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Calcium Hydroxyapatites as Efficient Catalysts for the Michael C−C Bond Formation

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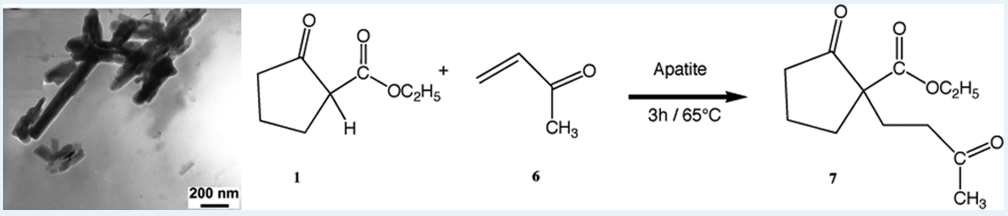
ABSTRACT:



Calcium hydroxyapatites of different compositions and various specific surface areas (SSA) are shown to be efficient catalysts for the Michael reaction involving ethyl 2-oxocyclopentanecarboxylate, methyl 2-oxocyclopentanecarboxylate, ethyl 2-oxocyclohexanecarboxylate, methyl 1-oxoindane-2-carboxylate and ethyl 3-oxo-3-phenylpropanoate with 3-buten-2-one. The reaction without solvent is nearly quantitative and leads to the expected addition products. The catalyst can be easily recovered by filtration. From deuterium labeling experiments, a mechanism based on the basic properties of the calcium hydroxyapatite surfaces is proposed to explain their ability to catalyze the Michael reaction.

KEYWORDS: hydroxyapatite, Michael addition, catalyst

INTRODUCTION

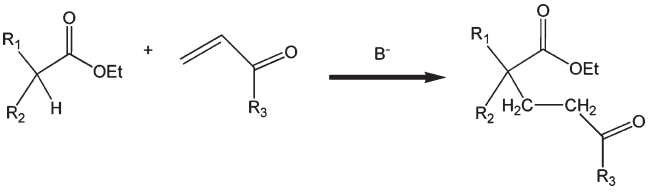
Michael reaction refers to the addition reaction of carbanion to unsaturated conjugated systems, such as enones, leading to the formation of a new C−C bond as shown in Scheme 1.[1,2]

In the first step of the reaction, the use of a strong base (B^-) is necessary to generate the organic anion. In the literature, the use of many organic or inorganic bases is reported.[3−5] In addition, various transition metal complexes acting as Brønsted bases are described.[6−8] In particular lanthanum derivatives appear to be efficient catalysts for the Michael reaction.[9] Recently, the "concerto metal catalysts" concept[10] has been introduced. According to this concept, phosphate apatites are only used as a mineral support for various transition metal moieties acting as catalysts, where the supporting solid permits a heterogeneous reaction, making the final separation step between the final products and the catalyst easy.[11,12] This approach has been used with success to carry various catalytic reactions, including the Michael addition using as catalysts:

a Lanthanum-modified fluorapatites in which the catalytic entity is described as a $[La^{III}(OH)]^{2+}$ moiety, replacing a Ca^{2+} cation at the apatite surface;[11,12]

b Vanadium apatites in which a $[PO_4]^{3-}$ group is substituted by $[VO_4]^{3-}$.[13,14] In this case, the catalytic activity is attributed to a $[VO_3OH]^{2-}$ moiety resulting from partial dissolution of the apatite in water used as the reaction medium. In these reactions, it has been postulated that the apatite surface has a weak basicity or acidity rendering it inert from a catalytic point of view. This hypothesis is not in agreement with the results obtained by Sebti et al.,[15] who described some addition reactions of (RS^-),[16] as well as the Knoevenagel reaction[17] on conjugated enones catalyzed by fluor- or hydroxyapatites, the properties of which should be related to the existence of acidic and basic Brønsted sites located on the surface of the apatites. Accordingly, natural phosphates or apatites, regardless of their low specific surfaces compared with zeolites, are good catalysts for many organic reactions.[15]

