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REVIEW

Synthesis, Characterization, Applications and Utilization of Hybrid Micro-Nano-Structured Zeolite Materials

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Abstract

Hybrid micro-nano-structured zeolite materials are complex matrices in which zeolite acts as a reservoir for adsorbed active principles, this being the main reason for their increasing applicability in medical sciences. MCM-41 has attracted considerable attention in the pharmaceutical field by the possibility of controlled release of active principles adsorbed on the surface and zeolite pores, and because the mesostructure provides the required pore size for the adsorption of compounds with large molecular masses and large specific surface area (900 -1200 m^2/g). The paper presents aspects of the concept and methods for the obtaining of porous silica based materials at room temperature, as well as the specific characterization methods and the related applications.

The synthesis of the MCM-41 type material is performed by the sol-gel method using tetraethylortho silicate (TEOS) source at ambient temperature and pressure. Characteristic parameters of the synthesized materials were determined by X-ray diffraction (XRD), Scanning Electrone Microscopy (SEM), Transmission Electron Microscopy (TEM), Brunauer-Emmett-Teller method (BET), and Fourier Transform Infrared Spectrometry (FT-IR) techniques.

Incapsulation of the plant active principles in the zeolite structures can lead to high-tech pharmaceutical devices, with design resulting from optimized chemical synthesis processes, according with *in vitro / vivo* toxicity and efficacy. The adsorption of the active principles in the zeolite matrix coated with a biopolymer film by successive loading and encapsulation processes lead to MCM - 41 - biologically active material - biopolymer complex obtaining, with projection in pharmaceutical applications as a controlled slow release device.

Key words*:* MCM – 41, zeolite, mesostructure, biopolymer, active principles.

Introduction

Zeolites belong to a very large category of aluminosilicates. They were discovered for the first time by Cronstedt, a Swedish scholar, in 1756, when a certain type of silicon ore was used in a heating treatment, (subjected to heat treatment), and the zeolites formed foam and bubbles emanating vapors, therefore they were named zeolites (Greek zeo = boil and lithos = stone).

At the beginning of the nineteenth century, zeolites had begun to be studied even if the scientific community did not show any particular interest in them. The term “molecular site” was attributed by McBain in 1931 when he discovered that chabazite, a mineral, possesses the ability to selectively adsorb molecules with a diameter of less than 5Å [1].

In other words, molecular sites have the property of retaining the particles that fit inside the channels and let the larger molecules to pass. The term "molecular site" is applicable to substances that have selective sorption properties. A few years later, Barrer and his associates, studied the sorption properties of chabazite and other porous materials, and realized that nitrogen and oxygen could be separated using a properly treated zeolite, in order to have a selective form for the size of the two atoms. Later, the zeolites began to be used on an industrial scale to separate pure oxygen from the air. Between 1949 and 1954, Breck et al., synthesized various zeolites (zeolite A, X and Y) that have been used for the purification of various small molecules [2]. Since then, the nomenclature of this type of compound has become well-known. The success of the synthesis of crystalline aluminosilicates, and in particular the discovery of a new category of aluminophosphates and silicoaluminophosphate did the concept of molecular zeolites and molecular sites more complex [3,4].

Due to the small porous area of the zeolits (0.4 nm to zeolite A) they are very attractive for commercial applications because this feature allows selective absorption based on small differences between gas molecules. In addition, these molecules have attracted the attention of scientists interested in catalysis. At first, the petroleum industry was not very interested in this type of compound because it was believed they have far too small pores to be effective in thermal cracking, but Rosinski and his collaborators have shown the opposite.

Since then, the scientists tried to expand the pore size of the microporous field in the mesoporous field in order to integrate into industrial applications. These could include separation of heavy metal ions from industrial waters,

sorption and separation of various large organic molecules from water, encapsulation of metal complexes in the networks, and introduction of nanoparticles into pores for electronic and optical applications [5, 6, 7]. Yanagisawa et al. described in 1990 the synthesis of a zeolite very similar to MCM-41. Their method is based on the intercalation of a long chain (typically C-16) of alkyltrimethylammonium cation, into the canymite-type silicate, followed by calcination to remove organic matter, which is called surfactant, resulting a mesoporous material. The silicate layers condense to form a three-dimensional structure with nano-sized pores.

