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Tetrahedron
Tetrahedron 63 (2007) 363–373

Improving the gelation properties of 3,5-diaminobenzoate-based organogelators in aromatic solvents with additional aromatic-containing pendants

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Received 25 August 2006; revised 12 October 2006; accepted 25 October 2006
Available online 13 November 2006

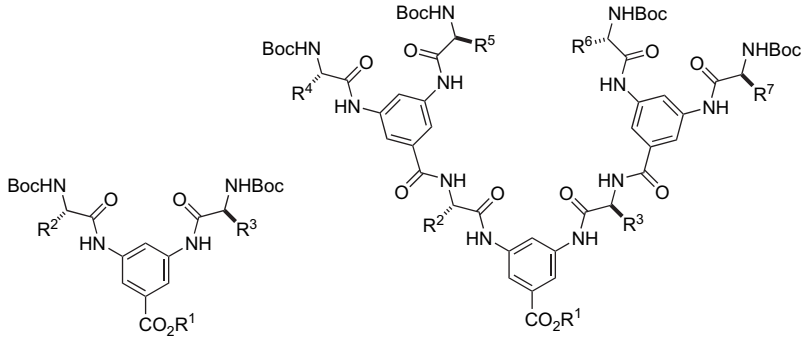
Abstract—A family of 3,5-diaminobenzoate derivatives containing different Cbz-protected α- or β-amino side pendant chains and different aromatic-containing ester functionalities was prepared. It was found that the additional aromatic rings in the Cbz- and aromatic-containing ester moieties significantly improved the gelation properties of the resulting organogelators in aromatic solvents. Infrared and circular dichroism spectroscopy revealed that both H-bonding and π–π aromatic stacking interactions were the main driving forces for gelation.

1. Introduction

Low molecular weight organogelators are an interesting class of molecules that possess many applications in medicine, environmental science, separation technology, and catalysis.[1] These small molecules are capable of forming a non-covalently linked three-dimensional network structure with a specific solvent system that result in the immobilization of solvent molecules.

A key to the design of organogelators is how to fine-tune the strength of the inter-molecular driving forces that hold them together. If the binding interactions are too strong, precipitation or crystallization, rather than gelation will occur. On the other hand, if the binding forces among the organogelators are weak, dissolution or weak gelation would result. Among the various driving forces, ionic, hydrogen bonding, π–π stacking, and hydrophobic interactions are the most commonly encountered ones. However, the latter two are sometimes too subtle to be characterized experimentally.

Our group recently reported a series of α-amino acid-based dendrons **1** and **2** and showed that they are powerful organogelators with minimum gelation concentration (MGC) as low as 2 mg/mL.[2] We also demonstrated for the first time that their gelation strength was strongly dependent on the nature of the focal point functionality (i.e., R^1) and the amino acid side chain residues (i.e., R^2–R^7). In our previous study,



1 **2**

Keywords: Amino acids; Organogelators; H-bonding; π–π Aromatic stacking.
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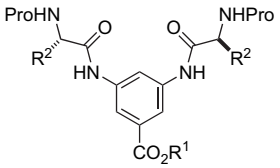
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.066

we focused our attention only on three different kinds of α-amino acids, namely, alanine (Ala), phenylalanine (Phe), and valine (Val) (i.e., R^2–R^7=Me, Bn or *i*-Pr). Due to the ready availability of the 20 naturally occurring amino acids, it would be of particular interest to investigate other amino acids on the gelation properties.[3] In this paper, we report an optimization study on the gelation property of C_2-symmetrical 3,5-bis(*N*-protected diamino) benzoates **3** by employing different amino acid residues as pendant side chains. It was found that among all the amino acids studied, phenylalanine and valine derivatives proved to possess the best gelating power. We also examined the effect of the carboxylic acid focal point functionality (i.e., R^1) on gelation while keeping the amino acid side chains as valine (i.e., R^2=*i*-Pr). As a result of this optimization study, several stronger organogelators (MGC down to 0.8 mg/mL) were found. We also gathered concrete experimental evidence to support that both π–π aromatic stacking, in addition to H-bonding interactions, were the driving forces behind their excellent gelation ability.



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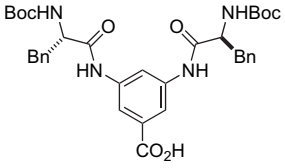

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2. Results and discussion

2.1. Structural variations and optimizations

The best organogelator originated from our initial study was the Boc-protected phenylalanine carboxylic acid **4** (MGC=2 mg/mL in nitrobenzene).[2a] We envisaged that insertion of additional aromatic moieties into this lead molecule would further enhance its gelation ability through additional π–π interactions with aromatic solvents. Examination of the structure of compound **4** revealed that there were three possible positions to accommodate the extra aromatic moieties (Fig. 1).

(a) Changing of the *tert*-butyloxylcarbonyl (Boc) NH-protecting group to an aromatic-containing NH-protecting group such as benzyloxycarbonyl (Cbz).
(b) Modifying the carboxylic acid functionality to an aromatic-containing carboxylic ester.
(c) Introduction of aromatic rings to the amino acid side chains. This would involve the use of aromatic amino acids such as phenylalanine and tyrosine, etc.

Our immediate goal was then to develop an efficient synthetic protocol to assemble the various Cbz-protected amino acids and aromatic-containing alcohols to the central 3,5-diaminobenzoic acid core.

2.2. Synthesis

The general synthetic route to the target compounds was shown in Scheme 1. 3,5-Di-(*tert*-butyloxycarbonylamino)-benzoic acid **5**[4] was reacted with benzyl bromide **6a** in the presence of K_2CO_3 and 18-crown-6 to give the corresponding benzyl ester **7a** in 61% yield. The Boc protecting groups were then removed by trifluoroacetic acid (TFA) to furnish the diaminoester **8a**[5] in 67% yield. Finally, coupling of **8a** with various Cbz-protected amino acids or Cbz-protected β-alanine in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) gave the target compounds aa-**9a** or β-Ala-**10**, respectively, in yields ranging from 45% to 86%. The benzyl ether of the tyrosine derivative [i.e., Tyr(OBn)-**9a**], on the other hand, was prepared from Tyr-**9a** using Williamson ether synthesis.

For the introduction of the aromatic-containing ester functionality, compound **5** was converted to various esters **7b**–**7d** by coupling with various aromatic-containing alcohols **6b**–**6d** in the presence of dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), and 4-dimethylaminopyridine (DMAP) in 57–84% yield. The two Boc groups were removed under acidic conditions to furnish the 3,5-diaminobenzoates **8b**–**8d**. Coupling of **8b**–**8d** with Cbz-protected valine produced the target organogelators Val-**9b**–Val-**9d** bearing different aromatic-containing ester group. An ethyl ester Val-**9e** was also prepared as a reference compound. A list of the target compounds is shown in Table 1.

2.3. Characterization

2.3.1. NMR spectroscopy. The structural identities of all intermediates and target compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectra of all target organogelators were composed of two characteristic features. One was a set of invariable signals originated from the common 3,5-diaminobenzoic acid central core that was shared among the gelators. Hence, the central aromatic proton signals appeared as a triplet (δ~8.3) and a doublet (δ~8.0) for all the target compounds, while that of the anilide NH and Cbz-NH resonated at δ 10.3 and 7.6, respectively (Fig. 2). The signals of the benzylic and aromatic protons of the Cbz protecting groups were at δ 5.0 and δ 7.0–7.5, respectively. The other characteristic feature was a set of variable 'fingerprint' signals due to the protons originated from the different amino acid side chain and the focal point ester functionality. For example, the ^{1}H NMR spectrum of

