diffraction study on anhydrous L- and DL-DPPC from which it was concluded that the chains in L-DPPC are tilted with respect to the layer plane, whereas in the DL form essentially no tilting occurs.[24]

In bilayers of anhydrous L-DPPC 2 equiv of water can be accommodated without structural rearrangements in the hydrocarbon chains of a magnitude that they would impact the ^{13}C NMR chemical shifts. Although the changes in anhydrous DL-DPPC by water are not accompanied by a substantial increase in gauche conformations in the acyl chains of DL-DPPC, as was suggested by Raman spectroscopy,[9] there are certainly some pronounced differences in acyl chain and headgroup packings between the anhydrous and hydrated phases. Therefore, it is concluded that the discrepancy between the previous Raman[9] and the recently performed ^{13}C NMR study,[10] in which no changes in packing differences could be detected, can be largely ascribed to differences in optical purity of the used DPPC.

It is interesting to compare the present results with a detailed study on chiral aggregation phenomena in bilayers of DL- and L-DPPC in water.[25] Despite the high purity of the phospholipids, no significant differences could be demonstrated between racemic DPPC and its enantiomers by using various sensitive techniques. This finding is consistent with the present results on hydrated DPPC samples. However, our results also clearly point out that packing differences due to stereospecific interactions have to be taken into account in tightly packed anhydrous systems. Apparently, on hydrating anhydrous bilayers of DPPC, all chirally induced packing differences are overruled by the concomitant structural change in the lipid molecules. Vice versa, since dehydration of phospholipids is an important step in various membrane processes,[8,26] stereochemical control might be effected by different packing arrangements between phospholipids and other chiral molecules in the membrane bilayer. It was argued that in this way the membrane can act as a stereospecific screen toward molecules of unnatural chirality.[25]

Concluding Remarks

The ^{13}C NMR chemical shifts clearly indicate that the addition of 2 equiv of water to anhydrous DPPC bilayers results in a different packing of the hydrocarbon chains in the case of DL-DPPC. This change in packing results in a very similar structure as was found for anhydrous L-DPPC on the basis of the ^{13}C chemical shifts. On the other hand, the hydrocarbon chain arrangement of anhydrous L-DPPC is not affected by the addition of water. Apparently, in DL-DPPC a more tight packing is possible which is disturbed completely when at least 2 equiv of water is added. The structure obtained after the addition of only 1 equiv can be interpreted in terms of a coexistence of small domains of dihydrated and anhydrous DL-DPPC. In anhydrous L-DPPC such tight packing as in anhydrous DL-DPPC cannot be realized, and hence water can be accommodated without structural rearrangements in the hydrocarbon chains.

Registry No. L-DPPC, 63-89-8; DL-DPPC, 2797-68-4.

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Preferential Solvation in Two-Component Systems

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The theory of preferential solvation, originally developed for a three-component system,[1,2] is applied to two-component systems. The preferential solvation is computed for two sets of systems: the first includes mixtures of water with six organic liquids (methanol, ethanol, propanol, butanol, THF, and dioxane). The second includes mixtures of carbon tetrachloride with the same six organic liquids.

1. Introduction

Recently a new approach to solvation thermodynamics has been proposed and applied to a variety of systems.[1] On the basis of this approach we have suggested a new definition and a new way of measuring the preferential solvation (PS) of a solute in a two-component solvent.[2] The typical question that has been asked in connection with PS is the following. Having a two-component solvent, of A and B, with mole fraction x_A, and a solute S very

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