Solid state nuclear magnetic resonance spectroscopy 29Si indicates that a large number of incompletely condensed species Si (OSi) 3 (OH) (Q3) are converted to fully condensed species Si (OSi) 4 (Q4) during the intercalation and condensation process. X-ray diffraction presents only a peak without too much information centered at extremely low angles. Unfortunately, the incomplete data led to an ignorance of the results of this group [8].

Synthesis and Functionalization of Micro-Nano-Structured Hybrid Zeolites

In 1992, Mobil Corporation researchers discovered M41S family of silicate/aluminosilicates, mesoporous molecular sites with a very uniform and exceptionally high pore structure. The synthesis of this type of compounds is based on both, sol-gels and surfactants sciences. The template agent is not just a single solvated organic molecule or metal ion, is a molecular surface of the surfactant that self-assembles. Within this family, it has been identified three different mesophases, lamellar (MCM-50), hexagonal (MCM-41) and cubic (MCM-48). The hexagonal mesophase, called MCM-41, possesses very regular surfaces of uniformly sized channels whose diameter varies between 15-100 Å depending on the template used, the addition of auxiliary organic compounds and reaction parameters [9, 10]. MCM-41 was the most studied member of the family because the others are thermally unstable or difficult to synthesize.

In any porous material, the pore shape can be approximated after one of the three cases:

- Cylindrical pores of circular section
- Ink droplets type, thin neck and large body
- Slotted parallel slit pores

Depending on the porosity, IUPAC, has classified these compounds into:

- microporous, with a pore size of less than 2 nm
- macroporous, with a pore size greater than 50 nm
- mesoporous, with pore size between 2 and 50 nm

Pore size is defined as the distance between two opposing walls. Obviously, the size of the pore makes sense only when there is a well-defined geometric shape. The porosity of a material is usually defined as the ratio between the volume occupied by pores and the volume occupied by the solid [11, 12]. Porous materials are also defined depending on their adsorption properties, the adsorption term denotes the condensation of a gas on a free surface, generally opposed to the mass input phenomenon as in the absorption. However, this distinction is not always clear and the way the gas is taken up by porous materials is usually called adsorption or simply sorption without thinking about the mechanism by which it is done. Adsorption of a gas on a porous material is usually described quantitatively by an adsorption isotherm at constant temperature as an amount of gas adsorbed depending on pressure [13,14].

Mesoporous materials have begun to be used on a wider scale in applications such as catalysis, separation, selective adsorption, new functionalized materials, and as hosts for molecules that fit into the pores. This type of solids has a high thermal stability and high adsorption capacity. Mesopores are present in aerogels and pillared clays that have a rather messy pore system and a very wide pore size distribution. Many applications require a specific pore size with a very narrow distribution. Following the initial announcement of the MCM-41, there were a series of published articles that involved it, but a study by Di Renzo and his collaborators identified a patent from 1971 indicating a procedure similar to that used by Mobil Corp to reach to "low density silica". The patent was reproduced and the resulting material had all the features of a well-developed structure of MCM-41, structure evidenced by electronic transmission microscopy (TEM), X-ray diffraction (XRD) and nitrogen adsorption.

However, only some of the features of the new material were described in the patent. It is Mobil Corp's merit that it has highlighted all the features of this new material [15]. The hexagonal mesophase composite is formed by condensation of the silicate species (formation of a sol-gel) around a predetermined hexagonal surfactant network or by adsorption of the silicate species onto the outer surface of some tube-shaped micelli randomly ordered by coulombic or other interactions type. Then these randomly ordered species spontaneously pack into a high-order mesophase with an energy-friendly

hexagonal arrangement followed by silicon condensation. Other researchers have further reviewed this mechanism. Chen and colleagues studied this mechanism by 14 N MRI spectroscopy in-situ.