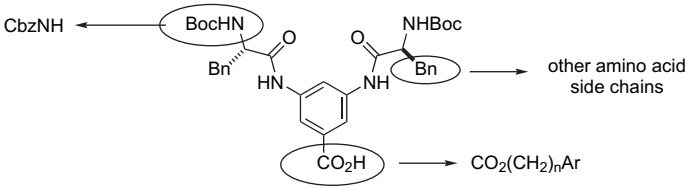
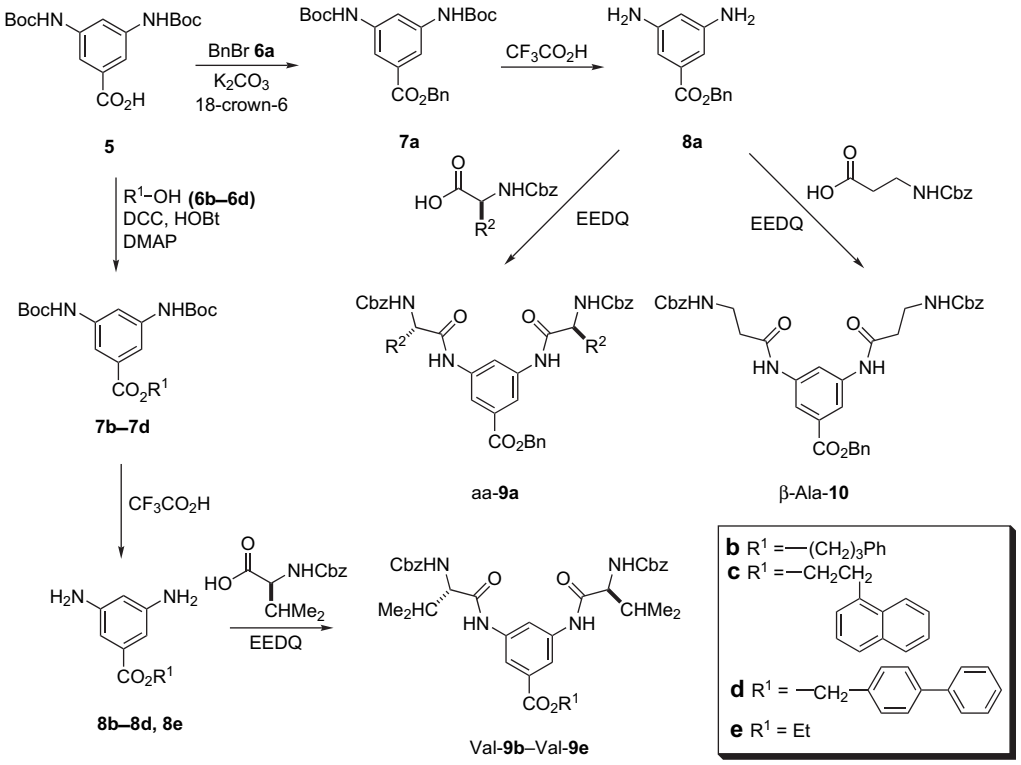


Figure 1. Structural modifications of the lead compound **4**.



Scheme 1. General synthetic routes to target organogelators **9** and **10**.

Table 1. List of target organogelators

Compound	R^1	R^2
aa-**9a**		
Gly-**9a**	—	H
Ala-**9a**	—	Me
Val-**9a**	—	*i*-Pr
Phe-**9a**	—	Bn
Leu-**9a**	—	CH_2(*i*-Pr)
Ser-**9a**	—	CH_2OH
Tyr-**9a**	—	$CH_2C_6H_4OH$
Tyr(OBn)-**9a**	—	$CH_2C_6H_4OBn$
Gln-**9a**	—	$CH_2CH_2CONH_2$
Val-**9b**	$(CH_2)_3Ph$	—
Val-**9c**	$(CH_2)_2$(2-Np)	—
Val-**9d**	$CH_2C_6H_4Ph$	—
Val-**9e**	Et	—
β-Ala-**10**	—	—

compound Val-**9a** showed the presence of the valine isopropyl side chain as a doublet at δ 0.91 and a multiplet at δ 1.91–2.11, together with the benzyl ester signals at δ 5.35 and 7.0–7.6. Likewise, the corresponding feature signals of

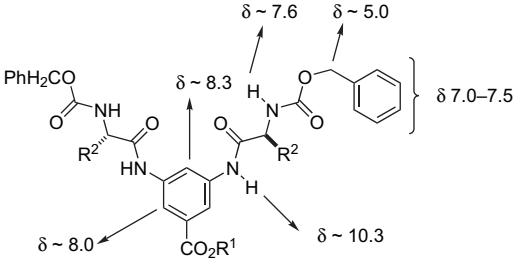


Figure 2. Common ^{1}H NMR spectral features shared by the target organogelators.

Gln-**9a** were found at δ 1.69–2.31 (CH_2CH_2), 6.81 (one of the $CONH_2$, the other NH was merged with the aromatic signals), 5.36 and 7.0–7.6 (benzyl ester). The switching of a benzyl to other esters at R^1 could also be reflected from the resulting ^{1}H NMR spectra. For example, the ^{1}H NMR spectrum of Val-**9c** showed, in addition to the isopropyl side chain signals, the presence of the 2-(naphthalen-1-yl)ethyl ^{1}H signals at δ 3.52, 4.58, and 7.2–8.3.

The ^{13}C NMR spectra of the target compounds also shared a common spectral feature; the chemical shift values of the carbon nuclei due to the common backbone skeleton were nearly the same. Hence, the carbon signals of the Cbz groups were found to situate at δ 66 and 114–129, while the aromatic carbon signals of the 3,5-diaminobenzoate moiety were found between δ 130 and 140. Three sets of C═O signals located at ~δ 156, 165, and 171 were found. The signal at the most upfield position could be assigned to the Cbz carbamate C═O while the intermediate signals could be attributed to the benzoate C═O. On the other hand, the most downfield signal could be assigned to the anilide C═O. Similar to the case in the ^{1}H NMR spectroscopic analysis, the chemical identities of the amino acid side chains could be ascertained by their respective 'fingerprint' ^{13}C NMR signals.

2.3.2. Mass spectroscopic analysis. The structures of all target organogelators were characterized by FAB or positive ion EI mass spectroscopy. In addition to molecular ions in the form of M^+ or $(M+H)^+$, dimeric M_2^+ or $(M_2+H)^+$ ions were also found (Fig. 3), suggesting the presence of molecular aggregates in the solution states. The exact mass of the molecular ion peak matched well with the theoretical value.

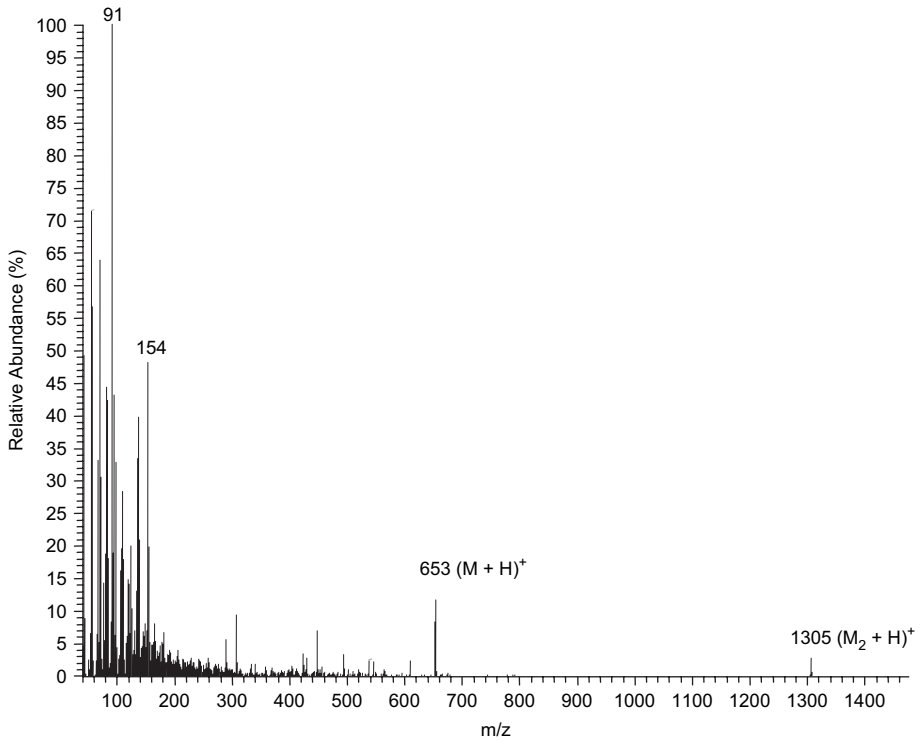


Figure 3. Mass spectrum of compound Ala-**9a**.

2.4. Gelation properties

The gelation properties of the target compounds were examined in various solvents and, as expected, strong gels were formed mainly in aromatic solvents. The gelation effect of changing the Boc into the Cbz protecting group was dramatic. Hence, the Cbz-protected valine ethyl ester Val-**9e** was a much powerful organogelator (MGC=3 mg/mL) as compared to the previously reported Boc-protected analogue **3** (Pro=Boc, R^1=Et, R^2=*i*-Pr) (MGC∼100 mg/mL) (Table 2). This finding suggested that the two added phenyl rings in the Cbz moieties enhanced the gelation property by increasing π–π interactions with the aromatic solvents. Nonetheless, it was noted that the gels so formed were translucent (TG) and fragile. Addition of the third aromatic ring by replacing the ethyl ester moiety in Val-**9e** with a benzyl ester gave compound Val-**9a**, which had similar MGC values (3–10 mg/mL) as the corresponding ethyl ester. However, the gels formed were mostly transparent (CG) and had good physical strength. This finding therefore suggested that the third aromatic ring further improved the π–π interactions with the solvents.