Scheme 1. The Michael Addition Reaction



In the field of catalysis, apatites (modified or not) are also used for oxidation reactions.[18−23] Mechanistic studies clearly show[24]

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Table 1. Composition and Specific Surface Area of the Catalysts

apatite	HAp1	HAp2	HAp3	HAp4	DAp4	FAp
SSA, $m^2 \cdot g^{-1}$	37.9	24.4	99.0	82.3	86.3	26.5
Ca/P, mole ratio	1.44	1.61	1.55	1.67	1.68	1.66
H_2O, % wt	4.0	2.4	6.3	5.5	5.5	1.2
CO_2, % wt	0.6	0.3	0.6	0.6	0.7	0
F, % wt	0	0	0	0	0	3.4

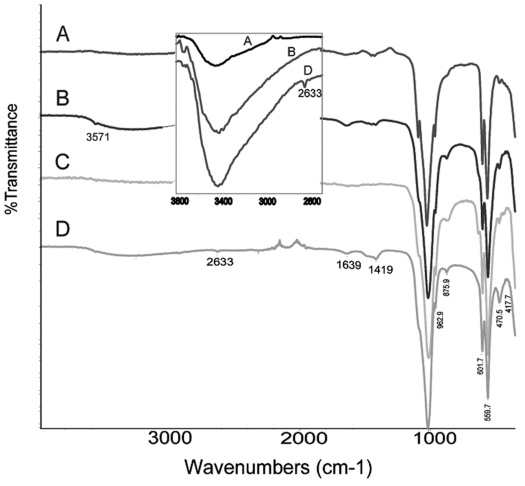


Figure 1. FTIR spectra of FAp (A), HAp4 (B), HAp1 (C), DAp4 (D).

that stoichiometric apatites act as a base catalyst. The surface basicity is related to the preparation mode of the material and especially correlated to the Ca/P ratio.[25]

Taking into consideration that the catalytic process requires that interactions occur between the substrate and the apatite surface, one can consider this to be a key point in understanding the mechanism of the reaction. Therefore, we decided to investigate the efficiency of apatites as catalysts for the Michael C−C addition, and we focused our attention on the reaction of ethyl 2-oxocyclopentanecarboxylate **1**, methyl 2-oxocyclopentanecarboxylate **2**, ethyl 2-oxocyclohexanecarboxylate **3**, methyl 1-oxoindane-2-carboxylate **4** and ethyl 3-oxo-3-phenylpropanoate **5** with 3-buten-2-one **6** using calcium apatites of different stoichiometries and specific surfaces.

EXPERIMENTAL DETAILS

Starting Materials. Ethyl 2-oxocyclopentanecarboxylate, methyl 2-oxocyclopentanecarboxylate, ethyl 2-oxocyclohexanecarboxylate, methyl 1-oxoindane-2-carboxylate, ethyl 3-oxo-3-phenylpropanoate 3-buten-2-one, *S*(−)-proline, D_2O, and hydroxyapatite HAp1 (Fluka, fast flow) were used as purchased.

Analysis. *Solution NMR Spectroscopy.* ^1H (300.13 MHz), $\{^1H\}^{13}C$ (75.5 MHz), and ^2H (46.07 MHz) NMR solution spectra were obtained at room temperature in 5 mm o.d. tubes on a Bruker Avance II 300 spectrometer equipped with a QNP probehead. Chemical shifts are referenced with respect to TMS ($SiMe_4$) using the solvent signals as secondary standard ($CHCl_3$, δ (^1H) = 7.26 ppm; $CDCl_3$, δ (^{13}C) = 77.16 ppm. The deuterium spectra were acquired without field-frequency lock (sweep-off mode) from reagent grade CH_2Cl_2 solutions; the doublet (^2J ($^1H-^2H$) ∼ 1.3 Hz) arising from natural abundance $CHDCl_2$ (δ (^2H) = 5.32 ppm) was easily identified after ∼400 transients. Nonconventional hardware configuration of the spectrometer allowed us to obtain the deuterium spectra; namely, the output of the transmitter was directed to the probehead lock coil.

