Sol–Gel Glass with Enantioselective Catalytic Activity

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Cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] entrapped in a silicon based sol–gel glass matrix induces catalytic hydrocyanation of benzaldehyde to (*R*)-mandelonitrile with e.e. ≥ 94%.

The advent of the sol–gel process for the preparation of sol–gel glass materials having a diversity of physical properties is an important development in material science and porous glass materials may be obtained by various methods[1,2,3]

In principle, with a properly selected dopant, an aerogel may be used as a chemically active catalyst, the activity of which is due to the immobilized compound. This was recently demonstrated,[4] using sol–gel encapsulated transition metal quaternary ammonium salts which exhibited catalytic properties, superior in some cases relative to the naked catalysts.

We now report the enantioselective catalytic activity of an entrapped organic molecule in a sol–gel matrix. The chiral sol–gel catalyst was prepared by polymerizing $Si(OMe)_4$ and $MeSi(OMe)_3$ with H_2O in the presence of the soluble cyclopeptide, cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] (CPH) in MeOH. The gel was dried with CO_2 at its critical point in a standard critical point drying chamber. Several washing cycles were required in order to completely replace the reaction solvent with the liquid CO_2. Porous glass material (aerogel) having a bulk density of *ca.* 0.1 g CO apparently retaining its original gel network structure, was obtained. It is assumed that the cyclopeptide has been entrapped in the sol–gel matrix. In the IR spectrum, measured in a pressed aerogel disk, Fig. 1, amide bands I (1638–1663 cm^{-1}) and II (1460 cm^{-1}) of the entrapped cyclopeptide are clearly visible and differ only slightly from those of the non-encapsulated peptide measured in KBr. The strong O–H stretching band indicates non-polymerized free hydroxy groups of the glass. The dominant band in the region of 1000–1200 cm^{-1} is due to Si–O stretching vibration.

Furthermore, the optical activity of a clear glass monolith, doped with CPH and prepared by slow drying of the $Si(OMe)_4$ gel at 40 °C for 6 days, was determined as $[\alpha]_D^{25} = -278$ (*c* 5.06, glass).†

Conventional drying of the gel resulted in a dense non-porous glass material (xerogel) with diminutive catalytic and enantioselective activity.

Cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] is a known efficient asymmetric hydrocyantion catalyst.[5] Remarkably, maximum chemical and enantioselective activity were attained when the cyclopeptide itself is in a gel form.[6] Consequently its mode of drying was found to be crucial for its activity.[7] Reported[8] covalent immobilization of CPH to various supports led in all cases to hydrocyanation reactions with e.e. <30%.

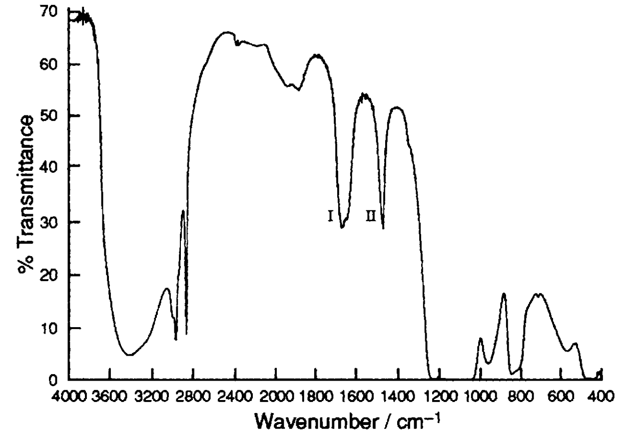

Fig. 1 IR transmittance spectrum of cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl], encapsulated in Si-based aerogel as a pressed disk

The hydrocyanation of benzaldehyde with HCN in toluene in the presence of the chiral aerogel material described above, led to the formation of (*R*)-(+)-mandelonitrile‡ in good yield and excellent enantioselectivity, under optimised reaction conditions (Table 1). In a control experiment with an aerogel devoid of the catalyst, no mandelonitrile could be detected.

Runs 1–4 exhibit excellent enantioselectivity and good yields. Raising the temperature to 20 °C (Run 4) accelerated the reaction without affecting the enantioselectivity. Raising the water concentration (Runs 5 and 6) decreased both the chemical yield and the enantioselectivity. This is attributed to formation of aerogels with a higher degree of cross linking and density, locking in some of the active CPH molecules.

The results from recycling the encapsulated catalyst are disappointing (Runs 1–4). Various separation techniques of the solid glass from the liquid reaction solution were attempted (see Table 1), however, both the yield and e.e. stayed low, although recycling of the solid aerogel catalyst by decanting the reaction solution (Run 3) seems promising. In view of the fact that only little leaching (6.8–14%) of the catalyst had occurred (*vide infra*), the reason for this behaviour is still obscured and is currently under study. Obviously, a solution to this problem is highly desirable for obtaining an efficient recyclable catalyst.

