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► To cite this version:

Massimo Petriccone, Regis Laurent, Cédric-Olivier Turrin, Rosa Maria Sebastián, Anne-Marie Caminade. Specific bifunctionalization on the phosphorus dendrimers. Encyclopedia Platform, 2022, entry 26972 - <https://encyclopedia.pub/entry/26972>. hal-03789588

HAL Id: hal-03789588

<https://hal.science/hal-03789588v1>

Submitted on 27 Sep 2022

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Specific Bifunctionalization on the Phosphorus Dendrimers

Subjects: [Chemistry](#), [Organic](#)

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Dendrimers are highly branched three-dimensional macromolecules, whose properties are essentially dependent on the type of their terminal functions. Dendrimers are synthesized by iterative processes, which afford a new generation at the end of each sequence, characterized by a multiplication of the number of terminal functions. Such processes generate identical terminal functions on the surface of the dendrimers. However, it is sometimes desirable to have two types of surface functions in order to fulfil specific properties. Numerous properties have been explored already, most of them being related to catalysis, materials, or biology/nanomedicine. Strategies to get two types of terminal functions will be illustrated with polyphosphorhydrazone (PPH) dendrimers.

dendrimer

properties

bifunctionalization

I 1. Introduction

Dendrimers are synthesized by iterative processes, which afford a new generation at the end of each sequence, characterized by a multiplication of the number of terminal functions, most generally by two ^[1] or three ^[2], depending on the branching motives. Such processes generate identical terminal functions on the surface of the dendrimers, of course depending on the type of dendrimers, and on the synthetic process used. Such terminal functions can be modified uniformly to bring new properties. However, it is desirable in some cases to have two types of terminal functions, each type of functions affording eventually its own properties (for instance, one function for the solubility, the other affording properties for catalysis or biology, or one type of function for the grafting (for instance to materials), with the other functions bringing another property).

In most cases, the presence of two (or even more) functions on the surface of dendrimers is carried out using a stochastic approach (i.e., an uncontrolled number and location of each type of functions). However, this approach is contradictory with the aim of having a perfectly controlled and reproducible structure for the dendrimers, contrarily to classical polymers. Even if efforts have been carried out to increase the purity of compounds issued from the stochastic approach ^[3], batch-to-batch inconsistencies are unavoidable, and induce in particular undesirable varying biological activities ^[4]. To solve this type of problem, it is highly desirable to synthesize dendrimers precisely bifunctionalized on their surface. **Figure 1** displays the difference between both approaches.

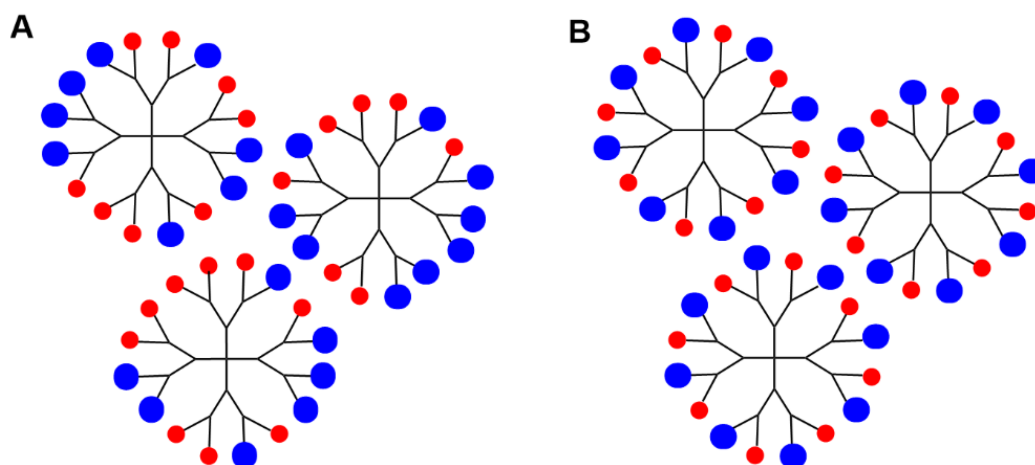
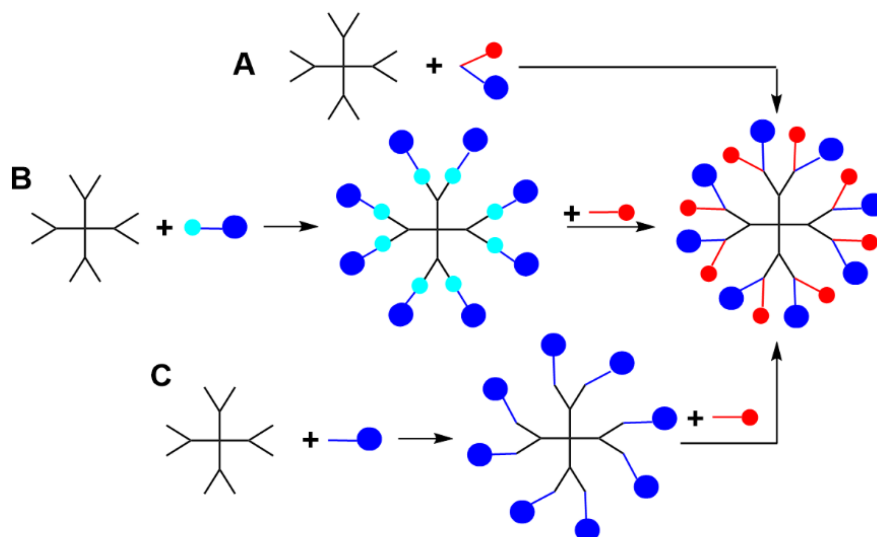


