Impressive Gelation in Organic Solvents by Synthetic, Low Molecular Mass, Self-Organizing Urethane Amides of L-Phenylalanine

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Synthetic routes leading to 12 L-phenylalanine based mono- and bipolar derivatives (**1**−**12**) and an in-depth study of their structure−property relationship with respect to gelation have been presented. These include monopolar systems such as *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-alkylamides and the corresponding bipolar derivatives with flexible and rigid spacers such as with 1,12-diaminododecane and 4,4′-diaminodiphenylmethane, respectively. The two ends of the latter have been functionalized with *N*-[(benzyloxy)carbonyl]-L-phenylalanine units via amide connection. Another bipolar molecule was synthesized in which the middle portion of the hydrocarbon segment contained polymerizable diacetylene unit. To ascertain the role of the presence of urethane linkages in the gelator molecule protected L-phenylalanine derivatives were also synthesized in which the (benzyloxy)carbonyl group has been replaced with (*tert*-butyloxy)carbonyl, acetyl, and benzoyl groups, respectively. Upon completion of the synthesis and adequate characterization of the newly described molecules, we examined the aggregation and gelation properties of each of them in a number of solvents and their mixtures. Optical microscopy and electron microscopy further characterized the systems that formed gels. Few representative systems, which showed excellent gelation behavior was, further examined by FT-IR, calorimetric, and powder X-ray diffraction studies. To explain the possible reasons for gelation, the results of molecular modeling and energy-minimization studies were also included. Taken together these results demonstrate the importance of the presence of (benzyloxy)carbonyl unit, urethane and secondary amide linkages, chiral purities of the headgroup and the length of the alkyl chain of the hydrophobic segment as critical determinants toward effective gelation.

1. Introduction

Small molecule (MW <1000) mediated gelation of organic solvents is receiving increasing attention recently.[1,2] Gels are wet and soft and appear like a solid substance, but are capable of undergoing large deformation. Various parts of living organisms are made of gels. Except for bones, teeth etc., mammalian tissues are highly gelatinous and are primarily composed of polymeric substances such as protein and polysaccharide networks. A number of synthetic polymers also show excellent gelation properties.[3,4] Gels made from small organic molecules may however, have advantages over traditional polymeric gels. This is because of the reversible nature of the noncovalent interactions that hold these small molecule based assemblies together. In addition, since these materials are made up of low molecular mass systems, they could be made to flow like small molecules in dilute solutions or at elevated temperatures.[5] Consequently, organogels are receiving widespread attention in diverse fields, such as cosmetics, implants, pharmacology, medicine, hardeners of toxic solvent spills and even in environmental cleanup.[6]

Solvent-selective gelation is thought to proceed via the formation of highly fibrous aggregates in which the gelator molecules are held together by noncovalent interactions which produce a three-dimensional, highly entangled "network" in which the specific solvent molecules could be entrapped. Frequently these three-dimensional networks are built up through several