Solid State NMR. ^1H and ^2H MAS NMR spectra were recorded at room temperature on a Bruker Avance 500 spectrometer (Larmor frequencies: $\nu_{^1H}$ = 500.2 MHz, $\nu_{^2H}$ = 76.8 MHz) using a 4 mm MAS probe. The ^1H and ^2H chemical shifts were externally referenced to adamantane and D_2O at 1.85 and 4.7 ppm, respectively.

FTIR spectra were recorded from pure products using a Bruker Tensor 27 equipped with a diamond ATR setup in the range from 400 to 4000 cm^{-1}.

Elemental analysis (H, C) of the organic product was performed on the SIARE (Université Pierre et Marie Curie).

Chemical composition of apatites was obtained using standard chemical methods for phosphorus and calcium; fluorine, by a fluorine-selective electrode CyberScan pH/Ion 510 electrode

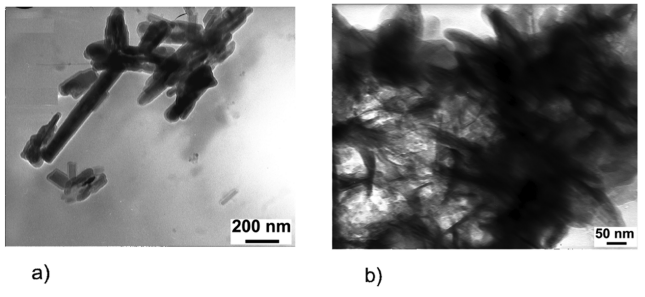
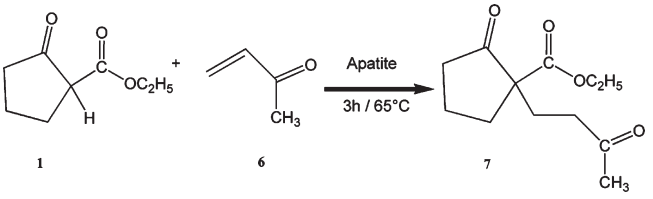


Figure 2. TEM images for HAp2 (a), HAp3 (b), HAp4 (c), and DAp4 (d).

Table 2. Converstion Degree for the Addition Product 7 Using Different Apatites

catalyst	% conversion
HAp1	90
HAp2	90
HAp3	90
DAp4	90
HAp4	90
FAp	65



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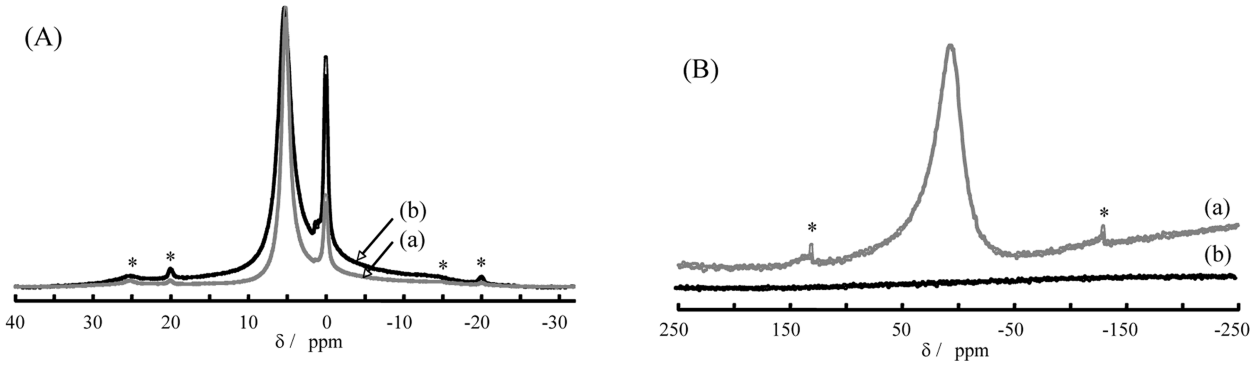

Figure 3. ^{1}H MAS NMR spectra (A) and ^{2}H MAS NMR spectra (B) of DAp4 (a) and HAp4 (b). The asterisk indicates spinning side bands.

