Sol–gel encapsulated cobalt(III) acetylacetonate for air oxidation of penicillin derivatives

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Abstract

The sulfoxides of penicillin derivatives are important pharmaceutical intermediates and can be prepared by air oxidation of corresponding sulfides catalyzed by cobalt(III) acetylacetonate ($Co(acac)_3$). However, when using the homogeneous catalyst, it is very difficult to separate the catalyst from product, which makes it impossible to reuse the catalyst directly. While the heterogeneous $Co(acac)_3$ encapsulated by sol–gel method can solve the problem. They have high selectivity and activity. They are leach proof and can be recycled in numerous runs. The sol–gel precursor can be tetraethoxysilane (TEOS) or tetrabutyl titanate (TBOTi) or triisopropyl aluminate (TIOAl). FT-IR and N_2 adsorption was employed to characterize the sol–gel catalyst. HPLC was used to analyze the conversion of penicillin derivatives.
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1. Introduction

Since the late of 1980s, there has been a worldwide enthusiasm over studying the application of sol–gel technique in immobilization of catalysts. The immobilization of transition metal complexes leads to systems that are able to combine the advantages of homogeneous and heterogeneous catalysis. There are two principle methods to immobilize metal complexes by sol–gel technique:

- directly physical doping procedure [1,2]; and
- functional modification of the ceramic matrix by copolymerization with organometallic alkoxides beforehand [3].

In general, the direct, physical doping procedure is simple and straightforward and it can convert a variety of soluble metal complexes into leach proof recyclable catalysts that are more stable under ambient conditions than their homogeneous analogues.

In our study, cobalt(III) acetylacetonate ($Co(acac)_3$) was physically encapsulated into SiO_2, Al_2O_3 or TiO_2 matrix separately by sol–gel method and characterized by FT-IR and N_2 adsorption. They were utilized in air oxidation of penicillin G derivatives to their corresponding sulfoxides. Sulfoxides of penicillin derivatives are important pharmaceutical intermediates and can be prepared by air oxidation of corresponding sulfides catalyzed by $Co(acac)_3$. However, when using the homogeneous catalyst [4], it is very difficult to separate the catalyst from product, which makes it impossible to reuse the catalyst directly. While the heterogeneous $Co(acac)_3$ encapsulated by

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sol–gel method can solve the problem. Furthermore they have high selectivity and activity. They are leach proof and can be recycled in numerous runs.

2. Experimental

2.1. Catalysts preparation

Homogeneous $Co(acac)_3$ is prepared by the method of Shalhoub [5].

2.1.1. The preparation of silica supported catalyst

A mixture of 15 ml tetraethoxysilane (TEOS) and 7.25 ml distilled water and 4 ml ethanol was stirred till completely homogeneous solution was obtained. Then the pH value was regulated to 2, 5 with sulfuric acid or 8 with ammonia solution separately and 0.2 g $Co(acac)_3$ was added. The pH was determined using a calibrated pHS-2C pH meter equipped with a E-201-C and 65-1AC combination pH electrode. The stirring was continued under 60 °C until gelation was completed. Then the catalyst was dried under 60 °C till a constant weight was obtained. Before use, the catalyst was washed with boiling water and then extracted with fresh dichloroethane in Soxhlet extractor. The exact $Co(acac)_3$ content of the sol–gel catalyst was determined by subtraction of the $Co(acac)_3$ content in the combined washings (analyzed by HPLC) from the original amount employed.

2.1.2. The preparation of titania supported catalyst

A mixture of 13.5 ml tetrabutyl titanate (TBOTi) and 6 ml ethanol and 0.2 g $Co(acac)_3$ was stirred. Then 2.5 ml distilled water adjusted to pH 5 with sulfuric acid beforehand was added dropwise. The stirring was continued under 60 °C until gelation was completed. The other procedures were the same as those for silica supported catalyst.