Figure 1. Examples of batches of bifunctionalized dendrimers. **(A)** Stochastic functionalization on the surface of dendrimers. **(B)** Precise bifunctionalization on the surface of dendrimers.

The easiest way to get dendrimers specifically bifunctionalized on their surface consists in grafting on each terminal function a compound bearing already both desired functions (**Scheme 1A**). Such a method has been applied to different types of dendrimers and functions. One can cite for instance as an early example the presence of both a phenyl and a pyrene on the surface of a series of dendrimers built on an aryether scaffold, and used for studying charge-transfer processes from the core to the surface ^[5]. More recent examples concern PAMAM (polyamidoamine) dendrimers functionalized with different aminoacids, to have NH₂ groups together with either OH, SH, or other functional groups, and tested for drug delivery ^[6]. Polyester dendrimers functionalized with both OH and azide, used later on in click chemistry to afford biosensors ^[7] or functionalized with both azide and alkyne, as a multipurpose platform, in particular to afford implant adhesives in bone fracture applications ^[8] are other more recent examples. Azide alkyne monomeric compounds have been used for synthesizing by click chemistry multifunctional nanocarriers bearing as terminal functions a model drug (R-lipoic acid), a fluorescent dye (BODIPY), and a poly(ethylene glycol) (PEG) chain ^[9]. Other recent examples of grafting directly two functions concern PPI (polypropyleneimine) dendrimers functionalized with both an electroactive carbazole and a mesogenic unit, all dendrimers of this family being liquid crystalline ^[10], and also Newkome-type polyamide dendrimers, functionalized with both one azide and two olefins ^[11]. A series of bifunctional dendrimers has been obtained from either a polyester-polyamide, or polyester-lysine, or polyamine-lysine hybrid internal structure functionalized on the surface with orthogonally protected aspartic acid ^[12]. The selective and sequential deprotection of the amine and of the carboxylic acid of the protected aspartic acid was carried out to graft a long PEG (115 units in average), and either a gadolinium complex ^[13], ^[14] or diverse other lanthanide complexes (Dy, Yb ^[15], Eu, and Sm ^[16]) for magnetic resonance imaging (MRI), or two synthetic tubulysin analogues against C26 colon carcinomas ^[17]. Lysine derivatives protected by two different protecting groups, were grafted on the surface of lysine dendrimers and dendrons. Selective deprotection afforded dendrimers bearing both gadolinium complexes and PEG as MRI contrast agents ^[18]. The same process was applied to a series of dendrons having a carboxylic acid at the core and both a gadolinium complex and galactosyl moieties on the surface, as liver targeting imaging probes ^[19]. Another lysine-dendron bearing a long PEG chain at the core (114 units in average) and both a porphyrin analogue and cholic acid, was used for near-infrared fluorescence imaging (NIRFI), magnetic resonance imaging (MRI), positron emission tomography (PET) and dual modal PET-MRI ^[20].