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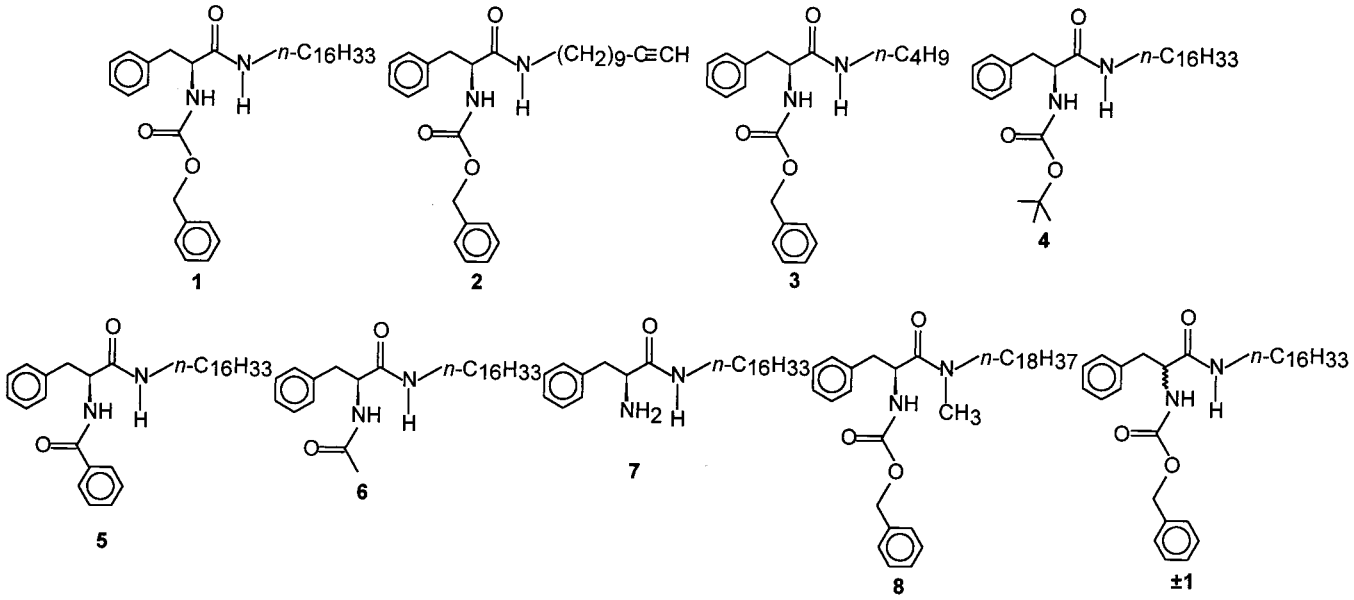
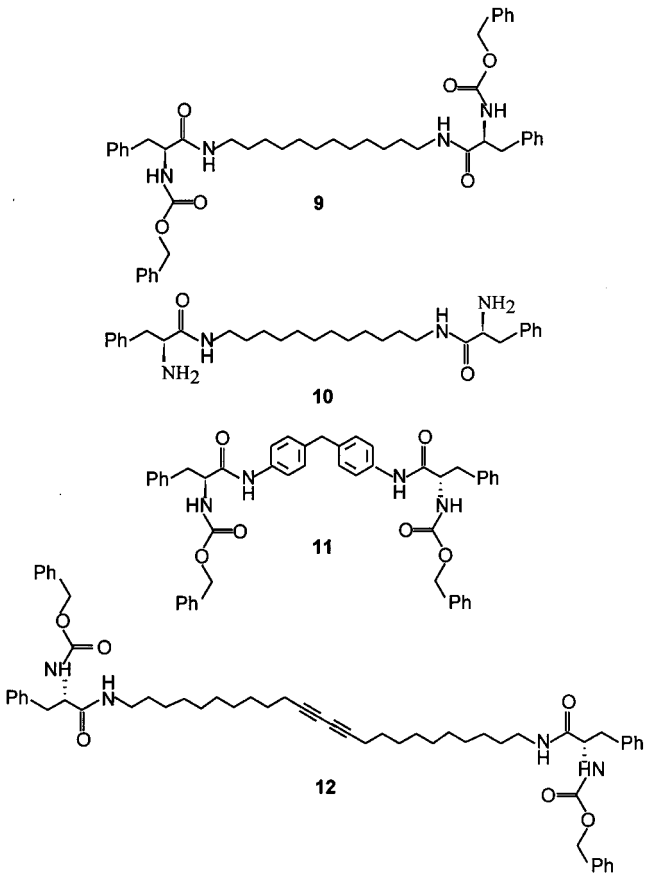
Chart 1



hydrogen bonding and/or van der Waals contacts. Molecules of widely different structures may produce such aggregation behavior. Hence compounds as diverse as anthracene alkyl ethers,[7a] cyclic depsipeptides,[7b] gluconamides,[7c] steroid analogues,[7d] and polar compounds containing long apolar moieties,[7e] all show gelation abilities in different solvents.

Due to our continuing interest in designing new synthetic amphiphiles[8] and examination of their aggregation behavior,[9] we have been developing a range of chiral amphiphilic molecules.[10] In a preliminary communication,[11] we also reported the exceptional gelation properties of six novel L-phenylalanine-based amphiphiles. In the present study to explore the impact of molecular structures on gelation of L-phenylalanine derivatives, we present the full details of the synthesis of altogether 12 L-phenylalanine-based mono- (Chart 1) and bipolar (Chart 2) derivatives, **1**−**12** including the ones described in earlier communication. Newly synthesized systems also include one with a rigid diaminodiphenylmethane anchor, the two ends of which have

Chart 2



been functionalized with *N*-[(benzyloxy)carbonyl]-L-phenylalanine units via amide connection. Another novel bipolar system was synthesized in which the middle portion of the hydrocarbon segment contained a diacetylene unit, making the resulting self-assemblies upon gelation polymerizable under the exposure of light. For comparison, the corresponding monopolar analogue with a terminal acetylenic (C≡C) residue was also prepared. To ascertain the role of the presence of urethane linkages in the gelator molecule, protected L-phenyla-

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lanine derivatives were also synthesized in which the (benzyloxy)carbonyl group has been replaced with (*tert*-butyloxy)carbonyl, acetyl, and benzoyl groups, respectively.

Upon completion of the synthesis and adequate characterization of the newly described molecules, we thoroughly examined aggregation and gelation properties of each of them in a few solvents or in their mixtures. The systems that formed gels were further characterized by optical microscopy and by electron microscopy. A few representative systems, which showed excellent gelation behavior, were further examined by FT-IR, calorimetric, and X-ray diffraction studies. To explain the possible reasons of gelation, the results of molecular modeling studies were also included.