Table 2. Effects of additional aromatic rings on gelation properties[a]

Solvent	**3** (Pro=Boc, R^1=Et, R^2=*i*-Pr)[b]	Val-**9e**	Val-**9a**
Benzene	TG (100)	P	CG (3)
Toluene	TG (80)	TG (3)	CG (3)
o-Xylene	TG (80)	TG (3)	CG (4)
Anisole	TG (90)	TG (3)	TG (5)
o-Dichlorobenzene	PG	TG (3)	CG (6)
Nitrobenzene	TG (90)	CG (3)	CG (10)

The values given in parentheses are the minimum concentration (mg/mL) to achieve gelation at 25 °C.

[a] CG—transparent gel; PG—partial gel; TG—translucent gel; P—precipitation.

[b] Data taken from Ref. 2a.

The effects of the various amino acid side chains on the gelation properties were also examined (Table 3 and Fig. 4). For compounds containing side chains that are highly hydrophilic (Gln-**9a** and Tyr-**9a**) or bearing small alkyl groups (Gly-**9a**, Ala-**9a**, and β-Ala-**10**), they possessed poor solubility in aromatic solvents and tended to precipitate and did not form gels. For Leu-**9a** having highly hydrophobic side chains, it dissolved well in aromatic solvents and again failed to form gels. More interestingly, compounds with aromatic side chains such as Phe-**9a** and Tyr(OBn)-**9a** were good organogelators (MGC∼0.8–3 mg/mL). The effect of protecting the phenolic functionality in Tyr-**9a** as the benzyl ether was obvious. The resulting compound Tyr(OBn)-**9a** now became less hydrophilic and contained two extra aromatic rings, and was a much better organogelator. To our surprise, the moderately hydrophobic compound Val-**9a** (MGC∼3–10 mg/mL) and the highly hydrophilic Ser-**9a** (MGC∼1–10 mg/mL) were also excellent organogelators. The organogelating power of such amino acid containing compounds had been shown previously to be highly dependent on the amino acid compositions.[2a] We believed that the amino acid side chain, in addition to interacting with the gelating solvents, also played a crucial role in determining the packing arrangement of the organogelators inside the gels.

Having studied the effect of the amino acid side chains, we then turned our attention to the effect of modifying the ester moiety and Val-**9a** was chosen as our lead molecule even though Phe-**9a** possessed slightly better gelation power in some selected solvents. This was because Phe-**9a** inadvertently exhibited poor solubility in some aromatic solvents

Table 3. Gelation properties of various Cbz-protected benzyl benzoates[a]

Compound	Benzene	Toluene	*o*-Xylene	Anisole	*o*-Dichlorobenzene	Nitrobenzene
Gly-**9a**	NS	NS	NS	P	P	P
Ala-**9a**	TG (27)	P	P	S	P	TG (50)
Val-**9a**	CG (3)	CG (3)	CG (4)	TG (5)	CG (6)	CG (10)
Phe-**9a**	P	TG (2)	CG (0.8)	P	CG (3)	OG (50)
Leu-**9a**	S	S	S	S	S	S
Ser-**9a**	OG (7)	OG (7)	CG (1)	TG (4)	CG (6)	TG (10)
Tyr-**9a**	NS	NS	NS	TG (3)	TG (10)	TG (10)
Tyr(OBn)-**9a**	CG (3)	CG (2)	CG (2)	CG (35)	CG (3)	S
Gln-**9a**	NS	NS	NS	NS	NS	TG (6)
β-Ala-**10**	P	NS	TG (10)	TG (10)	OG (14)	P

The values given in parentheses are the minimum concentration (mg/mL) to achieve gelation at 25 °C.
[a] CG—transparent gel; OG—opaque gel; TG—translucent gel; NS—insoluble; S—soluble; P—precipitation.

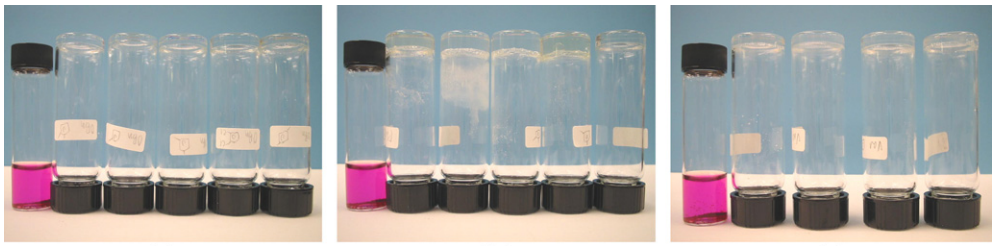


Figure 4. (a) Gels formed from Phe-**9a** at 5 mg/mL (left to right: $KMnO_4$ solution, toluene, *p*-xylene, *o*-xylene, *m*-xylene, and *o*-dichlorobenzene); (b) transparent gels formed from Tyr(OBn)-**9a** at 5 mg/mL (left to right: $KMnO_4$ solution, *o*-xylene, toluene, *m*-xylene, *o*-dichlorobenzene, and *p*-xylene); (c) transparent gels formed from Val-**9a** at 5 mg/mL (left to right: $KMnO_4$ solution, *p*-xylene, *o*-xylene, *o*-dichlorobenzene, and *m*-xylene).

such as benzene and anisole. Therefore, addition of more aromatic rings into the system would most likely further decrease the solubility. Hence, choosing valine as the amino acid residue, we replaced the benzyl alcohol moiety with aromatic-containing alcohols such as 3-phenylpropan-1-ol, 1-naphthaleneethanol, and biphenyl-4-methanol and obtained compounds Val-**9b**, Val-**9c**, and Val-**9d**, respectively. The gelation properties of the resulting compounds were tabulated in Table 4. As it turned out, none of these compounds showed superior gelating ability as compared to the parent benzyl ester Val-**9a**. The gels formed were either translucent or opaque with higher MGC values. It therefore appeared that this part of the molecule could not be altered without having negative impact on the gelation properties.

2.5. Gelation mechanism

The gelation mechanism of the organogelators was investigated by a number of techniques. Due to the rapid formation of gels from Phe-**9a**, Tyr(OBn)-**9a**, and Val-**9a**, we were unable to obtain their solution FTIR spectra at concentrations >20 mg/mL. On the other hand, the signal intensities of the FTIR spectra at an organogelator concentration of <10 mg/mL were too weak to be observed even after solvent signal subtraction. In the end, we chose a weaker organogelator **3** (Pro=Boc, R^1=Et, R^2=*i*-Pr) and recorded its FTIR spectra in both the solution and gel state at a concentration of 100 mg/mL in toluene. It was found that there was little difference between the solution and gel FTIR spectra. In particular, the N–H (3409 and 3311 cm^{-1}) and the C=O stretching frequencies (1726 and 1677 cm^{-1}) remained unchanged when switching from the solution to the gel states, suggesting that the extent of H-bonding did not have much difference between the two states in toluene. However, this finding was not surprising in view of the fact that this compound had already been shown to form dimeric species via H-bonds in nonpolar $CDCl_3$ solutions,[2a] and hence there was little change of the stretching frequency upon gelation in nonpolar toluene solutions.

A more interesting finding was revealed by studying the circular dichroism (CD) spectral behavior of a 3 mg/mL sample of Tyr(OBn)-**9a** in benzene at different temperatures (Fig. 5). Prior to gelation (temperature range=60–75 °C), one positive (λ_{max}=329 nm) and one negative (λ_{max}=313 nm) Cotton effects, with decreasing molar ellipticities at higher temperatures, were observed. After gelation (temperature range=20–40 °C), these signals were blue-shifted to λ_{max}=326 and 308 nm, respectively, indicating that the energy gaps of the electronic transitions were widened

Table 4. Gelation properties of Cbz-protected valine-based benzoates containing different aromatic ester pendant groups[a]

Compound	Benzene	Toluene	*o*-Xylene	Anisole	*o*-Dichlorobenzene	Nitrobenzene
Val-**9a**	CG (3)	CG (3)	CG (4)	TG (5)	CG (6)	CG (10)
Val-**9b**	TG (5)	TG (10)	TG (20)	TG (20)	TG (13)	P
Val-**9c**	TG (4)	NS	TG (10)	OG (5)	CG (11)	TG (6)
Val-**9d**	TG (10)	TG (10)	TG (10)	P	CG (11)	TG (20)

The values given in parentheses are the minimum concentration (mg/mL) to achieve gelation at 25 °C.
[a] CG—transparent gel; OG—opaque gel; TG—translucent gel; NS—insoluble; P—precipitation.

