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Synthesis of octacalcium phosphate with incorporated 1,4,5,8-naphthalenetetracarboxylate ions

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This study reports the successful synthesis of octacalcium phosphate (OCP) with incorporated 1,4,5,8-naphthalenetetracarboxylate ions. This material achieves a new record for the maximum molecular weight of carboxylic acids that can be incorporated into OCP. Furthermore, we identified a new tetracarboxylic acid that can be incorporated into OCP.

Octacalcium phosphate (OCP, $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$) has long been studied for use in biodegradable artificial bone materials,^{1–5} along with carbonate apatite.^{6–10} OCP has a layered structure composed of apatitic and hydrated layers.^{11,12} The hydrogen phosphate ions in the hydrated layer can be substituted by carboxylate ions, which in most cases are dicarboxylate ions.^{13–27} Among the tricarboxylic acids, only citric acid can be incorporated into OCP interlayers,^{28–30} whereas among the tetracarboxylic acids, 1,2,4,5-benzenetetracarboxylic acid can be incorporated.³¹

Research on OCP with incorporated carboxylate ions follows two main paths. One direction is the development of functional materials, exemplified by the recent research on fluorescent materials composed of OCP containing aromatic carboxylate ions.^{31–35} This cutting-edge research started with the synthesis of fluorescent OCP in 2019,³⁶ and is expected to contribute to the development of bioimaging probes and other biomedical applications in the future. The other research direction is the search for carboxylic acids that can be incorporated into OCP interlayers, and several appropriate carboxylic acids have been reported in recent years. For example, terephthalic acid derivatives³³ and *meso*-2,3-dimercaptosuccinic acid³⁷ were incorporated into OCP in 2024. These studies have contributed to strengthening the fundamental chemical

knowledge related to OCP, which may enable the prediction of carboxylic acids that can be incorporated into OCP in the future.

Considering this background, aromatic tetracarboxylic acids have only been successfully incorporated into OCP interlayers in one study,³¹ leaving room for further investigation of these acids as guest molecules in OCP. Furthermore, since aromatic tetracarboxylic acids are expected to exhibit fluorescence properties, OCP with incorporated aromatic tetracarboxylate ions may be suitable for biomedical applications. In this study, we successfully incorporated 1,4,5,8-naphthalenetetracarboxylic acid (NTCA) into OCP interlayers for the first time. Furthermore, we confirmed that the obtained OCP with incorporated 1,4,5,8-naphthalenetetracarboxylate ions exhibited fluorescence, and the novel findings are reported here.

The OCP samples were synthesized through a reaction using calcium carbonate and phosphoric acid in 2.5–20 mM NTCA solutions. The synthesis of OCP samples is described in detail in the SI. The sample names are defined as NTCA-*X*, where *X* indicates the NTCA concentration (mM) in the reaction solution. An OCP sample without carboxylate ions was synthesized as a control material through the reaction between calcium carbonate and phosphoric acid mixed in ultrapure water, and this sample is denoted as CONTROL.

The samples were characterised by X-ray diffraction (XRD) using a Cu-K α radiation source and by Fourier transform infrared (FTIR) spectroscopy using the KBr tablet method. Descriptions of these characterisation experiments and others are shown in the SI.

All synthesised samples were characterised using XRD (see Fig. S1). The samples with NTCA concentrations of 7.5 mM and 10 mM exhibit reflection peaks assignable to the OCP phase. For the sample synthesised using lower NTCA concentrations, OCP without incorporated 1,4,5,8-naphthalenetetracarboxylate ions was formed. On the other hand, the calcium salt of NTCA (Ca-NTCA) was formed as an impurity phase under higher concentration conditions. Therefore, we selected NTCA-7.5 for further evaluation instead of NTCA-10 to avoid the possible inclusion of a small amount of Ca-NTCA, which