2. Results and Discussion

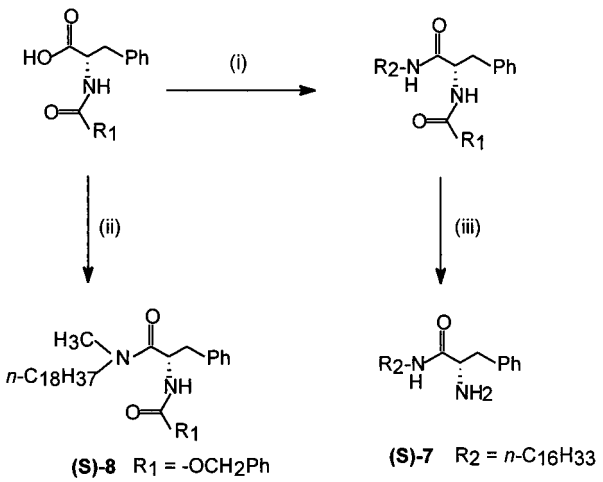
2.1. Molecular Design. We are interested in the study and understanding of the molecular systems which self-assemble by making use of the noncovalent interactions such as hydrogen bonding, aromatic stacking, hydrophobic interactions, etc. These forces promote the formation of supramolecularly held three-dimensional networks in which solvent molecules could be retained. From a glance of the relevant literature, it is apparent that for a system to self-assemble it should contain elements of hydrogen-bonding donors or acceptors such as acids, amides, urethanes, amines, or esters. Presence of long alkyl chains would reinforce van der Waals contacts and aromatic units, which should also help stabilize the assembly by interaromatic stacking forces. In addition to these elements, presence of chirality should endow "handedness" to the assembly.

In our endeavors to design and synthesize molecules which contain the above-mentioned functional elements, we chose an amino acid as the core. It is readily available, commercially inexpensive, naturally occurring, and can be obtained in enantiomerically pure form. In addition, amino acids contain both acid and amine residues, which can be chemically transformed into amide, urethane or ester linkages.

On the basis of these considerations we selected L-phenylalanine unit as the core, since it fulfills all the necessary requirements, i.e., contains an acid and amine functions, simple aromatic unit, and of course single chiral center. We have designed and synthesized a series of molecules **1**−**12**, keeping L-phenylalanine as the core, and studied in depth their self-assembly behavior to form macroscopic superstructures.

2.2. Synthesis. All the molecules that have been synthesized in the present study were based on L-phenylalanine derivatives and can be obtained in reasonable to good yield following simple synthetic strategy. A series of monopolar *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-alkylamides were prepared from *N*-[(benzyloxy)carbonyl]-L-phenylalanine and the corresponding alkylamines by using DCC-assisted amide-coupling reaction in the presence of catalytic amounts of DMAP (Scheme 1). The yields ranged from 60 to 80%. Due to the concomitant formation of dicyclohexylurea in the reaction mixture, the chromatographic separation required long, sometimes repetitive steps to ensure isolation of the pure products. In the case of bipolar derivatives same procedure was followed except that, monopolar

Scheme 1[a]



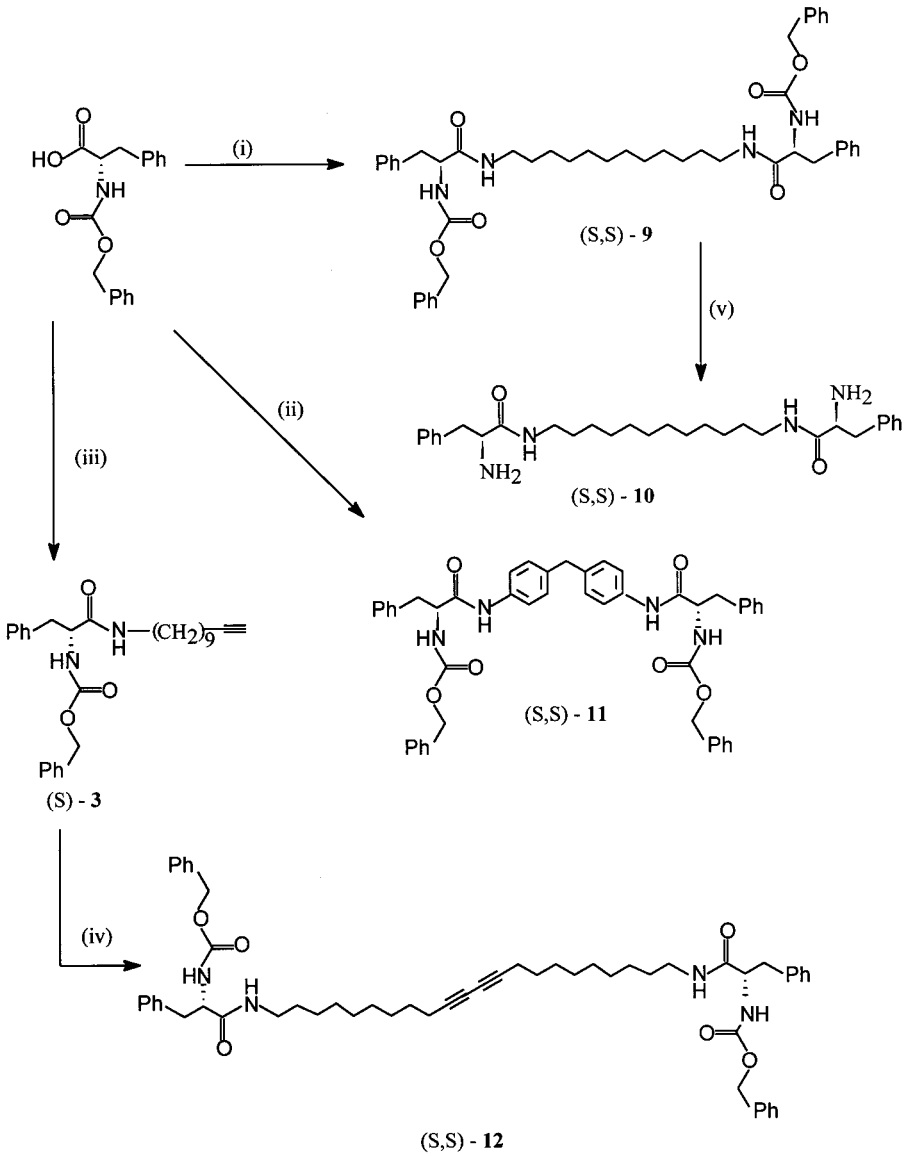
(S)-1 R_1= -OCH_2Ph; R_2 = *n*-$C_{16}H_{33}$ (82 %)
(±)-1 R_1= -OCH_2Ph; R_2 = *n*-$C_{16}H_{33}$ (82 %)
(S)-2 R_1= -OCH_2Ph; R_2 = *n*-$(CH_2)_9C{\equiv}CH$ (65 %)
(S)-3 R_1= -OCH_2Ph; R_2 = *n*-C_4H_9 (85 %)
(S)-4 R_1= -OBu^t; R_2 = *n*-$C_{16}H_{33}$ (65 %)
(S)-5 R_1= -Ph; R_2 = *n*-$C_{16}H_{33}$ (65 %)
(S)-6 R_1= -CH_3; R_2 = *n*-$C_{16}H_{33}$ (60 %)