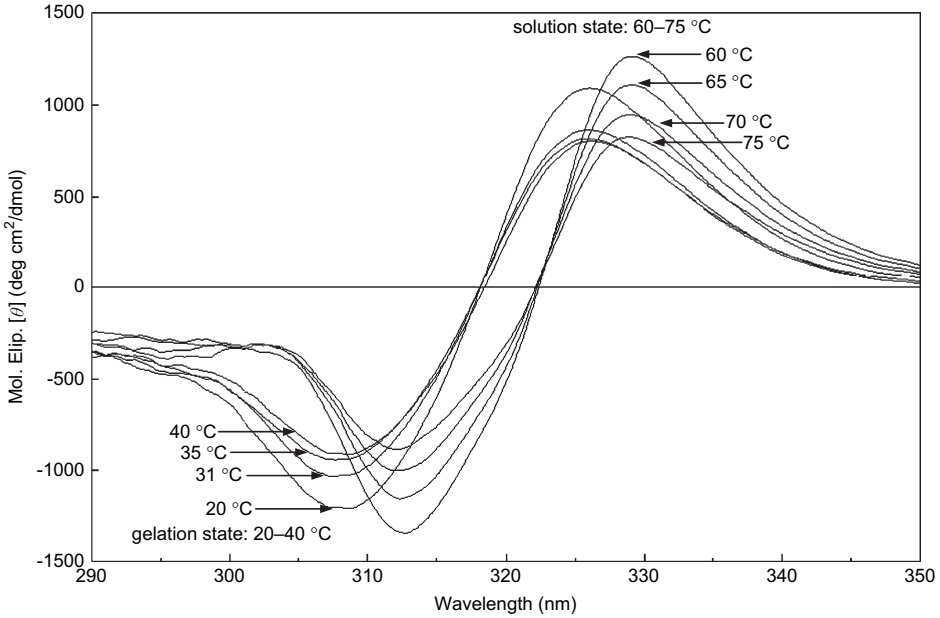


Figure 5. Temperature-dependent CD spectra of Tyr(OBn)-**9a** in benzene (3 mg/mL).

upon gelation. This was obviously due to a change of π–π interactions between the organogelator and the aromatic solvent (i.e., benzene) on going from the solution to the gel state. In contrast, the CD spectrum of the weak organogelator, Boc-protected **3** (Pro=Boc, R^1=Et, R^2=*i*-Pr), did not show any shift of λ_{max} value from the solution to the gel state, suggesting that π–π interactions contributed significantly to the gel stability of Cbz-protected organgelators.

2.6. Electron microscopy

The morphology of the gel structure was examined by scanning electron microscopy (SEM). All SEM images showed the presence of dense structures without clear, well-defined microscale architecture (Fig. 6). Although in some occasions we were able to locate fine fibers with diameters~0.1 μm protruding out from the dense particles, the existence of

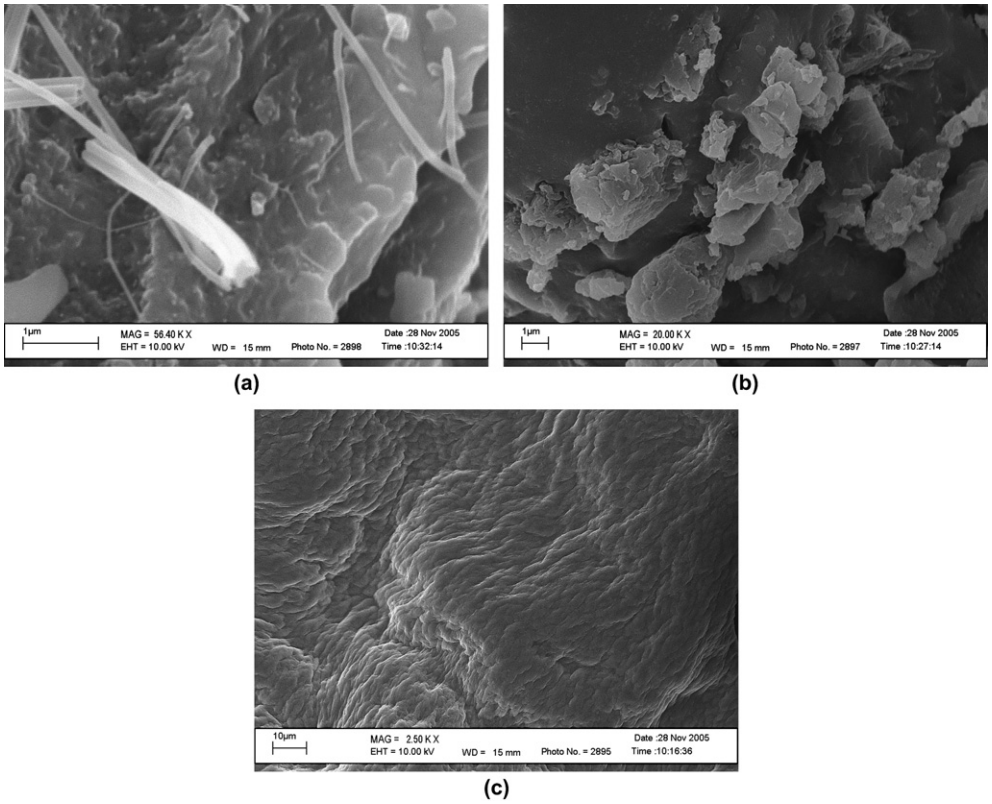


Figure 6. SEM images of freeze-dried samples of (a) Phe-**9a** (1 mg/mL in *o*-xylene), (b) Ser-**9a** (1.5 mg/mL in *o*-xylene), and (c) Tyr(OBn)-**9a** (2 mg/mL in *o*-xylene).

chiral morphology could not be observed. Such densed structures were most likely formed from the collapse of the gel microstructure during the freeze-drying process.

3. Conclusions

Starting from an ethyl 3,5-bis(Boc-protected aminoacylamido)benzoate as a lead compound, a series of 3,5-bis-(Cbz-protected aminoacylamido)benzoates bearing different α- or β-amino side chain residues and different aromatic-containing ester pendant groups were prepared. The additional three aromatic rings in the Cbz- and aromatic-containing ester moieties significantly improved the gelation properties (MGC decreased from ~100 to 0.8 mg/mL) of the resulting organogelators in many aromatic solvents. FTIR and CD spectroscopy revealed that both H-bonding and π–π aromatic stacking were the driving forces for gelation.

4. Experimental

4.1. General

THF was distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2 prior to use. Silica gel for flash chromatography is Macherey Nagel 60M (230–400 mesh) silica gel. CbzNH-L-amino acids (CbzNH-aa-CO_2H) and other reagents were used as supplied from Aldrich or Sigma. All reactions were conducted under dry N_2 unless otherwise stated. All NMR spectra were recorded in DMSO-d_6 (dried over molecular sieve 4 Å) on a Brüker DPX300 spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus at 25 °C unless otherwise stated. The residual proton or carbon signals of DMSO-d_6 (δ_H=2.50, δ_C=39.52) were used as internal references. All chemical shifts were reported in parts per million (δ) and coupling constants in hertz. Positive ion EI and FAB spectra were carried out on a Thermo Finnigan MAT 95XL mass spectrometer. Melting points were measured on an Electrothermal IA9100 Digital Melting Point Apparatus and were uncorrected. IR spectra were recorded on a Brüker Vertex 70 FT-IR spectrophotometer. Optical rotations were taken on a Perkin–Elmer 341 Polarimeter at 589 nm and at 20 °C, in a solvent mixture of 1,2-dichloroethane/HOAc (v/v=95/5) unless otherwise specified. CD spectra were recorded on a JASCO J-715 spectropolarimeter connected to a NESLAB RTE-211 temperature controller. Elemental analyses were performed at MEDAC Ltd., Brunel Science Center, Cooper's Hill Lane, Englefield Green, Egham, Surrey TW20 0JZ, UK.

4.2. Benzyl 3,5-di-(*tert*-butyloxycarbonylamino)-benzoate (7a)

A mixture of 3,5-di-(*tert*-butyloxycarbonylamino)benzoic acid **5**[4] (20.00 g, 56.8 mmol), K_2CO_3 (19.60 g, 141.9 mmol), benzyl bromide **6a** (8.78 mL, 73.8 mmol), and 18-crown-6 (5 mg) in acetone (150 mL) was heated to reflux for 24 h. The mixture was filtered and the filtrate was evaporated in vacuo to give a crude oil that was chromatographed on silica gel (eluent: hexane/EtOAc=6:1) to give the title compound **7a** (15.32 g, 61%) as a creamy white solid. Mp: 158–159.5 °C. R_f: 0.26 (hexane/EtOAc=5:1). ^{1}H NMR: 1.46 (18H, s, C(CH_3)$_3$), 5.33 (2H, s, CH_2), 7.30–7.49 (5H, m, Ar*H*), 7.72 (2H, s, Ar*H*), 7.97 (1H, s, Ar*H*), 9.53 (2H, s, N*H*Ar). ^{13}C NMR: 28.1, 66.1, 79.2, 112.5, 113.0, 127.9, 128.1, 128.5, 130.2, 136.2, 140.3, 152.7, 165.6. MS (FAB): 442 (M^+, 62%), 663 (M_3^{2+}, 43%), 885 [$(M_2+H)^+$, 6%], 1326 (M_3^+, 2%). Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.24; H, 6.89; N, 6.22.