2.1.3. The preparation of alumina supported catalyst

A mixture of 9.3 g triisopropyl aluminate (TIOAl) and 0.2 g $Co(acac)_3$ and 30 ml isopropyl alcohol was stirred. Then 2.12 ml distilled water in 10 ml isopropyl alcohol adjusted to pH 5 with sulfuric acid beforehand

was added dropwise. The other procedures were the same as those for titania supported catalyst.

### 2.2. Characterization of the entrapped catalyst

FT-IR spectra were recorded between 400 and $4000 \, cm^{-1}$ using a Bruker Vector 22 spectrophotometer. Analysis was performed by grinding samples together with KBr.

Nitrogen adsorption–desorption measurements were performed at 77 K on a Micromeristics ASAP 2010 sorptometer. Prior to measurement, all samples were dried under 110 °C for 3 h, and then degassed for 15 h at 110 °C. Surface areas were determined from the BET equation, while pore volumes were determined from the BJH equation.

2.3. Air oxidation of penicillin derivatives

Penicillin G p-methoxybenzyl ester (PGPMB) was prepared according to [6] and penicillin G diphenylmethyl ester (PGDPM) by the method of [7]. The air oxidation of the sulfides to corresponding sulfoxides was carried out with reference to the procedure reported by Tanaka et al. [4] with some changes (Scheme 1). A mixture of substrate 2.5 mmol, a sol–gel catalyst (0.006 g homogeneous $Co(acac)_3$ contained) and isobutylaldehyde 8.75 mmol in 1,2-dichloroethane 20 ml was stirred under air atmosphere (balloon) at room temperature and atmospheric pressure. TLC (ethylacetate/cyclohexane = 1:1) was employed to monitor the degree of reaction and HPLC to analyze the conversion of PGPMB or PGDPM. A Shimadzu LC-10AT VP Liquid Chromatograph with an ODS-C_{18} reversed phase stainless steel HPLC column (10 μm, 150 mm × 4.6 mm i.d.) was used. The mobile phase is 85% (v/v) methanol with the flow rate at $1 \, ml \, min^{-1}$. The detector wavelength was set at 270 nm. All measurements were taken at room temperature.

After the reaction completed, the mixture was filtered, the sol–gel encapsulated catalyst can be reused next time, the filtrate was washed with 4% $NaHCO_3$ aqueous solution and the organic layer was dried over anhydrous $MgSO_4$. After most of the solvent was distilled under reduce pressure, 2 ml methanol was added, then the sulfoxide (PGPMBO or PGDPMO) was crystallized.
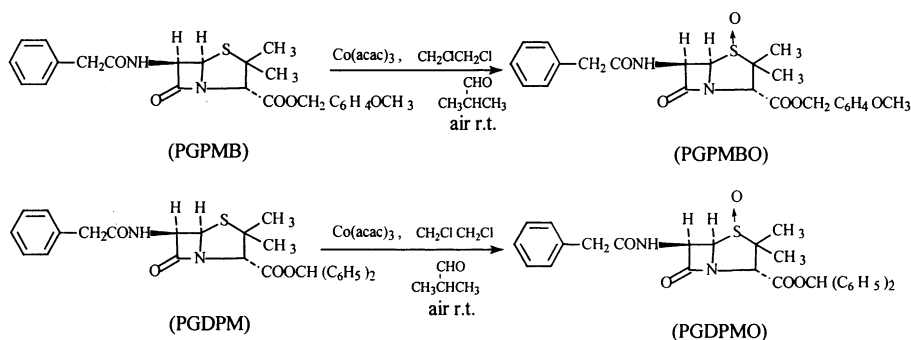
Scheme 1.

For the product, NMR spectra were determined with a Bruker AC-P 200 (200 MHz for proton and 50 MHz for carbon-13), FT-IR spectra were obtained with a Bruker Vector 22 spectrophotometer in wavenumber (cm^{-1}), and melting point was obtained with an XDC-1 Micro Melting Point Apparatus.