[a] Reagents, conditions, and yields: (i) R_2NH_2, DCC, DMAP, dry $CHCl_3$, stir, 12 h, RT; (ii) *n*-$C_{18}H_{37}NHCH_3$, DCC, DMAP, dry $CHCl_3$, stir, 24 h, RT, 68%; (iii) H_2, 10% Pd/C, EtOAc, 88%.

long chain alkylamines were replaced with 1,12-diaminododecane, 4,4′-diaminodiphenylmethane, and 1,22-diaminodocos-10,12-diyne, respectively. While the first two diamino precursors for **9** and **11** were commercially available, **12** was synthesized by a procedure involving oxidative dimerization (Glaser coupling reaction) of *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-undec-10-yn-1-amide (**2**) as described in the Experimental Section. To ascertain the role of (benzyloxy)carbonyl unit in gelation the L-phenylalanine-*N*-hexadecylamide was also prepared by removal of the *N*-(benzyloxy)carbonyl group upon hydrogenation over 10% Pd/C in EtOAc. Similarly the corresponding bis-L-phenylalanine-(1,12)-*N*,*N*-dodecyldiamide (**10**) was also prepared by deprotection of the (benzyloxy)carbonyl groups at the two ends of 9 (Scheme 2). In addition to these compounds *N*-(*tert*-butyloxy)carbonyl-, *N*-acetyl-, and *N*-benzoyl-protected L-phenylalanine derivatives of 1-hexadecylamine were also prepared by using the above-mentioned DCC−DMAP coupling strategy. All the compounds (**1**−**12**) isolated as solids after solvent evaporation from the eluted fractions gave analytical and spectroscopic data consistent with their structure, cf. Experimental Section.

2.3. Aggregate Formation and the Role of Solvent. Compounds **1**−**3**, when dissolved in polar, aprotic solvents, were found to self-assemble to form macroscopic tapes as revealed by microscopy (see below). This aggregation behavior was found to be solvent-dependent. However, in polar, protic solvents, these systems do not show any evidence of aggregation. In protic solvents, the hydroxyl group of the solvent molecules presumably compete with the substrate molecules toward hydrogen bonding interactions, which probably

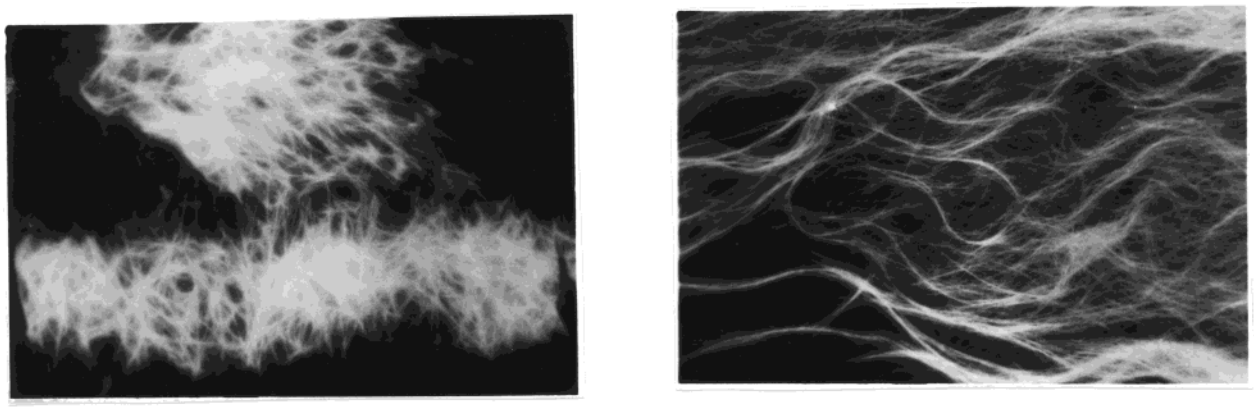
Scheme 2[a]