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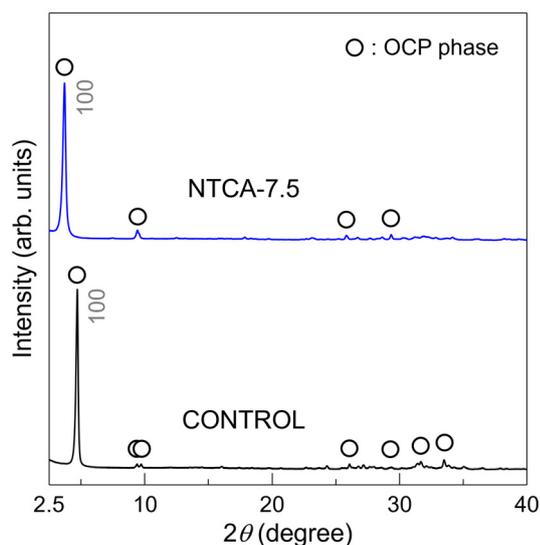


Fig. 1 XRD patterns of CONTROL and NTCA-7.5. (An enlarged XRD pattern of NTCA-7.5 is shown in Fig. S2.)

may be below the detection limit of XRD analysis. When NTCA-7.5 was observed using a scanning electron microscope equipped with an energy-dispersive X-ray spectrometer, a very small number of particles, presumably Ca-NTCA, were detected. Because the number of these particles was considered unlikely to significantly affect subsequent analyses, the analyses were carried out without further treatment. The XRD patterns for CONTROL and NTCA-7.5 are shown in Fig. 1. For both samples, reflection peaks assignable to the OCP phase are observed, with no other discernible peaks. The 100 reflection peak position of the OCP phase in the XRD pattern of NTCA-7.5 is observed at a lower angle than that observed for CONTROL.

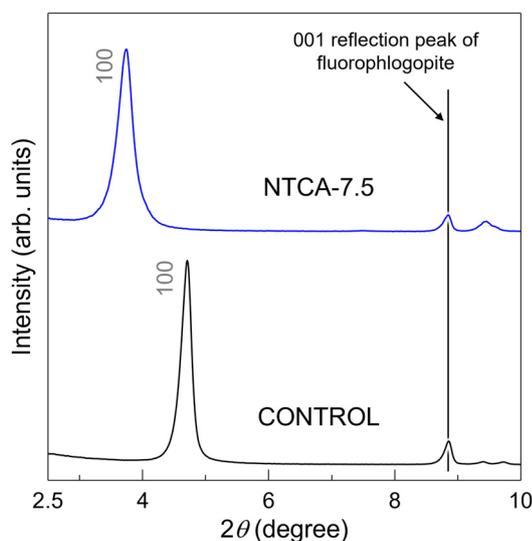


Fig. 2 Comparison of the XRD patterns of CONTROL and NTCA-7.5 mixed with fluorophlogopite as an angular standard material.

Fig. 2 shows the angle-corrected XRD patterns of CONTROL and NTCA-7.5 using fluorophlogopite as an angular standard. The 100 peaks for CONTROL and NTCA-7.5 are observed at 4.72° and 3.75°, respectively. The corresponding interplanar spacing (d_{100}) values for CONTROL and NTCA-7.5 are 1.87 nm and 2.35 nm, respectively. The expansion of interplanar spacing of (100) for OCP is attributed to the incorporation of carboxylate ions into the OCP interlayers.³⁸ Hence, the observed increase in d_{100} indicated that 1,4,5,8-naphthalene tetracarboxylate ions were incorporated into OCP interlayers.

The FTIR results support the incorporation of 1,4,5,8-naphthalene tetracarboxylate ions into OCP interlayers. The FTIR spectra of CONTROL and NTCA-7.5 are shown in Fig. 3, for which the observed peaks are assigned based on a previous report.³⁹ The major absorption peaks for CONTROL, except the peak at 1646 cm^{-1} related to the H_2O bending vibration, are attributed to phosphate species. In particular, the absorption peak at 1193 cm^{-1} is attributed to hydrogen phosphate ions in the OCP interlayer. This absorption peak is not observed for NTCA-7.5. In addition, absorption peaks related to COO vibrations are observed in the range of 1600–1300 cm^{-1} , and this chemical bonding occurs in 1,4,5,8-naphthalene tetracarboxylate ions. Hence, the XRD and FTIR results indicate that OCP with incorporated 1,4,5,8-naphthalene tetracarboxylate ions was successfully synthesised in this study.