2.3.1. p-Methoxybenzyl 6 β-(2-phenylacetamido)penicillanate 1-oxide (PGPMBO)

IR (KBr): 3360, 2961, 1796, 1745, 1688, 1515, 1252, 1206, 1035 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (s, 3H), 1.58 (s, 2H), 4.58 (s, 1H), 4.93 (d, J = 4.6 Hz, 1H), 5.18 (ABq, J = 11.7 Hz, 2H), 6.00 (dd, J = 4.6, 10.3 Hz, 1H), 6.84 (m, 2H), 7.03 (d, J = 10.3 Hz, 1H), 7.20–7.40 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.2, 19.2, 43.2, 55.1, 56.2, 66.0, 67.6, 75.2, 76.5, 114.0, 126.7, 127.2, 128.7, 129.1, 130.6, 133.8, 159.9, 167.6, 170.5, 173.4; mp 149 °C (lit. [8] 149 °C).

2.3.2. Diphenylmethyl 6 β-(2-phenylacetamido)penicillanate 1-oxide (PGDPMO)

IR (KBr): 3400, 1806, 1750, 1673, 1497 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.85 (s, 3H), 1.64 (s, 3H), 3.56 (2H), 4.69 (s, 1H), 4.92 (d, J = 4 Hz, 1H), 6.0 (dd, J = 10, 4 Hz, 1H), 7.0 (1H), 7.25–7.36 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 19.4, 43.4, 56.4, 66.2, 75.4, 76.4, 126.8, 127.4, 127.7, 128.3, 128.6, 128.9, 129.2, 133.6, 138.7, 139.0, 166.9, 170.6, 173.4; mp 129 °C (lit. [8] 128.5–130 °C); anal. calcd. for $C_{29}H_{28}N_2O_5S$: C, 67.42%; H, 5.46%; N, 5.42%;

S, 6.21%; found: C, 67.22%; H, 5.49%; N, 5.22%; S, 6.06%.

3. Results and discussion

3.1. Catalytic properties of sol–gel encapsulated catalysts

During the reaction, TLC was used to monitor the degree of reaction. After the end of the reaction, HPLC was employed to analyze the conversion of PGPMB or PGDPM directly in the mixture, which can reflect the actual conversion regardless of the loss during after treatment process. From TLC and HPLC, we can see that when the air oxidation of PGPMB proceeds for 2.5 h and of PGDPM for 1.5 h, the selectivity of the reaction to PGPMBO or PGDPMO is nearly equal to 100%, indeed, no appreciable other oxidation products were obtained. The HPLC results list in Table 1. From the data, we can see that whichever the matrices was used, SiO_2, TiO_2 or Al_2O_3, the catalysts have good to excellent activity.

Using sol–gel encapsulated $Co(acac)_3$, the after treatment is very simple and very pure product can be obtained easily. Moreover, the activity was improved compared with the homogeneous one. For the air oxidation of PGPMB, the turnover frequency (i.e. the average amount of substrate molecules converted by one catalyst molecule during unit time) is 46.3 h^{-1} when using sol–gel entrapped $Co(acac)_3$ but only 3.5 h^{-1} while using homogeneous one [4].

Table 1
Conversion of the air oxidation of penicillin derivatives catalyzed by a variety of sol–gel catalysts

Substrate	Matrix				
	SiO_2 (%)			Al_2O_3 (%)	TiO_2 (%)
	1[a]	2[b]	3[c]		
PGPMB	0	98.8	90.0	96.7	91.2
PGDPM	0	97.7	90.4	95.3	92.6

A mixture of penicillin derivatives (2.5 mmol) and sol–gel entrapped catalyst (0.006 g homogeneous Co(acac)$_3$ contained) and 8.75 mmol isobutylaldehyde in 1,2-dichloroethane (20 ml) was stirred under air atmosphere (balloon) at room temperature for 2.5 h for PGPMB and 1.5 h for PGDPM. PGPMB: penicillin G *p*-methoxybenzyl ester, and PGDPM: penicillin G diphenylmethyl ester.

