Optically Active Polyamides Having (−)-Anti Head-to-Head Coumarin Dimer Component. 3. Chiral Recognition Ability

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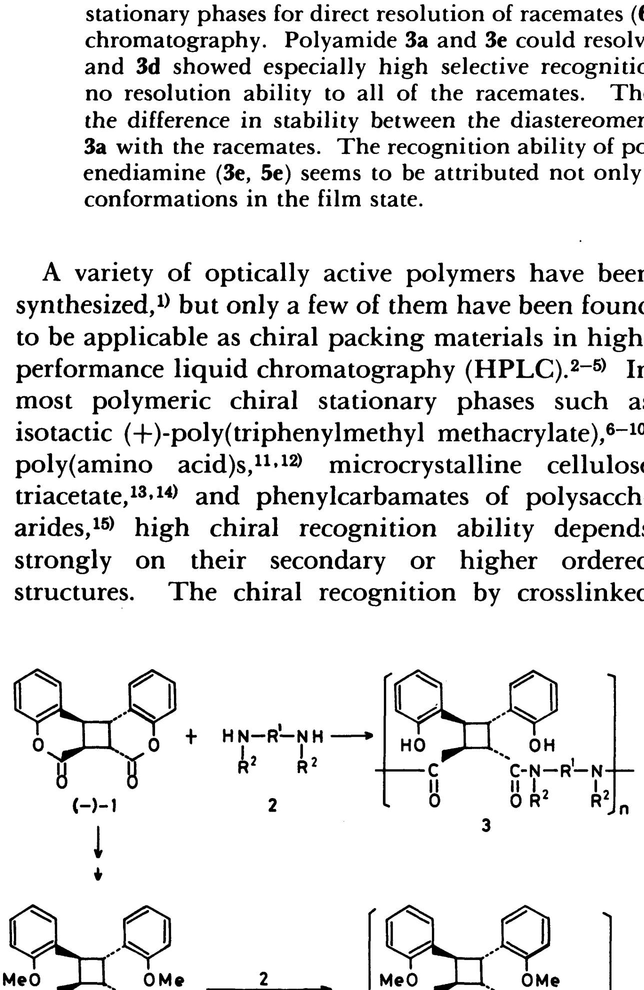
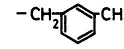
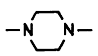
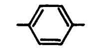
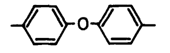
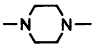
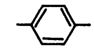
Optically active polyamides (**3a—f**) and *O*-methylated polyamides (**5a,d,e**), derived from (−)-anti head-to-head coumarin dimer [(−)-**1**], were absorbed on macroporous silica gel particles and used as chiral stationary phases for direct resolution of racemates (**6—13**) having aromatic moiety by high-performance liquid chromatography. Polyamide **3a** and **3e** could resolve **6—10** and **9—13**, respectively (separation factor $\alpha>1.03$), and **3d** showed especially high selective recognition ability to **7** ($\alpha=1.63$). However, **3c,f** and **5a** showed no resolution ability to all of the racemates. The high recognition ability of **3a** is attributed mainly to the difference in stability between the diastereomeric complexes formed by the simultaneous interaction of **3a** with the racemates. The recognition ability of polyamides derived from piperazine (**3d, 5d**) and 1,4-phenylenediamine (**3e, 5e**) seems to be attributed not only to the simultaneous interaction but also to their ordered conformations in the film state.

A variety of optically active polymers have been synthesized,[1] but only a few of them have been found to be applicable as chiral packing materials in high-performance liquid chromatography (HPLC).[2–5] In most polymeric chiral stationary phases such as isotactic (+)-poly(triphenylmethyl methacrylate),[6–10] poly(amino acid)s,[11,12] microcrystalline cellulose triacetate,[13,14] and phenylcarbamates of polysaccharides,[15] high chiral recognition ability depends strongly on their secondary or higher ordered structures. The chiral recognition by crosslinked polyacrylamides with chiral pendant group is known to be due to the contribution of hydrogen-bonding.[2,16] For low-molecular-weight chiral stationary phases, chiral recognition requires at least three simultaneous interactions between the chiral stationary phase and one of the enantiomer of racemate.[17–23]