4.3. Benzyl 3,5-diaminobenzoate (8a)[5]

A mixture of compound **7a** (11.90 g, 271 mmol) and TFA (41.75 mL, 542 mmol) in dry CH_2Cl_2 (150 mL) was stirred at 25 °C and the progress of deprotection was monitored by TLC. After complete deprotection (24 h), the solvent was evaporated on a rotary evaporator and the residue re-dissolved in EtOAc (50 mL). The solution was neutralized to pH=8 by $NaHCO_3$ solution. The organic layer was collected and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), water (100 mL), and saturated NaCl solution (100 mL) successively, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a pale brown solid that was chromatographed on silica gel (eluent: hexane/EtOAc=1:1) to afford the title compound **8a** (4.36 g, 67%) as a pale orange solid. Mp: 106–107 °C. R_f: 0.32 (hexane/EtOAc=1:1). ^{1}H NMR: 5.01 (4H, s, NH_2), 5.24 (2H, s, CH_2), 6.03 (1H, t, J=2.0, Ar*H*), 6.46 (2H, d, J=2.0, Ar*H*), 7.30–7.46 (5H, m, Ar*H*). ^{13}C NMR (some overlapping aromatic C signals): 65.6, 103.7, 103.8, 128.0, 128.5, 130.6, 136.5, 149.4, 166.7. MS (EI): 242 (M^+, 91%). HRMS (EI): $C_{14}H_{14}N_2O_2$ requires 242.1050; found: 242.1048.

4.4. General procedure for the preparation of aa-9a and β-Ala-10

EEDQ (2.25 g, 9.08 mmol) was added to a stirred solution of benzyl 3,5-diaminobenzoate **8a** (1.00 g, 4.13 mmol) and Cbz-protected amino acid (9.08 mmol) in THF at 20 °C. The mixture was kept at 20 °C for 24 h and the reaction was worked up according to the following procedure.

4.4.1. Gly-9a. After stirring for 24 h, a white precipitate was formed. It was collected by suction filtration and washed with THF, EtOAc, Et_2O, and hexane successively. The product was dried in vacuo to give a white powder (2.04 g, 79%). Mp: 220–221 °C. R_f: 0.18 (hexane/EtOAc=1:1). ^{1}H NMR: 3.81 (4H, d, J=6.0, NCH_2), 5.05 (4H, s, CH_2Ph), 5.35 (2H, s, CO_2CH_2Ph), 7.15–7.52 (15H, m, Ar*H*), 7.58 (2H, t, J=6.0, CbzN*H*), 7.96 (2H, s, Ar*H*), 8.27 (1H, s, Ar*H*), 10.24 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 44.4, 65.8, 66.6, 114.5, 115.0, 127.2, 127.9, 128.3, 128.5, 128.7, 130.6, 136.2, 137.2, 139.9, 156.9, 165.6, 168.6. MS (FAB): 625 [$(M+H)^+$, 6%]. HRMS (FAB): $C_{34}H_{33}N_4O_8$ requires 625.2293; found: 625.2303.

4.4.2. Ala-9a. The solvent was evaporated in vacuo and the residue was re-dissolved in EtOAc and washed with saturated Na_2CO_3, 10% citric acid, saturated Na_2CO_3 solution, water, and saturated NaCl solution successively. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was evaporated in vacuo to yield an oil that was chromatographed on silica gel (eluent: hexane/EtOAc=2:1 gradient to 1:1) to

produce the target compound as a pale yellow solid. Recrystallization of the solid from a mixture of THF and hexane gave pure Ala-**9a** (1.21 g, 45%) as a creamy white solid. Mp: 176–177 °C. R_f: 0.29 (hexane/EtOAc=1:1). $[\alpha]_D$ −59.6 (*c* 1.0). ^{1}H NMR: 1.29 (6H, d, *J*=7.2, CH_3), 4.18 (2H, quintet, *J*=7.2, NC*H*), 5.02 (2H, d, *J*=12.6, C*H*HPh), 5.04 (2H, d, *J*=12.6, CH*H*Ph), 5.36 (2H, s, CO_2CH_2Ph), 6.95–7.57 (15H, m, Ar*H*), 7.64 (2H, d, *J*=6.9, CbzN*H*), 7.97 (2H, s, Ar*H*), 8.32 (1H, s, Ar*H*), 10.25 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 17.9, 60.0, 65.5, 66.5, 114.5, 114.9, 127.0, 127.8, 128.3, 128.4, 128.6, 130.3, 136.1, 137.0, 139.8, 155.9, 165.4, 172.0. MS (FAB): 653 [(M+H)$^+$, 12%], 1305 [(M_2+H)$^+$, 3%]. Anal. Calcd for $C_{36}H_{36}N_4O_8$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.07; H, 5.61; N, 8.50.

4.4.3. Val-9a. The solvent was evaporated in vacuo and the residue recrystallized from a mixture of THF/hexane to produce the title compound Val-**9a** (2.40 g, 82%) as a white solid. Mp: 196–197 °C. R_f: 0.57 (hexane/EtOAc=1:1). $[\alpha]_D$ −30.1 (*c* 1.0). ^{1}H NMR: 0.91 (12H, d, *J*=6.3, CH_3), 1.91–2.11 (2H, m, Me_2C*H*), 3.98 (2H, t, *J*=7.8, NC*H*), 5.04 (4H, br s, CH_2Ph), 5.35 (2H, s, CO_2CH_2Ph), 7.04–7.58 (17H, m, Ar*H*+CbzN*H*), 7.98 (2H, s, Ar*H*), 8.34 (1H, s, Ar*H*), 10.31 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 18.5, 19.2, 30.2, 61.2, 65.5, 66.4, 114.4, 114.8, 127.0, 127.7, 128.2, 128.3, 128.6, 130.3, 136.0, 137.0, 139.5, 156.3, 165.3, 170.9. MS (FAB): 708 (M$^+$, 22%), 1416 ($M_2$$^+$, 3%). Anal. Calcd for $C_{40}H_{44}N_4O_8$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.54; H, 6.35; N, 7.72.

4.4.4. Phe-9a. The solution was concentrated under reduced pressure and the residue was recrystallized from THF/hexane to give the title compound (2.82 g, 85%) as a white solid. Mp: 133–135 °C. R_f: 0.63 (hexane/EtOAc=1:1). $[\alpha]_D$ +25.1 (*c* 1.0). ^{1}H NMR: 2.74–2.94 (2H, m, CH_2Ph), 2.94–3.14 (2H, m, CH_2Ph), 4.28–4.51 (2H, m, NC*H*), 4.97 (4H, s, CH_2Ph), 5.37 (2H, s, CO_2CH_2Ph), 6.99–7.58 (25H, m, Ar*H*), 7.76 (2H, d, *J*=8.1, CbzN*H*), 7.98 (2H, s, Ar*H*), 8.34 (1H, s, Ar*H*), 10.42 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 37.3, 57.1, 65.4, 66.5, 114.5, 114.9, 126.4, 126.8, 127.6, 127.8, 128.1, 128.3, 128.6, 129.2, 130.3, 136.0, 136.9, 137.8, 139.6, 156.0, 165.3, 170.9. MS (FAB): 805 [(M+H)$^+$, 10%], 1609 ($M_2$$^+$, 1%). HRMS (FAB): $C_{48}H_{45}N_4O_8$ requires 805.3232; found: 805.3243.