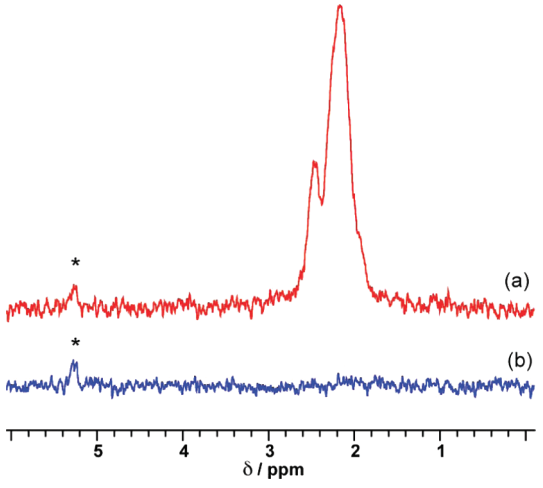

Figure 4. ^{2}H NMR spectra (46.07 MHz) of the reaction products **7** of Michael addition (**1** + **6**) using DAp4 (a) and HAp4 (b) as catalyst, respectively. Spectra acquired from CH_2Cl_2 solutions without field frequency lock. An asterisk indicates holds for the doublet arising from natural abundance (0.015%) $CHDCl_2$ (δ (^{2}H) = 5.32 ppm).

connected to a bench pH/ion/mV meter; carbonate content was determined using carbon analyzer ELTRA CS-580; and water content, by mass loss at heating up to 600 °C using thermal analyzer SETSYS (Setaram).

The SSA measurements were performed by the BET method (adsorptive gas N_2, carrier gas He, heating temperature 150 °C) using sorptometer EMS-53 and KELVIN 1040/1042 software (Costech International).

XR Powder diffraction (XRD) data were collected with a Bruker D5005 diffractometer (2θ 15−100°, step 0.02°, count time 15 s/step, Cu Kα radiation). The cell dimensions were determined using FullProf program. The median crystallite size was calculated from XRD patterns by the Scherrer equation.[26]

Transmission Electron Microscopy (TEM) observations were performed with a JEOL 100CXII transmission electron microscope at an accelerating voltage of 100 kV. The sample drops were deposited and dried on carbon-coated copper grids.

Apatites. Apatites FAp and HAp2 were synthesized according to ref 27; HAp3 was obtained in the presence of proline and K^+ ions at pH = 7.5, 25 °C; 1 M KOH solution was used for maintaining constant the pH value. HAp4 and DAp4 were synthesized by adding H_3PO_4 dropwise into CaO water (H_2O) or D_2O suspension at room temperature, mixed 24 h, centrifuged, and dried at 60 °C in vacuum.

Michael Reaction. Michael additions were performed under the same conditions for the five reagents **1**−**5**. The standard procedure is the following: 0.29 mL (2 mmol) of **1** with 0.24 mL (3 mmol) of **6** were mixed at 65 °C for 1−20 h in the presence of 65 mg (0.13 mmol) of catalytic material. After filtration through a polycarbonate membrane (0.4 μm, 25 mm), the filtrate was heated in a rotating evaporator to eliminate the 3-buten-2-one in excess. The resulting product, ethyl 2-oxo-1-(3-oxobutyl) cyclopentanecarboxylate **7**, was purified by column chromatography and identified. ^{1}H NMR ($CDCl_3$): δ 4.14 (q, J = 7.0 Hz, 2H), 2.71 (m, 1H), 2.5−2.2 (4H), 2.14 (s, 3H), 2.1−1.8 (m, 5H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 14.8, 20.4, 27.8, 30.5, 34.8, 38.6, 39.6, 59.8, 62.0, 172.1, 208.0, 215.5. IR-FT: 2970, 1746, 1712, 1162 cm^{-1}. Anal. calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.35; H, 8.25.