Polyamide	R¹	R²	η_{inh}
3a	$-(CH_2)_6-$	H	0.88
3b	$-(CH_2)_6-$	CH_3	0.35
3c		H	0.63
3d			0.51
3e		H	0.36
3f		H	0.31
5a	$-(CH_2)_6-$	H	1.01
5d			1.00
5e		H	0.50

Previously, we reported the synthesis of a series of optically active polyamides (**3a—f**), composed of (−)-anti head-to-head coumarin dimer component [(−)-**1**] subunit, and showed that by varying the rigidity of diamine component the ordered conformations of these polyamides in solutions can also be controlled to some extent.[24,25] Moreover, we reported briefly that some of polyamide **3a—f**, depending on the structure of diamine component, are applicable as chiral packing materials for direct HPLC resolution of racemates.[26] But the different chiral recognition behavior of **3a—f** could not be explained merely by the simultaneous interactions between the racemates and the interaction sites in the polyamides, i.e. phenolic hydroxyl group, aromatic group, and amide linkage, and/or the ordered conformation in solutions. In order to elucidate the recognition mechanism, we also synthesized *O*-methylated polyamides **5** and investigated the chiroptical properties of **3** and **5** in the film state,[27] which is considered to be analogous to the coated state for recognition process. Similar to the results obtained in solutions,[25] the conformations in the film state also depended strongly on the structure of diamine components. Polyamides derived from piperazine (**3d, 5d**) and aromatic diamines (**3e,f** and **5e**) formed ordered conformation, while other polyamides existed in random conformation in the film state. In this paper we wish to report in detail the chiral recognition ability of **3** and **5**, and possible correlation between the chiral recognition ability and the simultaneous interaction or ordered conformation in the film state.

Experimental

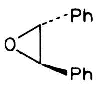
General. Synthesis, characterization, and chiroptical properties of optically active polyamides **3** and **5**, derived from (−)-anti head-to-head coumarin dimer, were described in previous papers.[25,26] Racemates **6**—**13** and diphenylsilane coupler were of commercial origins.

Chromatographic Resolution of Racemates. Direct chromatographic separation of racemates was accomplished on a Shimadzu LC-5A HPLC system equipped with a Toyo Soda UV-8-II detector and, in some cases, a Jasco DIP-181 polarimeter detector at room temperature. The eluent was a mixture of hexane and 2-propanol, but in some cases methanol or ethanol only was used. The flow rate was 0.5 ml $\mathrm{min^{-1}}$.

Macroporous silica gel particles (4.0 g) (Merck LiChrospher SI 1000),[28] pretreated with diphenylsilane coupler, were coated with about 25 wt% of polyamides in DMAc solution (ca. 0.85 g/8 ml) and then dried in vacuo at 60 °C for 5 h. The polyamide-coated silica gel thus obtained was packed in a stainless steel column [25×0.46 (i.d.) cm] by the slurry method. Theoretical plate number of the columns bearing **3a**—**f** for benzene were 2600, 2800, 4200, 2100, and 2200, respectively. Theoretical plate number of the columns bearing *O*-methylated polyamide **5a**, **5d**, and **5e** were 1600, 2200, and 1150, respectively. The void volume was estimated to be about 3.0 ml with a trace amount of water in methanol.

Results and Discussion

It is well-known that one of the driving forces for chiral recognition is a simultaneous interaction between the functional groups in a stationary phase and a solute.[3] Optically active polyamides **3** and **5** possess possible interaction sites for chiral recognition, i.e. phenolic hydroxyl (methoxyl) group, aromatic group, and amide linkage. Then, we expected that racemates **6**—**13**, having an aromatic group and a site for hydrogen-bonding, would be resolved by these polyamide-coated silica gel columns.