4.4.5. Leu-9a. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc=3:1) to afford the title compound (2.22 g, 73%) as a creamy yellow solid. Mp: 78–79 °C. R_f: 0.27 (hexane/EtOAc=5:2). $[\alpha]_D$ −30.9 (*c* 1.0). ^{1}H NMR: 0.90 (6H, d, *J*=6.0, CH_3), 0.91 (6H, d, *J*=6.3, CH_3), 1.33–1.84 (6H, m, CC*H* and CH_2), 4.07–4.34 (2H, m, NC*H*), 5.05 (4H, s, CH_2Ph), 5.37 (2H, s, CO_2CH_2Ph), 7.00–7.54 (15H, m, Ar*H*), 7.63 (2H, d, *J*=7.8, CbzN*H*), 8.01 (2H, s, Ar*H*), 8.40 (1H, s, Ar*H*), 10.34 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 21.5, 23.0, 24.4, 40.6, 54.0, 65.5, 66.5, 114.6, 114.9, 127.0, 127.7, 128.3, 128.4, 128.6, 130.3, 136.0, 137.0, 139.7, 156.1, 165.4, 171.9. MS (FAB): 737 [(M+H)$^+$, 11%], 1473 ($M_2$$^+$, 5%). Anal. Calcd for $C_{42}H_{48}N_4O_8$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.60; H, 6.56; N, 7.51.

4.4.6. Ser-9a. The solvent was evaporated in vacuo and the product was precipitated in hot hexane and filtered. Recrystallization of the solid from a mixture of THF and hexane afforded the title compound (2.15 g, 76%) as a creamy white solid. Mp: 196–197 °C. R_f: 0.62 (EtOAc). $[\alpha]_D$ −9.2 (*c* 1.0, DMSO). ^{1}H NMR: 3.52–3.77 (4H, m, CH_2OH), 4.22 (2H, q, *J*=9.0, NC*H*), 4.91–5.13 (6H, m, CH_2Ph and CH_2O*H*), 5.35 (2H, s, CO_2CH_2Ph), 7.01–7.56 (17H, m, Ar*H* and CbzN*H*), 8.00 (2H, s, Ar*H*), 8.32 (1H, s, Ar*H*), 10.27 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 57.9, 61.7, 65.6, 66.4, 114.6, 115.0, 127.0, 127.8, 128.2, 128.4, 128.6, 130.2, 136.0, 137.0, 139.6, 156.0, 165.4, 169.6. MS (FAB): 685 [(M+H)$^+$, 9%]. HRMS (FAB): $C_{36}H_{37}N_4O_{10}$ requires 685.2504; found: 685.2507.

4.4.7. Tyr-9a. The solvent was evaporated in vacuo and the product was precipitated in hot hexane and filtered. Recrystallization of the solid from a mixture of THF and hexane produced the target compound (2.73 g, 79%) as an ivory white solid. Mp: 216–218 °C. R_f: 0.25 (hexane/EtOAc=1:1). $[\alpha]_D$ +71.7 (*c* 1.0, DMSO). ^{1}H NMR: 2.64–2.81 (2H, m, C*H*HArOH), 2.81–2.98 (2H, m, CH*H*ArOH), 4.21–4.45 (2H, m, NC*H*), 4.97 (4H, s, CH_2Ph), 5.36 (2H, s, CO_2CH_2Ph), 6.66 (4H, d, *J*=8.4, Ar*H*), 7.12 (4H, d, *J*=8.4, Ar*H*), 7.21–7.53 (15H, m, Ar*H*), 7.66 (2H, d, *J*=8.1, CbzN*H*), 7.97 (2H, s, Ar*H*), 8.31 (1H, s, Ar*H*), 9.21 (2H, s, ArO*H*), 10.35 (2H, s, N*H*Ar). ^{13}C NMR: 36.7, 57.5, 65.4, 66.5, 114.4, 114.9, 121.5, 126.6, 126.8, 127.6, 127.8, 128.29, 128.34, 128.6, 129.5, 130.2, 136.0, 137.0, 139.6, 155.9, 156.0, 165.4, 171.1. MS (FAB): 837 [(M+H)$^+$, 6%], 1533 ($M_2$$^+$, 1%). HRMS (FAB): $C_{48}H_{45}N_4O_{10}$ requires 837.3130; found: 837.3121.

4.4.8. Gln-9a. The reaction mixture became turbid and the pale yellow product was collected by suction filtration. Recrystallization from a mixture of THF and hexane afforded the target compound (2.72 g, 86%) as a pale yellow solid. Mp: 207–208 °C. R_f: 0.66 (acetone/EtOAc=1/2). $[\alpha]_D$ −7.6 (*c* 1.0, DMSO). ^{1}H NMR: 1.69–2.03 (4H, m, CH_2CH_2CON), 2.03–2.31 (4H, m, CH_2CON), 4.11 (2H, q, *J*=6.8, NC*H*), 5.03 (4H, s, CH_2Ph), 5.36 (2H, s, CO_2CH_2Ph), 6.81 (2H, s, CON*H*H), 7.04–7.55 (17H, m, CONH*H*+Ar*H*), 7.63 (2H, d, *J*=7.5, CbzN*H*), 7.98 (2H, s, Ar*H*), 8.36 (1H, s, Ar*H*), 10.32 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 27.5, 31.6, 55.4, 65.6, 66.5, 114.5, 115.0, 127.0, 127.8, 128.3, 128.4, 128.7, 130.3, 136.1, 137.0, 139.7, 156.1, 165.4, 171.1, 173.6; MS (FAB): 767 [(M+H)$^+$, 13%], 1533 ($M_2$$^+$, 1%). Anal. Calcd for $C_{40}H_{42}N_6O_{10}$: C, 62.65; H, 5.52; N, 10.95. Found: C, 62.33; H, 5.61; N, 10.47.

4.4.9. β-Ala-10. The solvent was evaporated in vacuo and the product was precipitated in hot hexane and collected by suction filtration. Recrystallization of the solid from a mixture of THF and hexane afforded the title compound (2.26 g, 84%) as a white powder. Mp: 173–174 °C. R_f: 0.18 (hexane/EtOAc=1:2). ^{1}H NMR (acetone-d_6): 2.65 (4H, t, *J*=6.5, CH_2CH_2CON), 3.49 (4H, q, *J*=6.4, CbzNHCH_2), 5.05 (4H, s, CH_2Ph), 5.35 (2H, s, CO_2CH_2Ph), 6.46 (2H, br s, N*H*), 7.18–7.54 (15H, m, Ar*H*), 8.04 (2H, s, Ar*H*), 8.32 (1H, s, Ar*H*), 9.41 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 36.8, 37.0, 65.3, 66.4, 114.2, 114.6, 127.4, 127.8, 128.2, 128.4, 128.6,

130.3, 136.1, 137.3, 139.9, 156.2, 165.5, 169.7. MS (FAB): 653 [(M+H)$^+$, 24%]. Anal. Calcd for $C_{36}H_{36}N_4O_8$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.09; H, 5.54; N, 8.50.

4.4.10. Tyr(OBn)-9a. A mixture of Tyr-**9a** (2.00 g, 2.39 mmol), K_2CO_3 (1.65 g, 12.0 mmol), benzyl bromide **6a** (0.71 mL, 5.97 mmol), and 18-crown-6 (5 mg) was refluxed in a mixture of acetone (80 mL) and DMF (5 mL) for 24 h. The mixture was filtered and the filtrate evaporated in vacuo to give an oil that was purified by column chromatography on silica gel (hexane/EtOAc=2:1 gradient to 2:3) to afford a pale yellow solid. Recrystallization from a mixture of EtOAc and Et_2O gave the target compound (1.82 g, 75%) as white needles. Mp: 150–151 °C. R_f: 0.28 (hexane/EtOAc=2:1). $[\alpha]_D$ +14.9 (*c* 1.0). ^{1}H NMR: 2.68–2.87 (2H, m, C*H*H), 2.87–3.12 (2H, m, CH*H*), 4.21–4.48 (2H, m, NC*H*), 4.97 (4H, s, CH_2Ph), 5.05 (4H, s, CH_2Ph), 5.36 (2H, s, CO_2CH_2Ph), 6.92 (4H, d, *J*=9.0, Ar*H*), 7.06–7.57 (29H, m, Ar*H*), 7.70 (2H, d, *J*=8.0, CbzN*H*), 7.97 (2H, s, Ar*H*), 8.34 (1H, s, Ar*H*), 10.39 (2H, s, N*H*Ar). ^{13}C NMR: 36.5, 57.3, 65.4, 66.5, 69.2, 114.4, 114.9, 126.8, 127.6, 127.7, 127.8, 128.3, 128.4, 128.6, 129.9, 130.3, 136.0, 136.9, 137.2, 139.6, 156.0, 157.0, 165.3, 171.0; MS (FAB): 1017 [(M+H)$^+$, 5%]. HRMS (FAB): $C_{62}H_{57}N_4O_{10}$ requires 1017.4069; found: 1017.4086.

4.5. General procedure for the synthesis of 3,5-di-(*tert*-butyloxycarbonylamino)benzoates (7b–7d)

A mixture of compound **5** (1.0 equiv), the alcohol **6b–6d** (1.2 mol equiv), DMAP (0.1 mol equiv), HOBt (2 mol equiv), and DCC (3 mol equiv) was stirred in dry THF at 25 °C for 24 h. The white precipitate was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in EtOAc, washed with citric acid solution, Na_2CO_3 solution, water, and saturated NaCl solution successively. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude product. The crude product was further purified as described in the following text.