[a] The sol–gel catalyst was prepared under pH 2.
[b] The sol–gel catalyst was prepared under pH 5.
[c] The sol–gel catalyst was prepared under pH 8.

Because the SiO_2 encapsulated Co(acac)$_3$ has excellent physical rigidity, while either TiO_2 or Al_2O_3 entrapped catalyst shows little physical rigidity, so the emphasis was put on the catalysts using SiO_2 as matrix. The results stated that the catalyst entrapped in SiO_2 prepared under pH 2 (catalyst 1) has no activity, the one under pH 8 (catalyst 2) can catalyze finely though only a very small amount of Co(acac)$_3$ has

been actually encapsulated for most of which has been washed out. The one under pH 5 (catalyst 3) can not only entrap a larger amount of Co(acac)$_3$ that no appreciable amount of it can be washed out, but also has very good activity. Both the last two are practically leach proof, and could be utilized repeatedly in numerous runs. Catalyst 3, without any further treatment, could be recycled in more than 15 runs with hardly any loss in activity.

3.2. Physical properties of sol–gel encapsulated catalysts

3.2.1. FT-IR spectroscopy

Figs. 1–3 gives the FT-IR spectroscopy of neat and sol–gel encapsulated Co(acac)$_3$ and respectively the matrix SiO_2, Al_2O_3 and TiO_2 prepared by sol–gel method, from which some conclusions can be drawn as follows:

(1) The bands at 1574, 1519, 1381, 675, 635, 466 cm^{-1} which are characteristic of Co(acac)$_3$ in Fig. 1(c) can be apparently identified in Fig. 1(b). No appreciable change of displacement has been found, which suggests that Co(acac)$_3$ is physically encapsulated in the matrix without any chemical action.
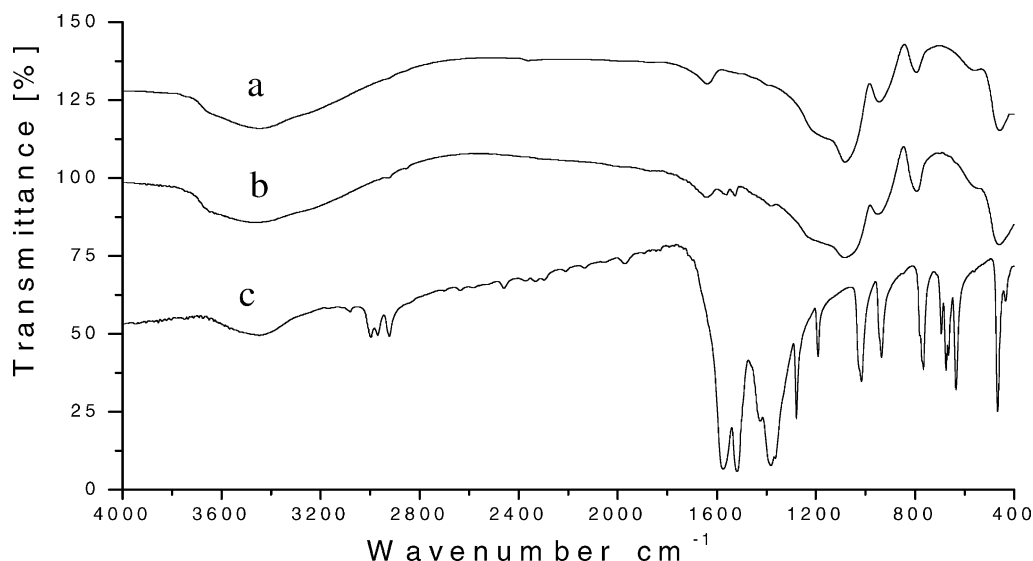