Scheme 1. Schematization of the different methods used for having precisely two types of different functions on the surface of dendrimers. **(A)** grafting on each terminal function a compound bearing already both desired functions. **(B)** modifying one function already on the surface, to generate two functions. **(C)** sequential grafting of one function, followed by the grafting of the second one.

Other methods to get two types of terminal functions have been very rarely used. One can cite the possibility to modify one function already on the surface, to generate two functions (**Scheme 1B**). Such type of reaction has been illustrated with functionalized amines used for opening cyclic carbonates on the surface of polyester dendrimers [21].

The last method concerns the sequential grafting of one function, followed by the grafting of the second one, as illustrated in **Scheme 1C**. Such a type of reaction is rare, and has been used essentially with dendrimers having dichlorotriazine as terminal functions, reacted in sequential nucleophilic aromatic substitution with two different amines [22]. MRI (Magnetic Resonance Imaging) contrast agents have been obtained in this way, one amine bearing a ligand suitable for complexing gadolinium, the other an alcohol [23].

Besides the different types of dendrimers indicated above, another type of dendrimer is known for the versatility of its chemistry, namely phosphorus dendrimers, and particularly polyphosphorhydrazone (PPH) dendrimers, which possess a phosphorus atom at each branching point [24]. They are generally built from either $P(S)Cl_3$ or hexachlorocyclotriphosphazene as core [25]. Their structure is illustrated in **Figure 2** with the first and second generations. Both generations are displayed as the full chemical structure, but also in a linear form with parentheses after each layer of branching points. The presence of either $P(S)Cl_2$ or aldehyde terminal functions, depending on the step considered, enables a versatile reactivity to fulfil the desired properties.

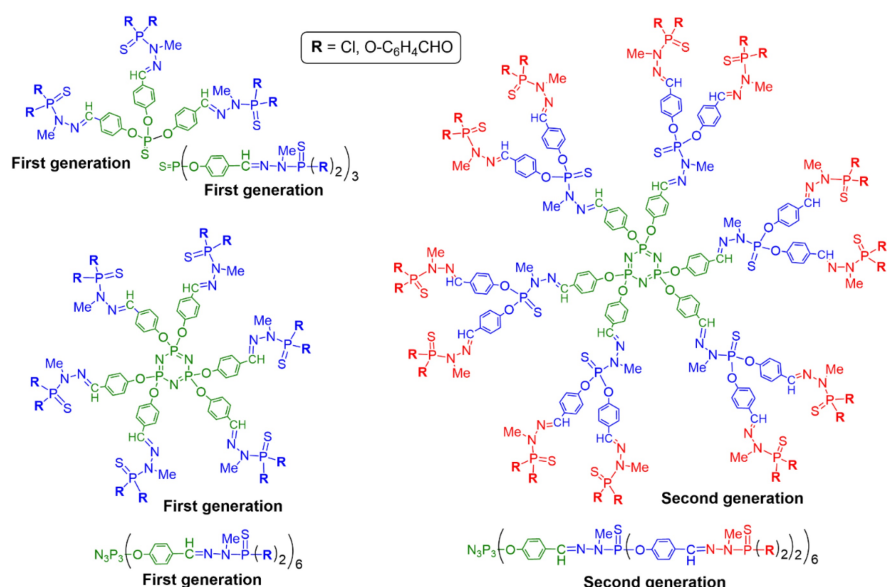
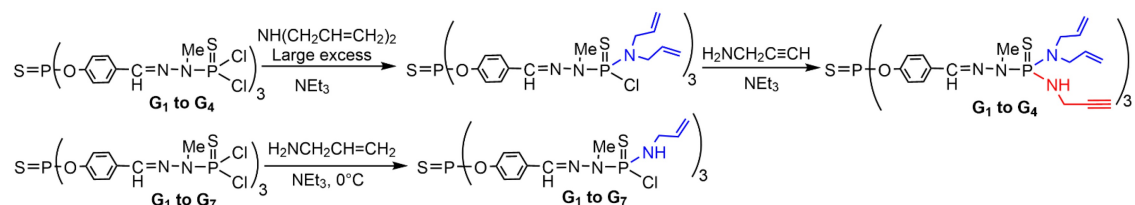


Figure 2. Two ways for drawing the 1st and 2nd generations of polyphosphorhydrazone dendrimers: full chemical structure, and linear structure with parenthesis after each layer of branching points.