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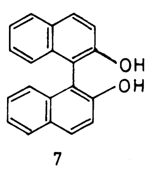

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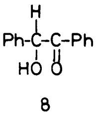
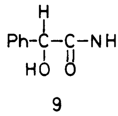
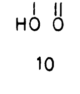

$\mathrm{Ph{-}\underset{HO}{\overset{H}{C}}{-}\underset{O}{\overset{}{C}}{-}Ph}$

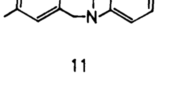
8


$\mathrm{Ph{-}\underset{HO}{\overset{H}{C}}{-}\underset{O}{\overset{}{C}}{-}NH_2}$

9


$\mathrm{Ph{-}\underset{HO}{\overset{H}{C}}{-}\underset{O}{\overset{}{C}}{-}OBz}$

10



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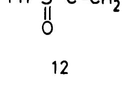
$\mathrm{Ph{-}\underset{O}{S}{-}\overset{H}{C}{=}CH_2}$

12

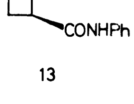

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Figure 1 shows the chromatograms of 2,2′-dihydroxy-1,1′-binaphthyl (**7**), benzoin (**8**), and *trans*-1,2-cyclobutanedicarboxanilide (**13**) on the columns bearing **3d**, **3a**, and **3e**, respectively. The chromatographic parameters for the resolution of **6**—**13** using the polyamide-coated silica gel columns are summarized in Table 1.

Contrary to the expectation, it was shown clearly that the chiral recognition by these chiral stationary phases was diverse and strongly depended on the structure of diamine component in the main chain.

Polyamide **3a** resolved **6**—**10** efficiently (α is larger than 1.10), which all contain an aromatic group and a site for hydrogen-bonding. This suggests that the chiral discrimination of **3a** would involve the simultaneous interactions of aromatic stacking and hydrogen-bonding with the racemates. The separation factor of **3a** has tendency to decrease as the inherent viscosity increases (Table 2). More importantly, **3a** with higher theoretical plate number for benzene (η_{inh} 0.68 and 0.98 dl $\mathrm{g^{-1}}$) showed smaller separation factors than those with lower theoretical plate number (η_{inh} 0.43 and 0.53 dl $\mathrm{g^{-1}}$). This phenomenon would be explained as follow; with

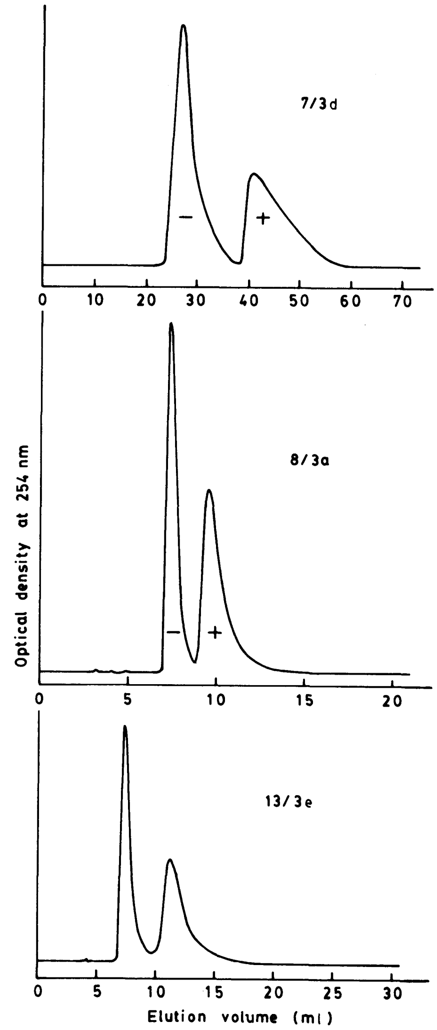

Fig. 1. Chromatograms of **7**, **8**, and **13** on the columns bearing **3d**, **3a**, and **3e**, respectively. Columns, 25×0.46 (i.d.) cm; eluent, hexane/2-propanol (v/v=9/1); flow rate, 0.50 ml $\mathrm{min^{-1}}$ at room temperature.

Table 1. Chromatographic Resolution of Racemates **6**—**13** by Polyamide-Coated Silica Gel Columns[a,b]