Fig. 1. FT-IR spectra of (a) SiO_2 prepared by sol–gel method at pH 5 and (b) sol–gel entrapped Co(acac)$_3$ in SiO_2 at pH 5 and (c) neat Co(acac)$_3$. Curves (a) and (b) are arbitrarily shifted upward.
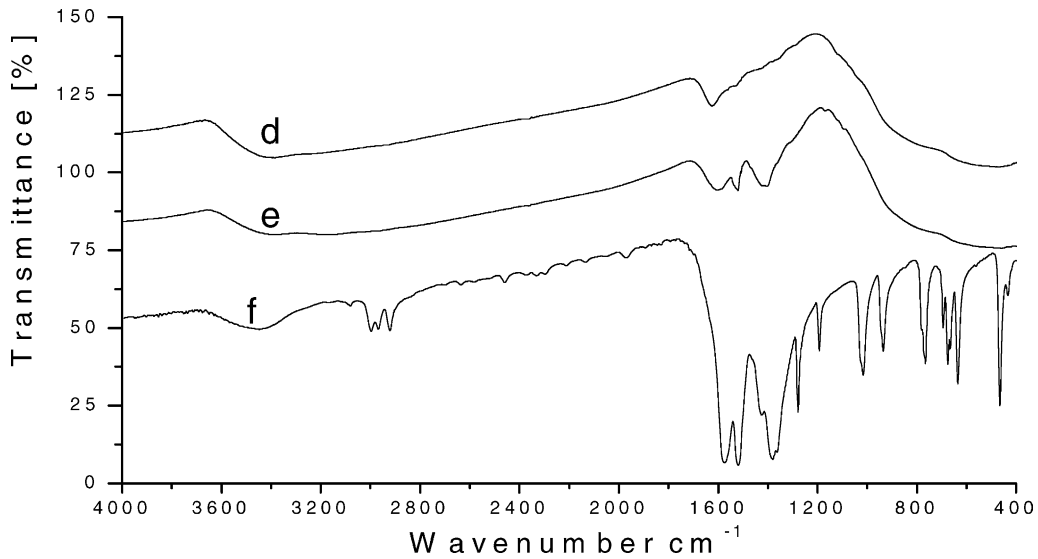
Fig. 2. FT-IR spectra of (d) TiO$_2$ prepared by sol–gel method at pH 5 and (e) sol–gel entrapped Co(acac)$_3$ in TiO$_2$ at pH 5 and (f) neat Co(acac)$_3$. Curves (d) and (e) are arbitrarily shifted upward.
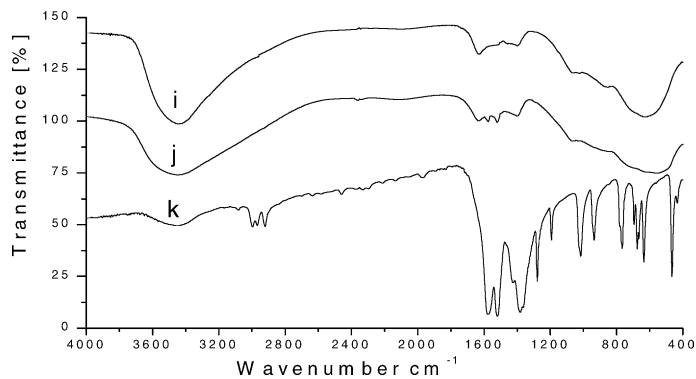

Fig. 3. FT-IR spectra of (i) Al$_2$O$_3$ prepared by sol–gel method at pH 5 and (j) sol–gel entrapped Co(acac)$_3$ in Al$_2$O$_3$ at pH 5 and (k) neat Co(acac)$_3$. Curves (i) and (j) are arbitrarily shifted upward.