It has been proposed that the d_{100} value of OCP with incorporated carboxylate ions and size of the incorporated carboxylate ions have a linear relationship.⁴⁰ The relationship between d_{100} and molecular size is expressed by the following equation:

$$d_{100} = 0.9355L + 1.7669 \text{ (nm)} \quad (1)$$

where L is the distance between the carbon atoms of the carboxy groups of the carboxylic acid, and is used as a para-

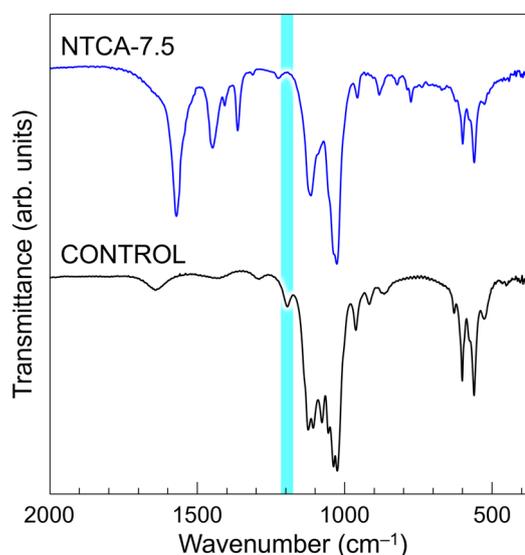


Fig. 3 FTIR spectra of CONTROL and NTCA-7.5. The blue band indicates the absorption band of hydrogen phosphate ions in OCP interlayers.



meter to represent the molecular size. This empirical equation was previously established for OCPs with incorporated dicarboxylate ions, and here it has been applied to our system with incorporated tetracarboxylate ions. Based on the XRD data in Fig. 2, the d_{100} of NTCA-7.5 is 2.35 nm, giving an L value of 0.62 nm (based on eqn (1)). For comparison, L values were obtained for the structure of NTCA under vacuum, optimized by the universal force field method⁴¹ using Avogadro software (Ver. 1.2.0).⁴² Fig. 4 shows three calculated L values for NTCA in three different directions, namely 0.30, 0.58, and 0.65 nm. The L value calculated from the XRD data (0.62 nm) lies between the calculated values of 0.58 and 0.65 nm. Hence, the combination of carboxy groups containing carbon atoms of (A) and (C), as well as (A) and (D), likely contributes to the bonding and formation of the layered structure of the OCP crystal.

A 3D photoluminescence (PL) spectrum of NTCA-7.5 is shown in Fig. 5. This figure clearly indicates that OCP with incorporated 1,4,5,8-naphthalenetetracarboxylate ions exhibits

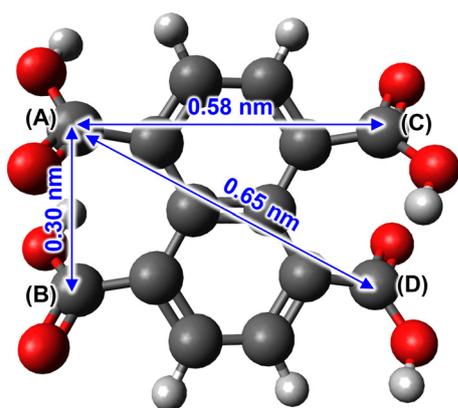


Fig. 4 L values calculated for the optimised structure of NTCA under vacuum conditions. (A), (B), (C), and (D) indicate carbon atoms of carboxy groups.