4.5.1. 3-Phenylpropyl 3,5-di-(*tert*-butyloxycarbonylamino)benzoate (7b). Starting from compound **5** (4.41 g, 12.5 mmol) and 3-phenylpropan-1-ol **6b** (2.05 g, 15.0 mmol), the title product **7b** was obtained as a white solid (1.34 g, 84%) after column chromatography on silica gel (eluent: hexane/EtOAc=5:1). Mp: 117–119 °C. R_f: 0.21 (hexane/EtOAc=5:1). ^{1}H NMR: 1.47 (18H, s, C(CH_3)$_3$), 1.90–2.07 (2H, m, PhCH_2CH_2), 2.74 (2H, t, *J*=7.7, PhCH_2CH_2), 4.21 (2H, t, *J*=6.3, ArCO_2CH_2), 7.14–7.34 (5H, m, Ar*H*), 7.75 (2H, d, *J*=1.8, Ar*H*), 7.97 (1H, t, *J*=1.8, Ar*H*), 9.55 (2H, s, N*H*Ar). ^{13}C NMR: 28.1, 29.9, 31.4, 63.7, 79.2, 112.4, 112.9, 125.9, 128.4, 130.4, 140.2, 141.1, 152.7, 165.7. MS (FAB): 470 (M$^+$, 70%), 940 (M_2^+, 5%). Anal. Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.66; H, 7.47; N, 5.83.

4.5.2. 2-(Naphthalen-1-yl)ethyl 3,5-di-(*tert*-butyloxycarbonylamino)benzoate (7c). Starting from compound **5** (2.00 g, 5.68 mmol) and 1-naphthaleneethanol **6c** (1.17 g, 6.81 mmol), the target product **7c** was obtained as a pale yellow solid (1.63 g, 57%) after column chromatography on silica gel (eluent: hexane/EtOAc=4:1). Mp: 131–134 °C. R_f: 0.29 (hexane/EtOAc=4:1). ^{1}H NMR: 1.48 (18H, s, C(CH_3)$_3$), 3.50 (2H, t, *J*=6.9, NpCH_2), 4.55 (2H, t, *J*=6.9, CO_2CH_2), 7.39–7.64 (4H, m, Ar*H*), 7.74 (2H, d, *J*=1.5, Ar*H*), 7.82 (1H, d, *J*=7.8, Ar*H*), 7.86 (1H, t, *J*=1.5, Ar*H*), 7.93 (1H, d, *J*=8.1, Ar*H*), 8.22 (1H, d, *J*=8.1, Ar*H*), 9.55 (2H, s, N*H*Ar). ^{13}C NMR: 28.1, 31.6, 64.7, 79.2, 112.6, 112.9, 123.6, 125.6, 125.7, 126.2, 127.1, 127.4, 128.6, 130.3, 131.5, 133.4, 133.8, 140.2, 152.7, 165.7. MS (FAB): 506 (M$^+$, 20%), 1013 [(M_2+H)$^+$, 2%]. Anal. Calcd for $C_{29}H_{34}N_2O_6$: C, 68.76; H, 6.76; N, 5.53. Found: C, 68.41; H, 6.87; N, 5.51.

4.5.3. Biphenyl-4-methyl 3,5-di-(*tert*-butyloxycarbonylamino)benzoate (7d). Starting from compound **5** (4.50 g, 12.8 mmol) and biphenyl-4-methanol **6d** (2.82 g, 15.3 mmol), the title compound **7d** was obtained as a white solid (1.86 g, 82%) after column chromatography on silica gel (eluent: hexane/EtOAc=9:2). Mp: 150–152 °C. R_f: 0.23 (hexane/EtOAc=9:2). ^{1}H NMR: 1.46 (18H, s, C(CH_3)$_3$), 5.38 (2H, s, ArCH_2), 7.33–7.59 (5H, m, Ar*H*), 7.63–7.73 (4H, m, Ar*H*), 7.75 (2H, d, *J*=1.8, Ar*H*), 7.99 (1H, t, *J*=1.8, Ar*H*), 9.55 (2H, s, N*H*Ar). ^{13}C NMR: 28.1, 65.9, 79.2, 112.5, 112.9, 126.7, 126.8, 127.6, 128.6, 129.0, 130.2, 135.3, 139.8, 140.0, 140.3, 152.7, 165.6. MS (FAB): 518 (M$^+$, 13%). HRMS (FAB): $C_{30}H_{34}N_2O_6$ requires 518.2411; found: 518.2411.

4.6. General procedure for the synthesis of 3,5-diaminobenzoates (8b–8d)

A mixture of the Boc-protected benzoates **7b–7d** and TFA (25 mol equiv) was stirred in CH_2Cl_2 at 25 °C for 3 h. The solvent was evaporated on a rotary evaporator and the residual was neutralized by $NaHCO_3$ solution until pH=8 at 5 °C. The residue was taken up in EtOAc (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water (100 mL) and then saturated brine (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude product. The crude product was purified as described in the following text.

4.6.1. 3-Phenylpropyl 3,5-diaminobenzoate (8b). Starting from compound **7b** (0.69 g, 1.47 mmol), the title product was obtained as a brown solid (0.33 g, 83%) after column chromatography on silica gel (eluent: hexane/EtOAc=1:1). Mp: 80–81 °C. R_f: 0.23 (hexane/EtOAc=1:1). ^{1}H NMR: 1.88–2.03 (2H, m, PhCH_2CH_2), 2.71 (2H, t, *J*=7.7, PhCH_2CH_2), 4.14 (2H, t, *J*=6.5, ArCO_2CH_2), 5.00 (4H, s, NH_2), 6.03 (1H, t, *J*=1.8, Ar*H*), 6.45 (2H, d, *J*=1.8, Ar*H*), 7.17–7.36 (5H, m, Ar*H*). ^{13}C NMR: 30.9, 32.5, 64.2, 104.6, 104.7, 126.9, 129.3, 129.4, 131.8, 142.1, 150.4, 167.8. MS (FAB): 270 [(M+H)$^+$, 98%]. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.75; N, 10.01.

4.6.2. 2-(Naphthalen-1-yl)ethyl 3,5-diaminobenzoate (8c). Starting from compound **7c** (2.96 g, 5.84 mmol), the target compound **8c** was obtained as a pale yellow solid (1.35 g, 75%) after column chromatography on silica gel (eluent: hexane/EtOAc=1:1). Mp: 124–128 °C. R_f: 0.23 (hexane/EtOAc=1:1). ^{1}H NMR: 3.46 (2H, t, *J*=6.9, NpCH_2), 4.48 (2H, t, *J*=6.9, ArCO_2CH_2), 4.99 (4H, s, NH_2), 6.03 (1H, t, *J*=1.8, Ar*H*), 6.42 (2H, d, *J*=1.8, Ar*H*), 7.42–7.49 (2H,

m, Ar*H*), 7.49–7.64 (2H, m, Ar*H*), 7.78–7.87 (1H, m, Ar*H*), 7.94 (1H, d, *J*=7.8, Ar*H*), 8.20 (1H, d, *J*=8.4, Ar*H*). ^{13}C NMR (some overlapping aromatic C signals): 31.6, 64.1, 103.7, 123.7, 125.6, 125.7, 126.3, 127.1, 128.6, 130.7, 131.6, 133.4, 134.0, 149.3, 166.8. MS (FAB): 306 (M^+, 55%). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.40; H, 6.00; N, 9.01.

4.6.3. Biphenyl-4-methyl 3,5-diaminobenzoate (8d). Starting from compound **7d** (1.61 g, 3.10 mmol), the target product **8d** was obtained as a pale pink solid (0.75 g, 76%) after column chromatography on silica gel (eluent: hexane/EtOAc=1:1). Mp: 162–165 °C. R_f: 0.27 (hexane/EtOAc=1:1). ^{1}H NMR: 5.03 (4H, s, NH_2), 5.29 (2H, s, ArCH_2), 6.03 (1H, t, *J*=1.8, Ar*H*), 6.48 (2H, d, *J*=1.8, Ar*H*), 7.29–7.41 (1H, m, Ar*H*), 7.41–7.57 (4H, m, Ar*H*), 7.57–7.76 (4H, m, Ar*H*). ^{13}C NMR: 65.3, 103.7, 103.8, 126.7, 126.8, 127.6, 128.7, 129.0, 130.5, 135.7, 139.8, 139.9, 149.5, 166.7. MS (FAB): 318 (M^+, 35%). HRMS (FAB): $C_{20}H_{18}N_2O_2$ requires 318.1363; found: 318.1362.