They have come to the conclusion that randomly ordered organic micelle-sized microbes interact with silicate species to form two to three silica monolayers at the surface of the micelles. Then these species are arranged spontaneously to generate the order on long distance present in the hexagonal MCM-41. They concluded that in the case of tetraethylortho silicate (TEOS) as a source of silica, the concentration of the surfactant should be greater than or equal to the concentration limit of the micelles to form MCM-41. Monnier et al. determined that the surfactant is already present in the lamellar phase regardless of the final compound obtained. This lamellar mesophase turns into a hexagonal phase as the silicon network condenses and grows. Steel and colleagues suggest that as the silica source is introduced into the reaction gel, it dissolves in the aqueous region around the surfactant molecules, promoting then the hexagonal phase organisation. The silicate is arranged in lines between the small hexagonal phases. The further ordering of silicate results in wrinkling, proximity and growth of lamells in hexagonal channels. The chemical and physical changes occurring in wet gels due to the continuation of condensation reactions are commonly referred to as "maturing". However, the term "gel maturation" identifies the permissible length of time for which the condensation reaction may be prolonged prior to the gelation step. Gel maturation is beneficial for better control of the size and structure of soil polymers.

Maturation is, however, affected by several important factors such as temperature, dilution and pH. Increasing the temperature usually results in increasing the rate of reaction as the increase in dilution decreases the reaction rate. pH, on the other hand, has a pronounced impact on the distribution of condensation products due to the fact that a pH variation induces changes in the reaction rate, the solubility of silicate species and their distribution. Several spectroscopic techniques have been implicated in the mechanism of elucidating the effect of maturation on the size and distribution of silicate species when using an acidic or basic catalyst, including silicon-29 nuclear magnetic resonance (NMR), FTIR, X-ray diffraction (XRD) at small angle and RAMAN [16, 17, 18, 19].

The MCM-41 materials are silicates obtained by hydrothermal synthesis using a liquid template mechanism. This type of material has distinguishable properties, such as well-defined shape and size porosity (size of channels between

2 to 10 nm), and the ability to arrange at micro level to generate networks whose hexagonal channels do not intersect. These types of properties are typically visible in TEM (electronic transmission microscopy) and XRD. This type of material has a very high specific surface, typically between 900-1000 m^2/g, as can be seen from the BET (Brunauer, Emmett, Teller) method. They are also extremely thermally, hydrothermal and hydrolytic stable. The walls of this compound are formed from amorphous SiO_2 and the porosity can constitute 80% of the total volume. The surfactants used may be cationic, anionic or neutral type. The size of the pore can be adjusted by changing the length of the used surfactant. Moreover, by changing the silica source (amorphous silica, colloidal silica, tetraethyl ortho-silicate), the surfactant (hexadecylamine, cetyltrimethyl ammonium bromide) or the auxiliary compounds (1,3,5-trimethylbenzene) or reaction conditions such as solvent, reaction temperature, the maturation time, the amorphous fraction of the reactant and the pH of the medium yields materials which differs by pores size, volume or wall thickness. At the same time, the properties of thermal, hydrothermal, and mechanical stability modify [20, 21, 22]. Functioning porous materials with inorganic or organic groups will lead to new sets of physical and chemical properties. The introduction of organic groups (functionalization) into the mesoporous material allows for surface properties (hydrophilicity, hydrophobicity, acidity, basicity and binding mode of guest-molecules), altering the reactivity of the surface, protecting the surface against chemical attack, hydrophobing the surface by silylating in order to get rid of water attack, and alter the bulk properties of the material through stabilization to hydrolysis. Mesoporous materials with a functionalized surface have an increased interest due to various applications and are an interesting support for organic groups due to their large surface area, wide and uniform pore distribution and fine pore size distribution. As long as the silica network provides thermal and mechanical stability, surface's organic groups provide many of the interface and volume properties, such as flexibility and optical properties. Various reports describe methods for functionalization of the inner surface of MCM-41 or SBA-15 pores [23, 24, 25].

These hybrid materials are usually synthesized by two methods. The first consists in the post-synthesis grafting method in which the surface of the pore wall in a pre-fabricated mesoporous material is modified with organosilane compounds after removal of the surfactant. Mesoporous materials possess silanol groups (Si-OH) that facilitate attachment of organic functions to the surface. The silylating reaction is

most common for surface modification. Another way to modify the surface is esterification. The most common silylating reactions are the following:

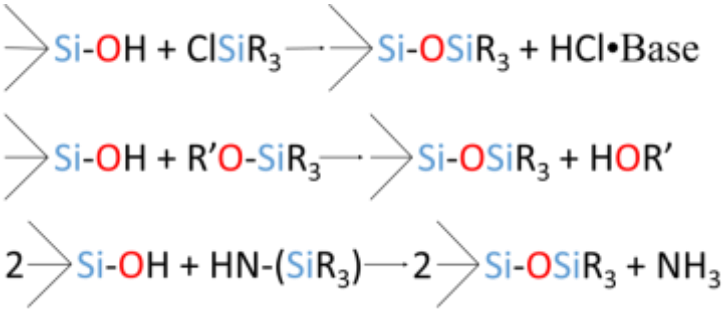

Figure 1. Scheme of common silylating reactions

The original structure of the mesopore support is usually preserved after surface modification. Silylation takes place in all free silanol groups on the surface. Those involved in hydrogen bonds are less accessible due to involvement in hydrophilic networks formation. In the post-synthesis grafting method, the host material must be completely dried prior to precursor's addition to avoid their autocondensation in presence of water. Another method of modifying the internal surface of mesoporous materials is by direct synthesis. This method is based on the co-condensation of a tetraalkoxysilane (siloxane) and one or more of the organoalkoxysilane precursors with Si-C bonds through a sol-gel process. Siloxane precursors are the main network of mesoporous material and the organoalkoxysilanic ones contribute to the network building and to the functional groups formation on the surface. Direct synthesis is more advantageous, as it leads to the formation of materials with a higher load of functional groups. Various grafts have been studied over time with both passive functional groups as alkyl and phenyl, and reactive groups such as amine, nitrile, thiol, halide type. The reactive ones can be used to adjust the size of the accessible pores and increase of surface hydrophobicity and the passive ones can be used to increase the hydrophilicity and allow subsequent functionalization. Several successive graftings have also been studied. In order to minimize external surface involvement in reactive processes and to optimize selectivity, grafting of passive groups on the surface and of reactive groups inside the pores was attempted. Each method has strengths and weaknesses. If an even surface coating of porous materials is desired, the direct method is the best. It also provides better control

over the amount of organic groups incorporated into the structure. However, post-synthesis functionalized compounds are structurally better defined and more hydrolytically stable. Although the size of the pores can be effectively controlled in both variants, it is easier to be done in the post-synthesis method [26, 27]. The large number of high reactivity primary amino groups allows wide limits in chemical modification variation by immobilization of specific affinity ligands. Such changes usually lead to improved adsorption characteristics of mesoporous materials. The studies focus on maximizing the concentration of functional groups (the degree of coverage) of the mesoporous surface while maintaining the pore size as high as possible. This is possible by using a mesoporous silica with large pores, high specific surface area and high concentration of silanol groups. However, thermal, mechanical and hydrothermal stability is also required. Control of synthesis conditions and the use of catalysts have a significant impact on the final product. The utility of amino functionalization of the free silanol groups of the silicon-based oxide compounds surfaces has a significant synthetic interest due to the change in the polarity of the active surface and by default in the increase of the adsorption specificity of the organic compounds. The main problem of the synthesis methods is, however, maintaining a suitable ratio between the active surface of the starting compound and the active surface of the reaction product [28, 29, 30, 31, 32, 33].

Use of mesoporous materials in controlled drug delivery

Over the years, the interest in nano-sized drug delivery vehicles has progressively increased due to its excellent biocompatibility, good control of target organs and sub-cellular dimensions. The most used vehicles in drug-controlled release are silicon-based porous materials due to the pore structure, pore size and volume, and the size of the specific surface. Colloidal mesoporous silica (CMS) nanoparticles, MCM-41, and SBA-15 are the silicon-based materials most commonly used as vehicles in controlled drug delivery [34, 35, 36]. In order to be useful in biomedicine, nanoparticles must gather certain criteria, such as better behave than existing compounds and at the same time have low cytotoxicity in vitro. In-vivo, nanoparticles must avoid unspecific plasma protein responses and escape or allow retention of the reticuloendothelial system, depending on the application, in order to effectively reach the target. It must also maintain its colloidal stability under physiological conditions, preferably in a wide range of pH domains. The nanoparticles used for transport should avoid premature