[a] Reaction conditions, reagents, and yields: (i) $H_2N(CH_2)_{12}H_2N$, DCC, DMAP, dry $CHCl_3$, stir, 20 h, 74%; (ii) 4,4′=diaminodiphenylmethane, DCC, DMAP, dry THF, stir 30 h, 40%; (iii) 1-aminoundec-10-yne, DCC, DMAP, dry $CHCl_3$, stir 20 h, 65%; (iv) dry methanol, CuCl, dry pyridine, stream of air, 9 h, 70%; (v) EtOAc, H_2, 10% Pd/C, 75%.

disturbs the intermolecular hydrogen bonding interactions that is normally present among the substrate molecules. We tried to generate aggregates from various solvents and solvent mixtures and found that in *n*-hexane−EtOAc (70−30% v/v) these molecules self-assembled and formed a stable macroscopic aggregate. Gentle warming in a mixture of *n*-hexane and EtOAc (70−30% v/v) followed by cooling for ∼30 min resulted in the formation of an aggregate. It took almost an hour to complete the aggregation, generating the formation of fibrous assemblies. The rate of aggregate formation was also found to depend on the ratio of the solvents employed in the mixture. While at lower percentages of EtOAc, it took longer time to induce aggregation (∼4 h). The aggregation time was considerably shorter at higher percentages (50%) of EtOAc. However, the gelation capacities decreased with increase in percentage of EtOAc. These molecules were also found to aggregate in a series of other non-hydroxylic organic solvents, e.g., CH_2Cl_2, $CHCl_3$, CCl_4, 1,2-dichloroethane, benzene, THF, toluene, etc. Table 1 records the relative gelation properties of these systems in various solvents.

2.4. Gelation Behavior. Each of the L-phenylalanine-based urethane amides **1**−**9** was subjected to gelation conditions as described in the Experimental Section. Compounds **1**−**3** readily self-assembled to form fibrous networks which also entrapped solvent molecules in the network with very high gelation capacities, typically 400 molecules of solvent per molecule of **1** in hexane−EtOAc (70:30 v/v). The dried gels from **1** were found to be quite stable to mechanical disturbances. The corresponding gels did not transform into viscoelastic fluids or crystallized on prolonged storage in stoppered vessel. In the case of **3**, the dried version of the gel formed was however, quite fragile to mechanical agitation. Even upon a gentle shaking, this gel was transformed in to a sol. The average gelation capacity was ∼100 molecules of solvent (70:30 v/v hexane−EtOAc) per molecule of **3**. As is perhaps expected, **2** formed a considerably stable gel with moderately high gelation



a b

Figure 1. Optical micrographs of two specimens of gel formed from **1** in hexane−EtOAc (70:30 v/v): (a) view at 100 times magnification and (b) view of another sample at 300 times magnification.

Table 1. Gelation Properties of 1 (0.1 mmol) in Various Organic Solvents[a]

entry	solvent	wt of the solvent (g)[b]	mole ratio of solvent[c]	gel melting *T* (°C)[d]
1	hexane	3.24	371	49
2	EtOAc	3.42	388	56
3	THF	1.95	270	56
4	benzene	2.40	319	54
5	toluene	2.74	297	58
6	dioxane	3.16	359	56
7	CH_2Cl_2	3.61	425	*e*
8	$CHCl_3$	3.32	278	46
9	CCl_4	2.97	193	48
10	$C_2H_4Cl_2$	4.27	440	51

[a] Gelation was observed at room temperature. A weighed amount of **1** (0.1 mmol) was dissolved in a given organic solvent by warming in a stoppered tube. Resulting solution was cooled to ambient temperature and allowed to stand for ∼1 h. [b] Amount of solvent retained upon gelation after draining off excess ungelated solvent by turning the tube upside down. [c] Mole ratio represents the number of solvent molecules that adhere with gel per molecule of the gelator. The minimum concentrations refer to room temperature. [d] This represents the temperature (±1 °C) at which the gels break apart upon heating. [e] Not determined.

capacity ∼300 molecules of solvent (70:30 v/v hexane−EtOAc). The corresponding gel was also quite stable to mechanical disturbances and has a sufficiently long (>2 months) shelf life. The minimum concentration that was necessary for **1** to gelate and its gelation capacities in various solvents are summarized in Table 1.

2.5. Characterization of Gels. The gels formed from **1**−**3** and **9** were characterized by various microscopic methods as described below.