Racemates	Column bearing **3a**			Column bearing **3d**			Column bearing **5d**			Column bearing **3e**			Column bearing **5e**		
	k_1'	α	Rs	k_1'	α	Rs	k_1'	α	Rs	k_1'	α	Rs	k_1'	α	Rs
6	0.40	1.42	0.92	0.64(−)	1	PR[c]	0.88	1.11	0.4	0.41	1	NR[d]	0.62	1	NR
7	4.36(−)	1.17	0.60	9.91(−)	1.63	1.19	5.06	1	NR	2.19	1	NR	18.67	1	NR
8	1.91	1.46	1.45	4.17(+)	1	NR	8.24	1	NR	2.16	1	NR	5.20	1.15	0.50
9	5.59(−)	1.29	0.88	—	—	—	11.06	1	NR	8.04(+)	1.03	0.50	14.25	1.22	0.52
10	1.60	1.10	0.60	3.12(−)	1.04	0.50	8.70	1	NR	1.68(−)	1.05	0.50	5.00	1.20	0.4
11	0.57	1	NR	1.15(−)	1	PR	0.58	1	NR	0.89	1.12	0.60	0.83	1	NR
12	2.12(+)	1	PR	5.80	1	NR	1.64	1	NR	5.64	1.04	0·50	6.92	1	NR
13	1.40	1	NR	3.30	1	NR	7.85	1	NR	2.00	1.81	1.73	11.20	1	NR

a) Eluent, hexane-2-propanol (v/v=9/1); flow rate, 0.50 ml min^{-1}. k_1' (capacity factor for less retained racemate) =(retention volume−void volume)/void volume. α(separation factor)=(capacity factor for more retained racemate)/ k_1'. Rs(resolution factor)=2× (distance of the two peak position)/(sum of band-widths of the two peaks). The sign in the parentheses are those of optical rotations at 365 nm. b) Polyamide **3c**, **3f**, and **5a** showed no resolution ability to all of these racemates (α=1), polyamide **3b** resolved **13** only (α=1.38). c) PR: Partial resolution which could be detected only by a polarimeter. d) NR: No resolution.

Table 2. Chromatographic Resolution of Racemates **6**—**10** by **3a**-Coated Silica Gel Columns[a]

η_{inh}[b]	Theoretical plate number[c]	Separation factor/α				
		6	**7**	**8**	**9**	**10**
0.43	1430	1.64	1.46	1.64	1.25	1.10
0.53	1200	2.51	1.34	1.65	1.29	1.11
0.68	4000	1.31	1	1.45	1	1
0.88	2600	1.42	1.17	1.46	1.29	1.10
0.98	2900	1.37	1.18	1.38	1.17	1.09

a) Resolution conditions are the same as those in Table 1. b) 0.30 g dl^{-1} in DMAc at 30 °C. c) For benzene.

increasing π-π interaction ability of **3a**, which contributes to the theoretical plate number of the column, the π-π interaction between phenyl groups in **3a** and the racemates surpasses the polar interaction and the difference in stability between diasteriomeric complexes decreases. Moreover, **3b** and **5a** having no amide hydrogen or phenolic hydrogen showed no resolution ability to racemates **6**—**13**. These results indicate that hydrogen-bonding plays more important role than π-π interaction in the chiral recognition process by **3a**.

On the other hand, **3c** shows no resolving ability to all of the racemates, although it also possess the same interaction sites as **3a**. This can be caused by the interference of aromatic moiety in diamine residue during recognition process.

The influence of the eluent with different amount of 2-propanol was also investigated. As shown in Table 3, the racemates resolved by polyamide **3a** can be divided into two groups. Racemates **8**—**10** can form an intramolecular hydrogen-bonding, and the other racemates **6**, **7**, and **13** don't possess this possibility due to the lack of hydrogen-bonding pair for **6** or the trans orientation of the possible interaction sites for **7** and **13**. With increasing the content of protic solvent in the eluent from 10% 2-propanol (IPA) to ethanol only, the separation factor (α) of **8**—**10** all increased at first and then decreased. This phenomena would be caused by the equilibrium between the inter- and intramolecular hydrogen-bonding, which changes depending on the content of protic solvent in the eluent. At low content of protic solvent, the chiral recognition is lower due to the dominance of intramolecular hydrogen-bonding within the racemate, which is disadvantageous to the chiral discrimination. With increasing the ratio of 2-propanol, the racemate would be solvated and the interaction between the racemate and polyamide **3a** surpasses the intramolecular interaction within the racemate, resulting in better recognition. However, at very high content of protic solvent the interaction between the racemate and the eluent becomes major, and the interaction between the racemate and polyamide **3a** is diminished, resulting in low separation factor. For racemates **6**, **7**, and **13**, separation factor decreased harmoniously with increasing the content of protic solvent in the eluent. This would arise from the decrease of the interaction between the racemates and polyamide **3a** by solvation. These results also support the simultaneous interaction mechanism of chiral recognition by **3a**.