discharge and at the same time deliver the content to the target. Chemical modification of the surface of nanoparticles is required for specific interactions with biomolecules of interest [37]. Nanotechnology focuses primarily on the formulation of therapeutic agents within biocompatible nanocontainers, such as nanoparticles, nanocapsules, micelle systems and dendrimeries. The major advantage of nanotechnology is to deliver the drug directly to the target site of the disease. This is usually accomplished in two ways, either by passive targeting the drug to the target site or by actively targeting the drug itself[38]. Organic nanoparticles are also advantageous from transport capability point of view. However, loading with genes or other biomolecules is not always direct or simple. Many of the inorganic nanoparticles maintain biomolecules through the surface modifier, and the loading is limited by the surface of the particle to a large extent. Aggregation limits contact between nanohybrids and cells, thereby reducing transfer. Another possible problem is the excretion of inorganic nanoparticles and / or their accumulation in the cell that can damage cell growth. Due to chemical stability, inorganic nanoparticles can not be dissolved inside the cell and because of their relatively large size, they can not leave the cell as an ion. Exocytosis could be possible due to osmotic pressure, but with a very low rate due to low cell concentration [39,40]. Conventional mesoporous silica materials are promising for drug release applications due to the large surface area (800-1200 m^2/g), the arrangement of mesopores (hexagonal or cubic) and adjustable pore size between 2-15 nm. Although the capacity of these materials for the adsorption of drugs is high (about 15-30% w / w) [41,42], precise control of the kinetics of releasing the loaded drugs by attaching the functional groups to the pore surface is problematic and often during the release of the drug , a throwing effect can be observed [43,44]. Notably, CMS nanoparticles have been proposed as drug delivery vehicles due to the possibility of being internalized into cells [45,46]. Small dimensions (typically less than 300 nm) of CMS nanoparticles allow internalization by cell membranes, followed by localized release and drug adsorption [47]. In addition, many researchers have focused on applications of mesoporous silica as potential drug release systems due to its non-toxic nature and good biocompatibility [48, 49, 50, 51]. Like the typical mesoporous silicas, MCM-41 was used as a carrier for several different pharmaceutical compounds such as ibuprofen [52, 53], vancomycin [54], fluorescein - compound model [55], diflunisal, naproxen [56] hypocrelin A [57], and aspirin [58].

Controlled drug release aims to optimize their effectiveness while simultaneously reducing side effects. Several studies have shown that pharmacokinetics, drug efficacy and suppression of undesirable side effects in different pathological conditions (eg hypertension and rheumatoid arthritis) can be improved by optimal drug administration and control of drug delivery kinetics [59, 60, 61]. Until now, porous drug carriers have been exploited for pharmaceutical use; of these, porous silica, propylene foams and porous magnesium aluminosilicate, which are known under the trade names Sylysia, Accurel and Neusilin, respectively. Porous texture is recognized as an important factor in the control of diffusion and delivery rate of drugs [62, 63, 64, 65]. However, the less studied factors are the particle's size and shape (morphology) and the functionalization of the drug transport. Morphology determines the interface extension between the drug-bearing particle and the body fluids, and could therefore affect the release of the drug's kinetics [66]. The proper functioning of the interior walls of the pores of the carrier could also affect the release rate by determining the binding power of the drugs [67]. Silicon-based mesoporous materials are an amazing solid class with an ordered arrangement of pores, channels or cavities with different geometries built from [SiO4] tetrahedral. The pore size of these materials varies from 2 to 50 nm and can be reasonably controlled, modified, using various synthesis strategies. The most common such structures are two-dimensional planar-hexagonal type with a p6mm symmetry group, such as the MCM-41 and SBA-15 structures with pore size between 2 and 10 nm, and the cubic type Ia3d symmetry, such as MCM-48 with pores of approximately 3 nm. The most important feature of these materials, from a practical point of view, is the possibility to synthesize these materials with different porosity and geometry. This aspect opens new possibilities for the storage of larger molecules than those initially included in traditional microporous materials. This is a key aspect that makes it possible to make materials that can be used as a drug delivery device as the porosity becomes compatible with the molecular sizes of the drugs. The adsorption capacity of the silica walls can be modulated by functionalization with various chemical species depending on the molecule that is desired to be adsorbed.

The common method of realization is co-condensation, method by which the organic functional group is mixed with the silica precursors. The entire procedure is carried out in the same reaction vessel, in the post-synthesis reaction. Modification of silanol groups should be carefully chosen depending on the drug

molecule in order to achieve the desired release and controlled loading effect. Controlled drug release kinetics are usually studied over time to determine the desorption constants from mesopores. It is noted that for mesoporous materials, the desorption profile generally has an initial leap effect in the release curve, followed by a very slow profile.