Table 2
N$_2$ adsorption–desorption results of materials prepared by sol–gel method

Entry	Precursor	Co(acac)$_3$/precursor (mol%)	pH	Surface area[a] (m^2 g^{-1})	Pore volume[b] (ml g^{-1})	Average pore diameter[c] (nm)
1	TEOS	0	5	0.25	0.0003	5.23
2	TEOS	0.00838	2	446	0.232	2.08
3	TEOS	0.00838	5	268	0.138	2.05
4	TEOS	0.00838	8	122	1.055	34.5
5	TBOTi	0.00838	5	325	0.180	2.21
6	TBOAl	0.00838	5	353	0.314	3.56

TEOS, tetraethoxysilane; TBOTi, tetrabutyl titanate; and TIOAl, triisopropyl aluminate.

[a] Calculated from the BET equation.
[b] Calculated from the BJH equation.
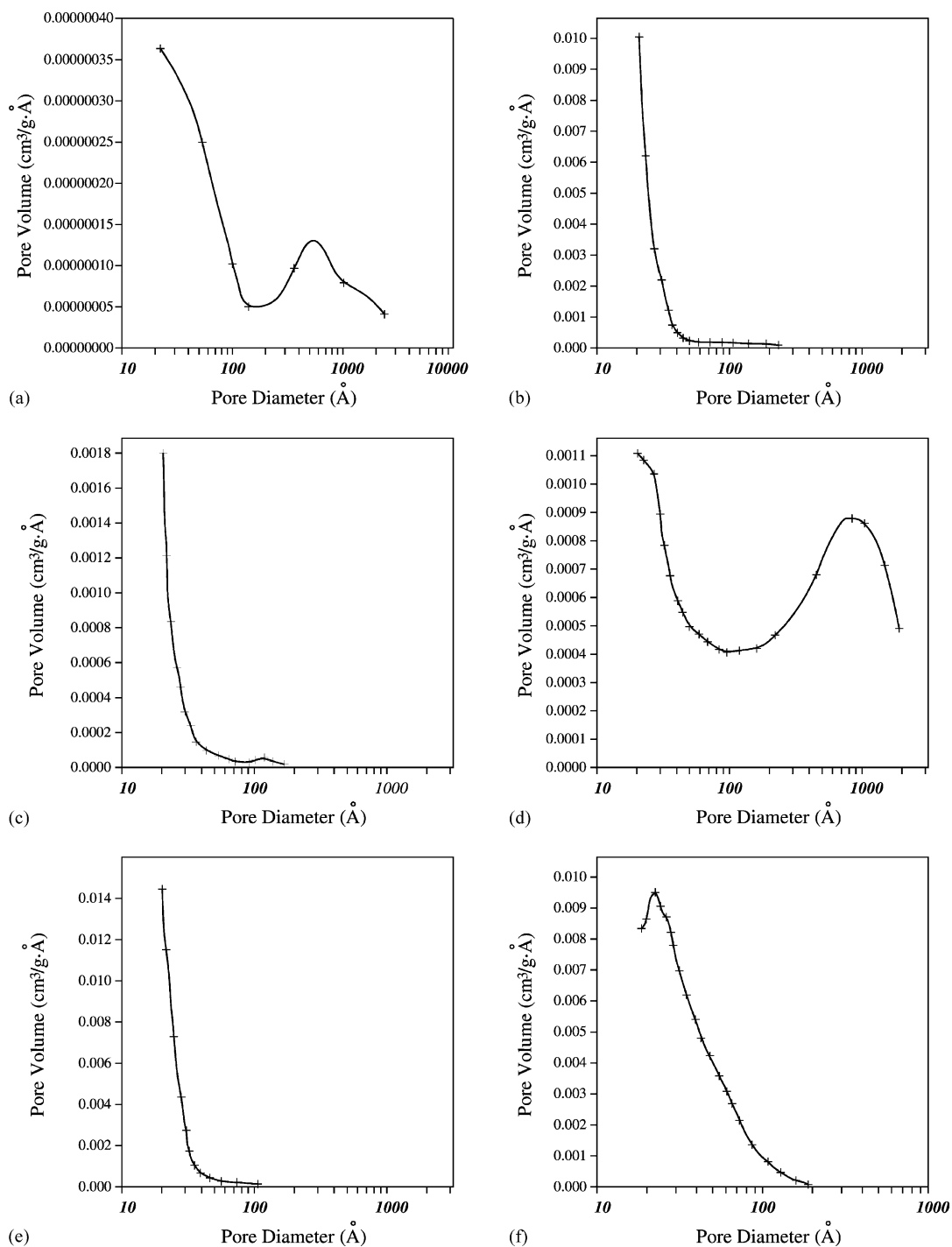[c] Average pore diameter = 4 × pore volume/surface area.