Polyamide **3e** resolved **9**—**13**, which is partially different from those resolved by **3a**. Especially, **13** with propeller-like phenyl groups was resolved with a high separation factor (α=1.81). Moreover, contrary to **5a**, *O*-methylated polyamide **5e** still showed resolution ability to **8**—**10** although it has no phenolic hydroxyl group, which exists in polyamide **3e**. From these results, it seems that the driving force for chiral recognition by **3e** is different from that by **3a**. Since

Table 3. Chromatographic Resolution of Racemates **6**—**13** by **3a** or **3e**-Coated Silica Gel Column Using Different Eluents[a)]

Racemates	Parameter[c)]	Column bearing **3a**				Column bearing **3e**[b)]	
		10% IPA[c)]	20% IPA	30% IPA	EtOH	10% IPA	30% IPA
6	k_1'	0.35	0.30	0.23	0.15	0.41	0.18
	α	2.51	2.27	2.29	15.1	1	1
7	k_1^1	7.22	3.17	2.50	0.33	2.19	0.83
	α	1.34	1.25	1	1	1	1
8	k_1'	2.53	1.50	1.03	0.13	2.16	1.11
	α	1.65	1.79	1.75	1.45	1	1
9	k_1'	9.33	2.70	1.57	0.20	8.04	1.43
	α	1.29	1.40	1.43	1	1.03	1
10	k_1'	2.13	1.13	0.74	0.11	1.68	0.72
	α	1.11	1.15	1.16	1	1.05	1
11	k_1'	0.71	0.47	0.37	0.29	0.89	0.47
	α	1	1	1	1	1.12	1
12	k_1'	2.12	1.40	0.87	0.13	5.64	2.17
	α	1	1	1	1	1.04	1
13	k_1'	1.41	0.63	0.48	0.12	2.00	0.60
	α	1.28	1.24	1	1	1.81	1.59

a) The resolution conditions and the definition of parameters are the same as those in Table 1; polyamide **3a** with $\eta_{\text{inh}}=0.53\ \text{dl g}^{-1}$ was used. b) It showed no resolution ability to all of the recemates when methanol was used as an eluent. c) Eluent used is a mixture of hexane and 2-propanol (IPA).

both **3e** and **5e** form an ordered conformation of macromolecular asymmetry in the film state,[27)] it is reasonable to say that this ordered conformation plays an important role in chiral recognition process. As shown in Table 3, with increasing the content of 2-propanol in eluent from 10 to 30%, **3e** showed no recognition to the racemates except for **13** (α=1.59). This is also quite different from the observed for **3a** which showed no resolution ability to **13** when an eluent containing 30% 2-propanol is used. From these facts, the chiral discrimination ability of **3e** can be attributed to its ordered conformation in the film state. The ordered conformation makes the difference in stability between diasteriomeric complexes large, which arises from the interaction of hydroxyphenyl groups of **3e** with aromatic groups of the racemates.

However, **3f** showed no resolution ability to all of the racemates, although it possesses polymer main chain structure with mesomeric aromatic residue similar to **3e**. This can be ascribed to its incompleteness of the ordered conformation[27)] or to longer and more flexible diphenyl ether linkage in comparison with 1,4-phenylene linkage in **3e**.

Polyamide **3d** resolved atropisomeric compound **7** with a high separation factor (α=1.63). *O*-methylated polyamide **5d** resolved **6** with trans phenyl groups. This high selective resolution ability of **3c** to **7** and **5d** to **6** would be attributed to their rigid and fixed structure,[25,27)] which makes the aromatic packing with racemates more stable for one of the enantiomer than the other.