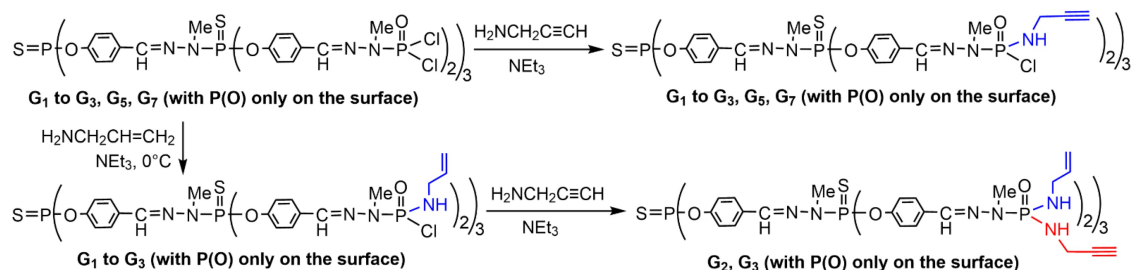
2. Sequential Grafting of a First, then a Second Function on the Surface of PPH Dendrimers

As indicated in the introduction, sequential grafting on the surface of dendrimers, as shown in **Scheme 1C**, is very rare, and has been carried out only and recently with triazine dendrimers [22,23]. On the contrary, such a type of reaction is carried out since a long time with polyphosphorhydrazone dendrimers, thanks to the specific reactivity of the P(S)Cl_2 terminal functions. The possibility of such sequential reaction was discovered first with secondary amines. Indeed, only one Cl of each P(S)Cl_2 terminal functions was able to react with diallylamine (even when used excessively). However, the remaining Cl was able to react with primary amines, such as propargylamine (**Scheme 2**). This sequential reaction is not limited to secondary amines. Indeed, depending on the conditions used (temperature and quantity of amine), it is possible to react only one allylamine on each P(S)Cl_2 terminal function. Some reactions were carried out up to the seventh generation [26].



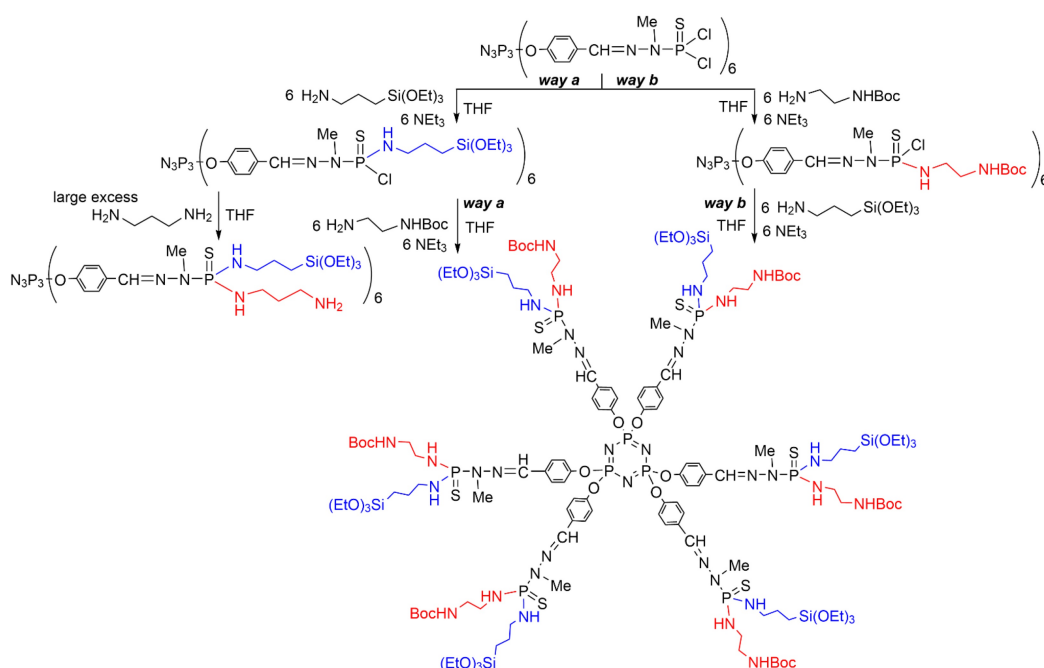
Scheme 2. Sequential addition of two different amines on the surface of PPH dendrimers.