2.5.1. Optical Microscopy. The gel formed from **1** was placed under vacuum for 2 h, and a small piece of this specimen was transferred on to a cover slip and observed under an optical microscope. Clusters of thick, long fibers were observed (Figure 1 a,b). To secure information at higher resolution, we then examined these and other aggregates by electron microscopy.

2.5.2. Scanning Electron Microscopy. Scanning electron micrographs (SEMs) were obtained for these compounds as described in the Experimental Section. The presence of highly intertwined fibrous meshwork was confirmed in each of these systems. To follow the steps that might be involved in gelation, the self-assembly process initiated by each of **1**−**3** were verified by dissolving each of these in various solvents and carefully studying their aggregation behavior. Compound **1** formed large white clothlike tapes in hexane−EtOAc mixture (70:30 v/v) on standing for ∼1 h as revealed from SEM (Figure 2 a,b). SEM further showed the presence of long, thick fibers with a typical aspect ratio of >36 in a meshwork. This aggregate was also found to be quite stable to mechanical disturbances.

Similarly, **2** also formed macroscopic aggregates in light petroleum ether or hexane−EtOAc (70:30 v/v) with moderate mechanical strength. SEM revealed the presence of sufficiently long fibers with an aspect ratio of >8 in the gels of **2** (Figure 2c). When set to aggregate from the same solvent mixture hexane−EtOAc (70:30 v/v), **3** formed rather brittle aggregates, which were found to be particularly susceptible to the mechanical disturbances. Examination of SEM suggests that these aggregates were made of very thin relatively short fibers in a meshwork in contrast to that of **1** and **2** (Figure 2d).

2.5.3. Transmission Electron Microscopy. The systems **1**−**3**, while undergoing self-assembly, produced various microstructures to entrap solvent molecules. These microstructures were further verified by transmission electron microscopy (TEM). From the TEM traces of **1**, it is evident that there exists a collection of fine reticules in these gels which might have an important role in entrapping the solvent molecules in the submicrometer-sized pores (typical diameter ∼1000 nm) of the gels (Figure 3a). Under high magnification, the presence of channels of different sizes in this network was observed. Closer examination of various sections of TEM images suggested that the fibers often existed in long tapelike morphologies with high aspect ratio, the typical widths of the tape being 30−50 nm. It also appears from the micrographs that these tapelike fibers are hollow with constrictions at regular intervals (Figure 3b).

2.6. Role of Molecular Subunits in Monopolar *N*-[(Benzyloxy)carbonyl]-L-phenylalanine-*N*-alkylamides (1−3). These molecules exhibited self-assembling properties in some solvents to form macroscopic aggregates exhibiting gelation property. To determine the significance of each of the functional units present in these molecules such as, the effect of chain length, role of urethane, phenyl rings and amide linkages, etc., which are believed to have active participation in the process of self-assembly, we examined the following parameters in some detail.