The initial salt is attributed to the immediate dissolution and release of the portion of the drug located very close to the surface of the pores or even on the surface. It is also observed that a total drug release from the pores is almost impossible to obtain due to the equilibrium that is established and favors partial retention in the pores at the end of the process. This equilibrium process is amplified for functionalized materials due to stronger interaction between the drug molecule and modified silica walls [68]. In terms of biocompatibility, silica has been intensively studied due to its association with occupational disease, with silicosis, which is directly associated with crystalline silica.

Cytotoxicity tests for amorphous silica did not show any toxic effect on tumor cells unless they were loaded with a cytostatic drug [69]. By using trimethyl ammonium C12-bromide instead of trimethyl ammonium C16-bromide during the self-assembly process, the pore distribution was readjusted from an average of 1.8 nm to 2.5 nm. The transport characteristics of mesoporous materials can be also modified by plugging the pores after filling with plugs that are removed only under certain conditions. On MCM-41, CdS plugs were made removable by certain stimulants, having applications in the field of neurotransmitters and drugs of this type.

The nanoparticles of MCM-41 were also modified with 2-(propyldisulfanyl) ethylamine and with CdS nanocrystals plugs derivatized with water-soluble mercaptoacetic acid by amidation reaction. Analog materials were synthesized using dendrimers and magnetic stoppers. It is relatively easy to modify the surface of these materials with various chemical groups, including saturated and unsaturated hydrocarbons, carboxylic acids, thiols, amines and alcohols. Inorganic nanoparticles are very stable over a wide range of temperature and pH, but their lack of biodegradability and low dissolution rates raise questions that have not yet been addressed, particularly in the case of long-term administration.

Moreover, nanoparticles can be used to alter the drug release profile, resulting in a sustained release and a lower dosing frequency [70]. One group of investigators combined the following drugs: hydrochlorothiazide, amlodipine,

losartan, and isimvastatin in a weight ratio of 12.5/2.5/25/40 under the name of polypill, loaded them on mesoporous silicon nanoparticles of MCM-41 type which are used as vehicles in the controlled release of these drugs. Following controlled release studies, the following were established: Hydrochlorothiazide was rapidly released from the MCM-41 surface, this rapid release being useful in medical emergencies in which the patient has hypertension, amlodipine, losartan, and simvastatin were released in a controlled manner from the system polypill-MCM-41, which is clinically useful to avoid too rapid drop in blood pressure [71].

Another confirmation of the fact that MCM-41 is an excellent vehicle in drug-controlled release is the study made by Asaad F. Hassan and others demonstrating that the MCM-41-MELOXICAM complex due to the ordered hexagonal structure of the MCM-41 increased the oral bioavailability of MELOXICAM which has an extremely low solubility in water compared to the oral bioavailability of MELOXICAM by itself[72].

Conclusions

Concerns about the amino functionalization of silanol groups refer either to the use of compounds such as amino functionalized organosilanes or to more complex compounds that can lead to functionalized surfaces with more specificity by useing more polar or ionizable groups with a sterically distribution that can be correlated with load distribution of the adsorbed compound. The correlation of the specific surface of the zeolitic reactant with that of the functionalized reaction product is a constant concern of the researchers, being important a specific surface loss as small possible through functionalization.

In order to obtain secondary functionalities, it is very useful a preliminary step of grafting of a reactive epoxy group which can lead to a significant widening of the range of grafted secondary compounds as well as to the shaping of the functionalized amino, diamino or mixed functional surface after load distribution of the adsorbed compound. Functionalities of the diamino or polyamino type allow for obtaining more efficient amino-type coatings for zeolite surfaces, presenting a potential interest for the future syntheses being approached, as long as it eliminates the risk of an uncontrolled reaction with the formation of dendritic compounds (with high potential complete blocking of zeolite material pores) by rigorously controlling the reaction conditions.

The use of micro-nano-structured zeolite materials as vehicles in controlled release drug delivery can lead to high-tech pharmaceutical devices with design resulting from optimized chemical synthesis processes in accordance with toxicity and efficacy in vitro/vivo.

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