In some cases, the surface functions are P(O)Cl_2 instead of P(S)Cl_2 , but they display the same specific reactivity. In particular, one propargylamine or one allylamine could be grafted on each P(O)Cl_2 function. As in the previous case, the second reaction can be carried out with propargylamine when allylamine was already grafted (**Scheme 3**) [26].



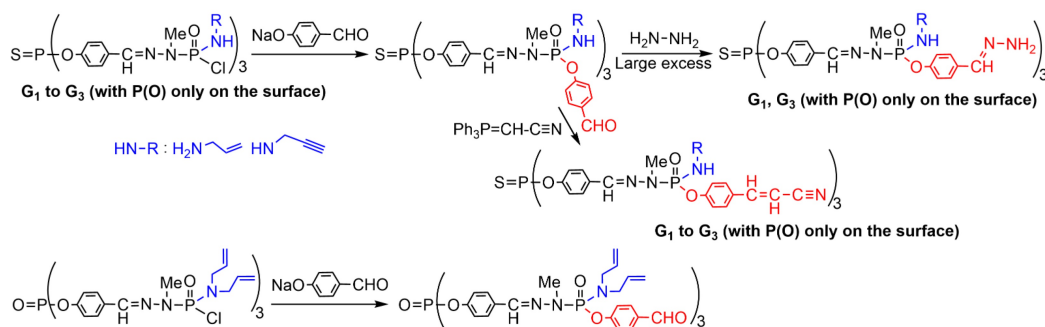
Scheme 3. Sequential addition of two different amines on the surface of polyphosphorhydrazone dendrimers having P(O)Cl₂ terminal functions.

The same type of reaction was carried out more recently to obtain compounds bearing both a triethoxysilane and a primary amine. Boc-monoprotected ethylene diamine as the amino part, and 3-(triethoxysilyl) propylamine as the silyl part were chosen. The first step was the grafting of one of the two amines (way a or way b, **Scheme 4**), followed by the grafting of the other amine in the second step, affording the same compound in both cases. Besides, a large excess of 1,3-diaminopropane can be used as the second amine, to directly afford a free amine as terminal function (**Scheme 4**) [27]. These compounds were tested among other dendritic structures possessing both types of functions for the grafting to silica, followed by attempts for trapping CO₂, after deprotection of the Boc-protected amine, to form a carbamate. These compounds having both types of functions on the surface were not the most efficient. Indeed, dendrons possessing a single triethoxysilyl group at the core and several primary amines on the surface were found to be more efficient [28].



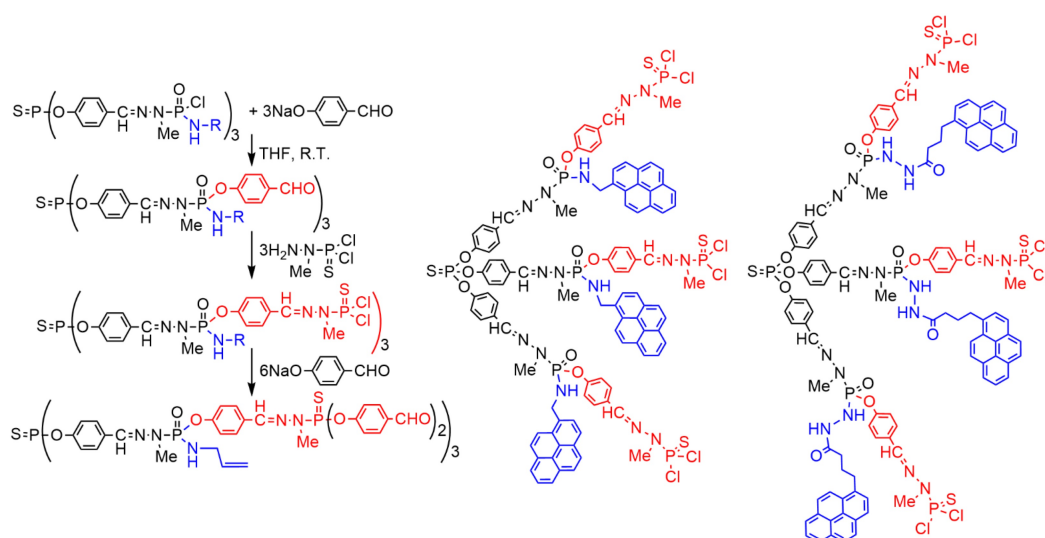
Scheme 4. Other examples of sequential addition of two different amines on PPH dendrimers, to be grafted to silica, and used for trapping CO₂.