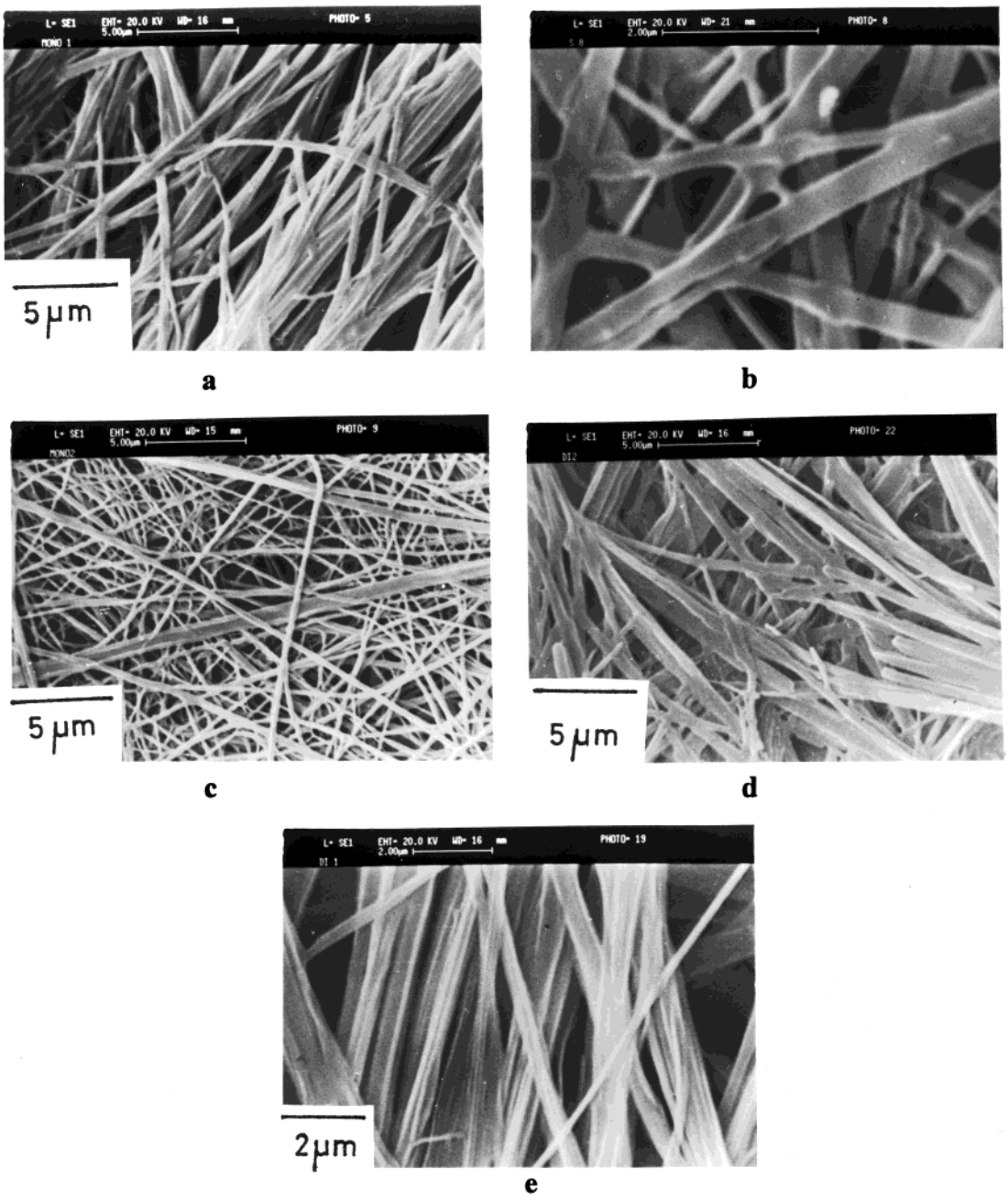


Figure 2. Scanning electron micrographs of the gels formed from **1, 2**, **3**, and **9** in hexane−EtOAc (70:30 v/v).

2.6.1. Alkyl Chain Length. Significance of the alkyl chain length on gel formation was evaluated by constructing various *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-alkylamides of variable chain lengths, **1**−**3**. It was observed that the mechanical strength of the gel had direct correlation with the chain lengths of the alkyl moiety. With a long *n*-hexadecyl chain in **1**, the gel formed was quite stable to mechanical disturbances. The fibers that could be seen were also quite long (aspect ratio >30), and its gelation capacity was found to be very high. On the other hand with an alkyl chain length of four carbons (*n*-butyl) in **3**, the corresponding gel was found to be especially sensitive even to little mechanical disturbances. Thus even with gentle agitation, the gel could be transformed into a sol. Consistent with poor mechanical strength, the gelation capacity of **3** was also much less compared to that of **1**. In the case of the 1-amino-9-undecyne **2**, the above-mentioned properties were found to be between that of **1** and **3**. Taken together, it is apparent that the compounds with longer chain length, the mechanical strength and gelation capacity was higher. This could be related to better van der Waals stabilization with compounds having longer chains in aggregates.

2.6.2. Effect of Replacement of the N-(Benzyloxy)-carbonyl Unit. The presence of a (benzyloxy)carbonyl group was found to be very important especially in the gelation properties manifested by some of the above compounds. It was found that the urethane moiety containing the benzyl group is very active in inducing the self-assembly to form the fibrous networks. When the (benzyloxy)carbonyl group was replaced by a (*tert*-butyloxy)carbonyl group such as in **4**, no aggregation was observed despite the presence of a urethane linkage in the latter case. The introduction of a *tert*-butyl group in place of a (benzyloxy)carbonyl unit disturbs the