Fig. 4. Pore size distribution of the catalysts. (a) SiO_2 prepared by sol–gel method at pH 5, (b)–(d) sol–gel entrapped $Co(acac)_3$ in SiO_2 at different pH values, (b) pH 2, (c) pH 5 and (d) pH 8, (e) sol–gel entrapped $Co(acac)_3$ in TiO_2 at pH 5, (f) sol–gel entrapped $Co(acac)_3$ in Al_2O_3 at pH 5.

(2) The high intensity of the siloxane bands ($1087\,cm^{-1}$) along with the very weak Si–OH at $940\,cm^{-1}$ in Fig. 1(a) and (b) indicates that the polymerization is extensive and a three dimensional network is formed.

(3) Similar results can be found in Figs. 2 and 3.

In a word, by sol–gel technology, the matrix such as SiO_2, Al_2O_3 and TiO_2 with a three dimensional network can be obtained and $Co(acac)_3$ has been encapsulated physically into them.

3.2.2. N_2 adsorption

Table 2 presents the BET surface area, pore volume and average pore diameter of sol–gel materials.

Employing sol–gel technique, highly porous materials are obtained with pore size distributions in the range of 2–10 nm and with surface areas in the range of several hundreds of $m^2\,g^{-1}$ [9]. But we can see a very strange phenomenon from Table 2 that the sol–gel matrix SiO_2 prepared at pH 5 has a very small surface area and pore volume, whereas all the others encapsulated with $Co(acac)_3$ at different pH values have larger surface areas and pore volumes, just the opposite to our expectancy. Furthermore the surface area, pore volume and average pore diameter of the sol–gel encapsulated materials above are the same as that reported by Mayo et al. [10] in quantitative level, so the measurement method is reliable. Since the nature of the entrapment is very complex and is yet not fully understood, we have no ready theory to cite. We think the reason may be that the introduction of foreign particles has changed the environment of pore formation, which gives rise to the better pore shape.

As for the entries 2, 3 and 4, everything else being held constant, the surface area falls and pore volume rises with increasing pH, which are in keeping with those reported in [11].

Fig. 4 presents the pore size distribution of the catalysts. When pH 2 or 5, whether the precursor is TEOS or TBOTi or TIOAl, the catalysts have micropore structures and pore size distribution is very narrow. However, when pH 8, the distribution of pore diameter is very broad from 2 to 100 nm which may be the

reason for bad encapsulation effect of $Co(acac)_3$. As for the fact that PGPMB can not be oxidized by air using sol–gel entrapped $Co(acac)_3$ prepared under pH 2, the reason may be that the $Co(acac)_3$ was decomposed when dried by heating under such strong acid condition.

From the above stated, different sol–gel process conditions lead to different pore structure of sol–gel materials, so controlling the conditions during sol–gel procedure can shape the desired pore structure according to the dopant molecules and other specified requirements.

4. Conclusion

In our study, $Co(acac)_3$ was successfully encapsulated by physical doping procedure of sol–gel method under very mild conditions. Either SiO_2, TiO_2 or Al_2O_3 can be used as matrix. The sol–gel entrapped $Co(acac)_3$ catalysts are leach proof and recyclable with high selectivity and activity for air oxidation of penicillin derivatives. Furthermore, maybe they can be used to desulfurize in environmental protection, which is under research.

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