Besides the grafting of two amines, it is also possible to graft both an amine and a phenol. Such type of reaction was carried out up to now only on P(O)Cl₂ terminal functions. After the grafting of either allyl amine or propargylamine, the second step was the grafting of 4-hydroxybenzaldehyde, in basic conditions. The aldehydes were then used for the condensation with hydrazine in large excess, or for Wittig reactions with the ylide Ph₃P=CH-C≡N (**Scheme 5**) [26]. Hydroxybenzaldehyde could react also when bulky diallylamine was grafted in the first step [29].



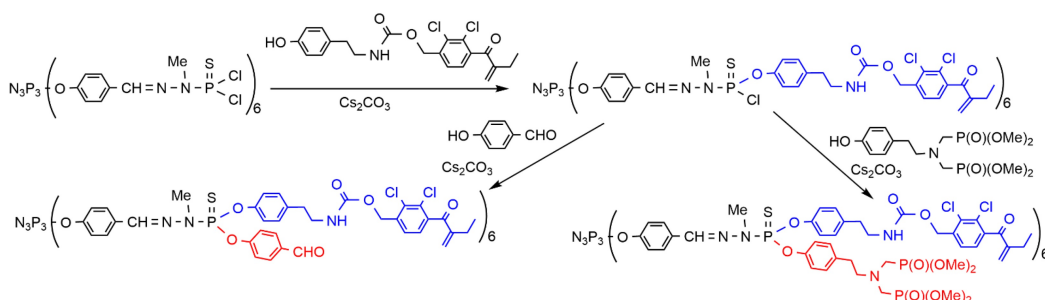
Scheme 5. Sequential addition of an amine and of 4-hydroxybenzaldehyde on the surface of PPH dendrimers.

The presence of the aldehydes as shown in **Scheme 5** enabled the continuation of the synthesis of dendrimers having pendant internal functions inside the structure. These pendant groups were either an allylamine, or 1-aminomethylpyrene, or 1-pyrenebutanoic hydrazide. The aldehydes were reacted with $\text{H}_2\text{NNMeP(S)Cl}_2$, as in the classical synthesis of PPH dendrimers (**Scheme 6**) [30].



Scheme 6. Amino derivatives of allyl or pyrene as pendant functions inside polyphosphorhydrazone dendrimers.

Besides the sequential use of two amines, or of an amine and a phenol shown in the previous Schemes, the sequential use of two phenols was also attempted on the surface of polyphosphorhydrazone dendrimers. The reaction is less clean than with amines, as it is difficult to avoid a small percentage (less than 5%) of either homodisubstitution, or unreacted P(S)Cl_2 . The grafting of a phenol derivative of ethacrylic acid, followed by the grafting of either 4-hydroxybenzaldehyde or the phenol of the azabisphosphonate were carried out (**Scheme 7**). Ethacrylic acid grafted on the entire surface of phosphorhydrazone dendrimers was shown to display strong anti-proliferative activities against both liquid and solid tumors [31]. However, these unsymmetrical compounds were not tested [32].



Scheme 7. Grafting of a phenol derivative of ethacrylic acid and other phenols on the surface of

PPH dendrimers having anticancer properties.

In conclusion, the specific bifunctionalization on the surface of dendrimers is still an ongoing challenge. Despite being challenging, the specific presence of two functions on the surface of dendrimers offers new opportunities for the future, in particular for increasing the solubility in specific media such as water and for dendrimers having catalytic or biological properties. In this regard, efforts should be engaged to develop efficient new strategies leading to sophisticated and highly controlled multifunctional dendrimeric architectures.

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