4.7. General procedure for the synthesis of Val-9b–Val-9e

A mixture of the 3,5-diaminobenzoates **8b**–**8d** or **8e**,[6] Cbz-protected valine (2.3 mol equiv), and EEDQ (2.2 mol equiv) in THF was stirred at 25 °C for 24 h. The solvent was evaporated in vacuo and the residual was taken up in EtOAc. The organic layer was washed with Na_2CO_3 solution, citric acid solution, Na_2CO_3 solution, water, and saturated NaCl solution successively. It was then dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude product. The crude product was purified as described in the following text.

4.7.1. Val-9b. Starting from compound **8b** (0.25 g, 0.92 mmol), the product was obtained as a brown solid (0.47g, 69%) after recrystallization from a mixture of THF and hexane. Mp: 180–183 °C. R_f: 0.59 (hexane/EtOAc=1:1). $[\alpha]_D$ −22.9 (*c* 1.0). ^{1}H NMR: 0.92 (12H, d, *J*=6.6, CHCH_3), 1.92–2.12 (4H, m, PhCH_2CH_2 and C*H*Me$_2$), 2.75 (2H, t, *J*=7.5, PhCH_2CH_2), 4.00 (2H, t, *J*=7.5, NC*H*), 4.25 (2H, t, *J*=7.5, CO$_2$CH_2CH_2), 5.04 (4H, s, PhCH_2OCON), 7.05–7.42 (15H, m, Ar*H*), 7.54 (2H, d, *J*=8.4, CbzN*H*), 8.00 (2H, s, Ar*H*), 8.29 (1H, s, Ar*H*), 10.31 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 18.5, 19.2, 29.8, 30.2, 31.4, 61.2, 64.0, 65.5, 114.3, 114.9, 125.9, 127.7, 128.3, 130.5, 137.0, 139.4, 141.0, 156.3, 165.4, 170.9. MS (FAB): 737 [(M+H)$^+$, 12%], 1473 [(M$_2$+H)$^+$, 1%]. HRMS (FAB): $C_{42}H_{48}N_4O_8$ requires 737.3545; found: 737.3541.

4.7.2. Val-9c. Starting from compound **8c** (1.20 g, 3.92 mmol), the product was obtained as a white solid (1.95 g, 64%) after recrystallization from a mixture of THF and hexane. Mp: 233–239 °C. R_f: 0.66 (hexane/EtOAc=1:1). $[\alpha]_D$ −27.7 (*c* 1.0). ^{1}H NMR: 0.92 (12H, d, *J*=6.6, CHCH_3), 1.91–2.12 (2H, m, C*H*Me$_2$), 3.52 (2H, t, *J*=6.0, PhCH_2CH_2), 4.00 (2H, t, *J*=7.5, NC*H*), 4.58 (2H, t, *J*=6.0, PhCH_2CH_2), 5.05 (4H, s, PhCH_2OCON), 7.20–7.41 (10H, m, Ar*H*), 7.41–7.64 (6H, m, Ar*H* and CbzN*H*), 7.81 (1H, d, *J*=6.0, Ar*H*), 7.93 (1H, d, *J*=6.0, Ar*H*), 7.98 (2H, s, Ar*H*), 8.17–8.27 (2H, m, Ar*H*), 10.29 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 18.5, 19.2, 30.2, 31.5, 61.2, 64.9, 65.5, 114.4, 115.0, 123.7, 125.65, 125.71, 126.3, 127.2, 127.3, 127.8, 128.4, 128.6, 130.4, 131.5, 133.4, 133.8, 137.0, 139.4, 156.3, 165.5, 170.9; MS (FAB): 773 [(M+H)$^+$, 15%], 1544 (M$_2^+$, 2%). HRMS (FAB): $C_{45}H_{48}N_4O_8$ requires 773.3545; found: 773.3542.

4.7.3. Val-9d. Starting from compound **8d** (0.65 g, 2.04 mmol), the crude product was subjected to chromatographic purification on silica gel (eluent: hexane/EtOAc=9:4). The pure product was obtained as a white solid (0.94 g, 59%) after recrystallization from a mixture of THF and hexane. Mp: 184–187 °C. R_f: 0.64 (hexane/EtOAc=1:1). $[\alpha]_D$ −23.6 (*c* 1.0). ^{1}H NMR: 0.91 (12H, d, *J*=6.3, CHCH_3), 1.90–2.10 (2H, m, C*H*Me$_2$), 3.98 (2H, t, *J*=9.0, NC*H*), 5.04 (4H, s, PhCH_2OCON), 5.40 (2H, s, ArCO$_2$CH_2), 7.10–7.42 (11H, m, Ar*H*), 7.42–7.62 (6H, m, Ar*H* and CbzN*H*), 7.63–7.75 (4H, m, Ar*H*), 8.00 (2H, s, Ar*H*), 8.34 (1H, s, Ar*H*), 10.32 (2H, s, N*H*Ar). ^{13}C NMR (some overlapping aromatic C signals): 18.5, 19.2, 30.2, 61.2, 65.5, 66.2, 114.4, 114.8, 126.8, 126.9, 127.6, 127.8, 128.4, 129.0, 130.3, 135.2, 137.0, 139.5, 139.7, 140.2, 156.3, 165.4, 170.9. MS (FAB): 785 [(M+H)$^+$, 10%], 1569 [(M$_2$+H)$^+$, 2%]. HRMS (FAB): $C_{46}H_{48}N_4O_8$ requires 785.3545; found: 785.3544.

4.7.4. Val-9e. Starting from ethyl 3,5-diaminobenzoate[6] (0.77 g, 4.27 mmol), the product was obtained as a white solid (1.65 g, 60%) after recrystallization from a mixture of THF and hexane. Mp: 225–229 °C. R_f: 0.67 (hexane/EtOAc=1:1). $[\alpha]_D$ +39.6 (*c* 1.0, DMSO). ^{1}H NMR: 0.94 (12H, d, *J*=6.5, CHCH_3), 1.34 (3H, t, *J*=7.0, CO$_2$CH$_2$CH_3), 1.92–2.15 (2H, m, C*H*Me$_2$), 4.01 (2H, t, *J*=7.8, NC*H*), 4.34 (2H, q, *J*=7.0, CO$_2$CH_2CH$_3$), 5.06 (4H, s, PhCH_2OCON), 7.06–7.46 (10H, m, Ar*H*), 7.55 (2H, d, *J*=8.2, CON*H*), 7.99 (2H, s, Ar*H*), 8.29 (1H, s, Ar*H*), 10.33 (2H, s, N*H*Ar). ^{13}C NMR: 14.2, 18.5, 19.2, 30.2, 60.9, 61.2, 65.5, 114.2, 114.8, 127.0, 127.7, 128.3, 130.6, 137.0, 139.4, 156.3, 165.4, 170.9. MS (FAB): 646 (M^+, 100%), 1292 (M$_2^+$, 10%). Anal. Calcd for $C_{35}H_{42}N_4O_8$: C, 65.00; H, 6.55; N, 8.66. Found: C, 64.94; H, 6.63; N, 8.62.

4.8. FTIR experiments

Compound **3** (Pro=Boc, R^1=Et, R^2=*i*-Pr, 100 mg) was dissolved in hot toluene (1.0 mL) and transferred to a KBr cell. The IR spectra were recorded at *t*=0, 5.5, and 11 min. At *t*=0, the sample was in the solution state and at *t*=11 min it became a gel. For background scanning, a drop of toluene was added to the KBr cell. Background subtraction of both the solvent and components in air was already done.

4.9. CD experiments

Tyr(OBn)-**9a** (9 mg) was dissolved in hot benzene (3 mL) and transferred to a quartz cell (1 cm path length). It was allowed to cool down to allow for gel formation. The temperature of the cell was then increased to the specified temperature via the temperature controller. The measurement was done from gel state (20–40 °C) to solution state (60–75 °C) at increasing temperature.

4.10. SEM experiments

Phe-**9a** (1 mg), Ser-**9a** (1.5 mg), and Tyr(OBn)-**9a** (2 mg) were dissolved in *o*-xylene (1 mL) separately. The samples

were freeze-dried on a Labconco Freezone 6LT Freezer Dry System under 50×10^{-3} mbar at -47 °C for 7 days. The SEM images were taken by a Leo Scanning Electron Microscope as described previously.[2a]

Acknowledgements

The work described in this paper was supported by a Direct Grant (Account no. 2060245) and a Focused Investment into Areas of Strength: Specialized Areas (Scheme B) by The Chinese University of Hong Kong. H.-F.C. is a recipient of the Croucher Senior Research Fellowship, Hong Kong (2006–2007).

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