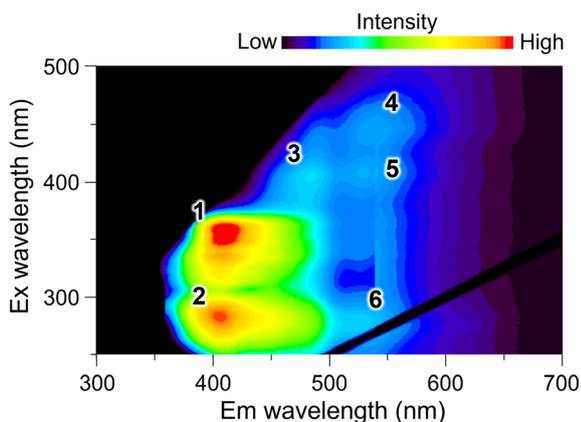


Fig. 5 3D PL spectrum of NTCA-7.5. To eliminate the influence of stray light, the difference spectrum between NTCA-7.5 and calcium carbonate (a sample without fluorescence) is shown here. The measured 3D PL spectra of NTCA-7.5 and calcium carbonate are shown in Fig. S3. The numbers 1–6 indicate distinct PL peaks.

fluorescence. Notably, multiple peaks are present in the spectrum: two main peaks (1 and 2) and four sub-peaks (3–6). The multiple PL peaks are likely a result of the multiple energy levels of NTCA, as a polycyclic aromatic compound. PL is observed for wavelengths beyond 500 nm (PL peaks no. 3–6), suggesting that the use of polycyclic aromatic compounds likely extends the fluorescence wavelength, a significant feature not seen in previous materials.⁴³ This finding guides the material design of future bioimaging probes with cell- and tissue-friendly optical properties using OCP with incorporated carboxylate ions.

The future prospects and limitations of this study are discussed below. To date, the only reported tetracarboxylic acid that was successfully incorporated into OCP was 1,2,4,5-benzenetetracarboxylic acid.³¹ This study shows that NTCA can also be incorporated into OCP, suggesting that tetracarboxylic acids should be further studied as carboxylic-acid candidates for incorporation into OCP interlayers. In addition, a previous study showed that the highest molecular weight carboxylic acid successfully incorporated into OCP interlayers was 1,2,4,5-benzenetetracarboxylic acid, with a molecular weight of 254.15 g mol⁻¹.³¹ However, the successful incorporation of NTCA (with a higher molecular weight of 304.21 g mol⁻¹) into OCP expands the range of suitable carboxylic acids. Increasing the upper limit of the molecular weight of carboxylic acids that can be incorporated into the limited space between OCP interlayers is significant from the perspective of solid-state chemistry. Furthermore, the structural analysis of OCPs containing carboxylate ions has been a challenge for many years. Computational chemistry is a promising approach and has been successfully applied to an OCP containing carboxylate ions.⁴⁴ However, experimental structural analysis remains difficult. Therefore, in this study, the steric structure of 1,4,5,8-naphthalenetetracarboxylate ions in the OCP interlayers was estimated by an indirect method using eqn (1). It is very difficult to elucidate the crystal structure of these substances using general laboratory analytical equipment. Crystal structural analysis using highly advanced methods, such as synchrotron radiation, is recommended to provide deeper structural information.

Conclusions

This study successfully incorporated 1,4,5,8-naphthalenetetracarboxylate ions into OCP. The molecular weight of this carboxylic acid is higher than that of any previously reported carboxylic acids that can be incorporated into OCP. In addition, we found that OCP with incorporated 1,4,5,8-naphthalenetetracarboxylate ions exhibits unique PL properties. Our findings are expected to improve the general understanding of OCP chemistry and contribute to the development of novel bioimaging probes.

Author contributions

Taishi Yokoi: conceptualization, methodology, investigation, project administration, resources, funding acquisition, visual-



ization, writing – original draft, writing – review & editing. Mio Yoshizaki: methodology, investigation. Masaya Shimabukuro: writing – review & editing. Peng Chen: resources, writing – review & editing. Kazuhiko Noda: resources, writing – review & editing. Masakazu Kawashita: resources, funding acquisition, writing – review & editing, supervision.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: Synthesis of OCP samples, characterisation, and additional XRD and PL data. See DOI: <https://doi.org/10.1039/d5dt02854j>.

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