Using HAp2 as catalyst, kinetic measurements were performed for reagent **1**−**5** with **6**. For each experiment, a blank was performed under the same conditions.

RESULTS AND DISCUSSION

In Table 1 are reported the compositions and characteristics of calcium apatites used as catalysts: stoichiometric fluorapatite (FAp), hydroxyapatites (HAp) with different Ca/P ratios and specific surface areas (SSA) (HAp1, HAp2, HAp3, HAp4), and deuterium hydroxyapatite (DAp4).

FTIR spectra of FAp, HAp4, HAp1, and DAp4 reported in Figure 1 clearly show that all these synthesized materials possess an apatite structure with little carbonate and water content (absorption bands at 1400−1500 and 865 cm^{-1} and at 1645 cm^{-1}, respectively). Introduction of OD in apatite structure is detected by the vibration at 2633 cm^{-1} assigned to the OD stretching vibration and increase in absorption intensity at 457−470 cm^{-1} caused by OD librational mode.[28]

HAp3 in accordance with the TEM image has the biggest SSA (Figure 2) in comparison with samples HAp2, HAp4, and DAp4. The median particle size calculated from XRD patterns varies from 15 to 25 nm.

Table 2 shows the results of the Michael addition using the different apatites in the case of the addition of **1** on **6** in standard conditions after 3 h of reaction.

Table 2 clearly shows that hydroxyapatites (HAp1−HAp4) and the deuteroxyapatite DAp4, regardless of their different stoichiometries and specific surfaces, are good catalysts for this

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Scheme 2. Proposed Mechanism for the Deuterium Transfer from the Apatite Surface to the Final Addition Product

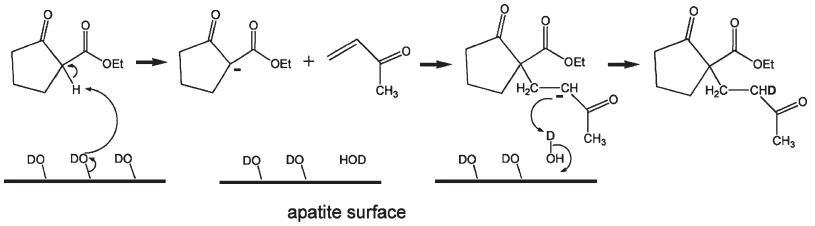
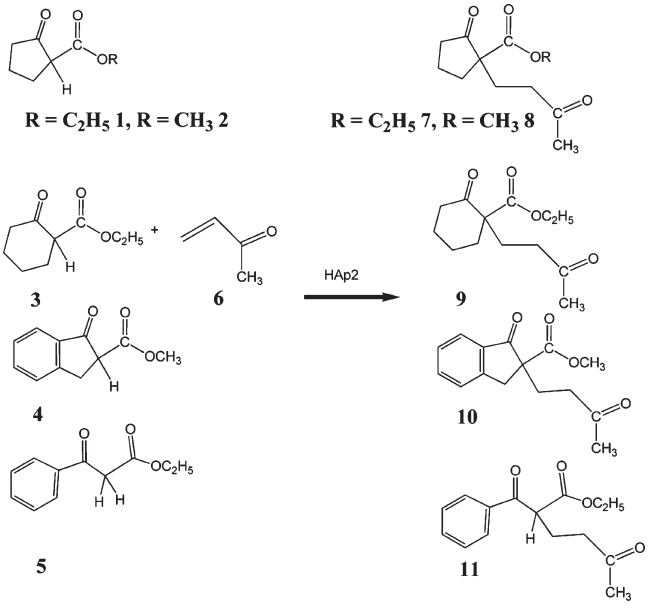


Table 3. Conversion Degree (%) in Addition Reactions 1−5 with 3-Buten-2-one Addition Using HAp2 as Catalyst at 65°C

reagents	time, h	final product	conversion, %
1	3	**7**	90
2	2	**8**	80
3	20	**9**	80
4	2	**10**	90
5	20	**11**	85