The present results show that optically active polyamides **3** and **5**, derived from (—)-anti head-to-head coumarin dimer, are useful as chiral stationary phases for direct resolution of racemates having aromatic groups by HPLC. Polyamide **3a** derived from 1,6-hexanediamine shows the best results, and its recognition ability is mainly attributed to the simultaneous interactions with the solutes. The chiral discrimination ability of polyamides **3e** and **5e**, derived from 1,4-phenylenediamine, may be attributed to their ordered conformation in the film state as well as the simultaneous interaction with the racemates. The selective recognition ability of **3d** to **7** and **5d** to **6** seems due to their rigid and fixed conformation in the film state. The ordered conformation of the polyamides derived from piperazine and 1,4-phenylenediamine are less effective for chiral recognition than the simultaneous interaction with polar groups in **3a** unless the ordered conformation is fully-developed.[6—10)]

References

1) E. Selegny, "Optically Active Polymers," D. Reidel, Dordrecht (1979).

2) G. Blaschke, *Angew. Chem., Int. Ed. Engl.*, **19**, 13 (1980).

3) W. H. Pirkle and J. Finn, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1983), Vol. 1, p. 87.

4) D. W. Armstrong, *J. Liq. Chromatogr.*, **7**(s-2), 353 (1984).

5) *J. Liq. Chromatogr.*, **9**(2/3) (1986). "Special Issue On Optical Resolution By Liquid Chromatography," ed by S. Hara and J. Cases.

6) H. Yuki, Y. Okamoto, and I. Okamoto, *J. Am. Chem. Soc.*, **102**, 6356 (1980).

7) Y. Okamoto, I. Okamoto, and H. Yuki, *Chem. Lett.*, **1981**, 835.

8) Y. Okamoto, I. Okamoto, and H. Yuki, *J. Polym. Sci., Polym. Lett. Ed.*, **19**, 451 (1981).

9) Y. Okamoto, S. Honda, I. Okamoto, and H. Yuki, *J. Am. Chem. Soc.*, **103**, 6971 (1981).

10) Y. Okamoto, S. Honda, E. Yashima, and H. Yuki, *Chem. Lett.*, **1983**, 1221.

11) S. Allenmark and B. Bomgren, *J. Chromatogr.*, **264**, 63 (1983).

12) J. Hermansson, *J. Chromatogr.*, **269**, 71 (1983).

13) G. Hesse and R. Hagel, *Chromatographia*, **6**, 277 (1973).

14) G. Hesse and R. Hagel, *Chromatographia*, **9**, 62 (1976).

15) Y. Okamoto, M. Kawashima, and K. Hatada, *J. Am. Chem. Soc.*, **106**, 5357 (1984).

16) G. Blaschke, H.-P. Kraft, and H. Markgraf, *Chem. Ber.*, **113**, 2318 (1980).

17) R. Baczuk, G. Landram, R. Dubois, and H. Dehm, *J. Chromatogr.*, **60**, 351 (1971).

18) W. H. Pirkle and D. W. House, *J. Org. Chem.*, **44**, 1957 (1979).

19) W. H. Pirkle and J. M. Finn, *J. Am. Chem. Soc.*, **103**, 2964 (1981).

20) W. H. Pirkle and J. M. Finn, *J. Org. Chem.*, **46**, 2935 (1981).

21) W. H. Pirkle and J. L. Schreiner, *J. Org. Chem.*, **46**, 4988 (1981).

22) W. H. Pirkle, C. J. Welch, and M. H. Hyun, *J. Org. Chem.*, **48**, 5022 (1983).

23) W. H. Pirkle and M. H. Hyun, *J. Org. Chem.*, **49**, 3043 (1984).

24) N. Yonezawa, T. Kanoe, K. Saigo, Y. Chen, K. Tachibana, and M. Hasegawa, *J. Polym. Sci., Polym. Lett. Ed.*, **23**, 617 (1985).

25) K. Saigo, Y. Chen, N. Yonezawa, T. Kanoe, K. Tachibana, and M. Hasegawa, *Macromolecules*, **19**, 1552 (1986).

26) K. Saigo, Y. Chen, N. Yonezawa, K. Tachibana, T. Kanoe, and M. Hasegawa, *Chem. Lett.*, **1985**, 1891.

27) Y. Chen, K. Saigo, N. Yonezawa, M. Hasegawa, *Bull. Chem. Soc. Jpn.*, **60**, 1895 (1987).

28) Macroporous spherical silica gel has 10 μm of mean particle size with 100 nm of mean pore diameter and 20000 $m^2\ kg^{-1}$ of specific surface area.