By noting the effect of the amount of water on the extent of the enantioselectivity, we have rationalized that using aerogel originating from $MeSi(OMe)_3$ monomer will result in less cross-linking of the silicate polymer. The results of hydrocyanation of benzaldehyde with an aerogel prepared by doping a 1 : 1 molar mixture of $MeSi(OMe)_3$ and $Si(OMe)_4$ with CPH are given in Table 2.

The yields of mandelonitrile are high and relatively constant throughout runs 7–9 (1st cycle). Again, the sensitivity of the e.e. values to the amount of water used in the gelation step is evident. The second hydrocyanation cycle does become

Table 1 Hydrocyanation of benzaldehyde with cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] encapsulated in a $Si(OMe)_4$ aerogel.[a]

	1st hydrocyanation cycle					2nd hydrocyanation cycle		
Run No.	Water/g (for gelation)	T/°C	*t*/h	Yield (%)	E.e. (%)	Recycling method	Yield[c] (%)	E.e. (%)
1	0.40	5	27	80	94	Filtration	65	3
2	0.40	5	27	74	98	Centrifugation	50	7
3	0.40	5	27	78	98	Decantation	48	32
4	0.40	20	5	83	94	Filtration	72	1
5	0.60[b]	20	8	66	23			
6	0.80	20	8	52	4			

[a] Cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] (60 mg, 0.21 mmol), methanol (5.5 ml), tetramethoxysilane (2.5 ml, 16.9 mmol) and water, in a glass vial were stirred and heated with a fan to give a stable homogeneous solution. After ageing for 3–7 days at ambient temp. a clear, stable gel was obtained, which was dried with CO_2 at its critical point. The resulting aerogel was stirred in a solution of benzaldehyde (0.9 g, 8.48 mmol) and HCN (0.7 ml, 17.8 mmol) in dry toluene (10 ml). [b] Stoichiometric amount. [c] The hydrocyanation reactions were terminated after the number of hours specified in column 4.

Table 2 Hydrocyanation of benzaldehyde with cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] encapsulated in a $Si(OMe)_4$–$MeSi(OMe)_3$ aerogel.[a]

Run no.	Water/g (for gelation)	1st hydrocyanation cycle yield (%)	E.e. (%)	2nd hydrocyanation cycle[c] yield(%)	E.e. (%)
7	0.40	85	90	60	34
8	0.53[b]	81	57	36	29
9	0.66	89	33	31	17

[a] Cyclo[-(*S*)-phenylalanyl-(*S*)-histidyl] (60 mg; 0.21 mmol), MeOH (5.5 ml), tetramethoxysilane (1.25 ml; 8.45 mmol), methyltrimethoxysilane (1.20 ml; 8.45 mmol) and H_2O were stirred in a glass vial and heated with a fan to give a stable homogeneous solution. After 24 h at ambient temp. a clear and stable gel was obtained, which was dried with CO_2 at its critical point. The resulting aerogel was stirred in a solution of benzaldehyde (0.9 g, 8.48 mmol) and HCN (0.7 ml 17.8 mmol) in dry toluene (10 ml) at ambient temp for 8 h. [b] Stoichiometric H_2O quantity. [c] Recycling by filtration of the catalyst.

sensitive to the amount of water used in the gelation step. Although the enantioselectivity also dropped in the second cycles, it holds better than in Runs 1 and 4.

The leaching problem was addressed as follows. The final hydrocyanation reaction solution was separated from the aerogel and washed with phosphoric acid 2 mol dm^{-3} to extract any leached peptide. The washings were concentrated to a known volume and the amount of peptide present was determined by measuring its optical rotation. In several such determinations, leaching of 6.8–14% of the CPH from the glass was found. However, leaching values of $<1\%$ were found in the second hydrocyanation cycles. This implies that the relatively high leaching values found in the first cycles are due to loosely glass bound CPH molecules.

In a separate experiment, imitating plausible catalysis by the leached catalyst, it was demonstrated that the observed results (Tables 1 and 2) cannot be accounted for on the basis of the leached peptide. Thus, hydrocyanation of benzaldehyde in toluene (no aerogel) using a CPH/benzaldehyde ratio of 0.011, based on 16.7% of leached catalyst, under conditions identical with the aerogel experiments, resulted in only 8% yield of the (+)-mandelonitrile with 81% e.e. after 8 h at 25 °C.

A CPH : benzaldehyde ratio identical with that used in Table 1 (no aerogel) resulted in 85% yield of (+)-mandelonitrile with 82% e.e. These last results are slightly inferior to those obtained with the entrapped aerogel catalyst, but in the present case, the isolated catalyst (phosphoric acid extraction) had to be reactivated by critical point drying with CO_2 for recycling.

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Footnotes

† For comparison $[\alpha[_D = -135$ (*c* 0.103, H_2O).

‡ The extent of the enantioselectivity was determined by optical rotation measurements; (*R*-(+)-mandelonitrile, $[\alpha]_D = +43.75$ (benzene).[9] It should be noted that cyclo[·(*S*)-phenylalanyl·(*S*)-histidyl] possesses specific rotation of opposite sign (see footnote †) and therefore could not contribute to the experimentally observed e.e. of the hydrocyanation process.

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