Michael addition. Fluorapatite (FAp) is less efficient (65%) than hydroxyapatites (90%). From these results, it appears that the surface of apatites is sufficiently basic to permit the abstraction of a proton from **1**, leading to a carbanion responsible for the formation of a new C−C bond by addition onto **6**. The presence of OH groups on the surface of the hydroxyapatites should be responsible for its basicity. In addition, the mineral surfaces of apatite often hold both positively and negatively charged groups at the same time, and their interaction may be the reason for the catalytic properties of apatites.[29,30] It is also very well-known that fluorapatites also possess some OH surface groups.[31] To establish the mechanism of the reaction on the surface, we have prepared under similar conditions a nondeuterated HAp4 and partially deuterated apatite DAp4. These two apatites are very similar in stoichiometry (Ca/P 1.67 and 1.68, respectively) and morphology (see Figure 2).

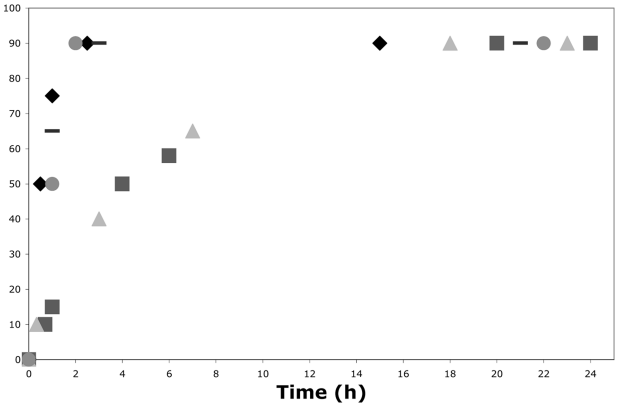


Figure 5. Conversion in addition product for the reaction of **1**♦, **2** ●, **3** ▲, **4** −, and **5** ■ with **6**.

^{1}H and ^{2}H solid-state MAS NMR spectra show the presence of hydroxyl and deuterioxyl on the surface of the material at 0.5 and 7.7 ppm, respectively (see Figure 3) These two apatites have the same catalytic efficiency toward the Michael addition (see table 2).

^{2}H NMR solution spectra of the reaction products clearly show that part of the deuterium atoms have been transferred from the partially deuterated apatite DAp4 to be incorporated into the CH_2 group adjacent to the ketone function of the 3-oxo-butyl chain of the final compound **7** (Figure 4).

This result indicates unambiguously that hydroxyl ions located on the surface of the apatite act as base to abstract the acidic proton of **1** leading to the formation of an anion and HDO, which can react further with the intermediate enol resulting from the addition of the anion on the conjugated ketone, leading to a partial introduction of deuterium atoms in the final product, as shown in Scheme 2. This result highlights that the surface of the hydroxyapatite acts as a basic catalyst able to lead to a carbanion by abstraction of an acidic proton.

In Table 3 are reported the results concerning the Michael addition involving reagents **1**−**5** with **6** catalyzed by apatite HAp2 under standard conditions. For all the reagents, the reaction occurs with good conversion and without formation of byproduct. The catalyst can be reused five times without significant loss of activity for **1**, **2**, and **4** and three times for **3** and **5**. Kinetic measurements (Figure 5) show that the reaction occurs significantly more quickly for **1**, **2**, and **4** than for reagents **3** and **5**. In all cases no reaction is observed without the presence of the apatite.

The reaction proceeds without solvent. The catalyst is easy to separate from the reaction mixture and, after two washings with an organic solvent (Et_2O or CH_2Cl_2), can be reused without any significant decrease in the catalytic activity.

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CONCLUSION

In this work, we demonstrated that calcium hydroxyapatites, which are inexpensive and simply obtained, are useful catalysts for the Michael C−C bond forming reaction with a good conversion rate. The catalyst is easily recovered by filtration. It is noteworthy that the absence of solvent in our reaction is a significant application in the field of green chemistry and for atom economy.

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