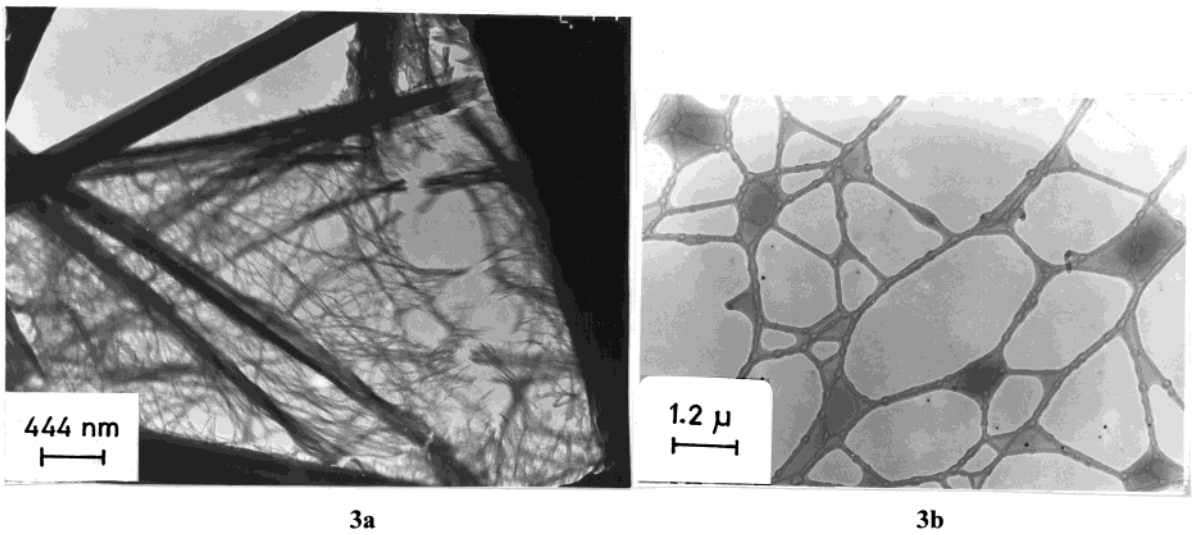
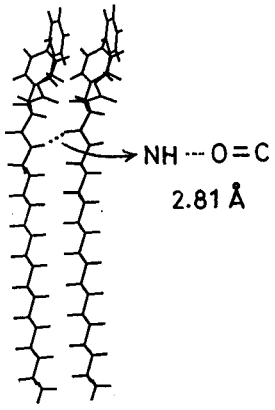
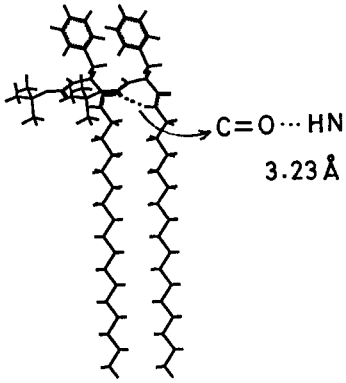


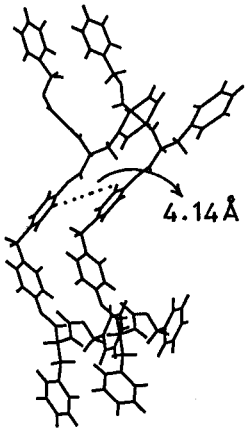
Figure 3. Transmission electron microscopic images of the gel sample of **1** formed in hexane−EtOAc (70:30 v/v).



(a)
N-benzyloxycarbonyl-L-phenylalanine-N-hexadecylamide



(b)
N-t-butyloxycarbonyl-L-phenylalanine-N-hexadecylamide



(c)
bis-(N-benzyloxycarbonyl-L-phenylalanine)4-4'-diaminodiphenylmethane

Figure 4. Energy-minimized molecular conformations of assemblies of (a) **1**, (b) **4**, and (c) **11**, respectively.

hydrogen-bonding environment at the urethane end thus hindering the self-assembly. The energy-minimization studies point to a similar conclusion. The bulky *tert*-butyl group comprising of three methyl groups causes pronounced crowding around the urethane group unlike, in (benzyloxy)carbonyl group where the benzyl group is a small residue capable of further stabilization through additional interaromatic π-stacking interactions via its flat phenyl rings from the benzyl group (Figure 4). However, in **4** the phenyl rings of the L-Phe units go out of plane, leaving little scope for any interaromatic π-stacking stabilization. This in turn increases the distance between each monomer of **4**, where one −N−H part of an amide of **4** remains >3.5 Å apart from >C═O part of an amide of another molecule of **4**. Clearly in this scenario, the intermolecular association through hydrogen bonding becomes not viable. Interestingly, compound with >N−H amides of

L-phenylalanine with acetyl and benzoyl groups did not aggregate effectively. This may be because of the following reasons. Calculations suggest that with *N*-benzoyl group present in **5**, the molecule cannot effectively allow both hydrogen bonding between the *N*-amide linkages and the interaromatic stacking interactions at the same time. If one of these two stabilizing interactions is absent, then the molecules of **5** can no longer effectively participate in intermolecular interactions that can result in the formation of a macroscopic aggregate or a gel. This argument was further strengthened when the *N*-(benzyloxy)carbonyl group in **1** was replaced with an *N*-acetyl group in **6**. Again the formation of neither an aggregate nor a gel was observed from a solution of **6** in above organic solvents. For the hydrogen bonding to prevail between the amide linkages of **6**, the interaromatic stacking interactions between the phenyl residues of the L-phenylalanine units could not be accommodated in the energy-minimized structures of **6**.

The energy-minimization calculations do not address why the sols form gels on cooling rather than induce a phase separation into solid and liquid. However, they provide useful insights pertaining to the structural factors at the molecular level that may be promoting the process of self-assembly of the individual phenylalanine derivatives, which in turn should be responsible for the gelation.

2.6.3. Effect of Removal of the N-(Benzyloxy)carbonyl Unit. To understand the significance of *N*-(benzyloxy)-carbonyl group further, we also examined the aggregation properties of L-phenylalanine-*N*-hexadecylamide **7**, which was synthesized upon hydrogenolysis of the *N*-(benzyloxy)carbonyl compound **1**. Notably, in any of the solvents discussed above and also in polar protic solvents, any sort of aggregation or gelation was not observed with **7**. Energy-minimization studies with an array of several molecules of **7** suggested that while hydrogen-bonding type association is still possible, it is the absence of additional interaromatic π-stacking from (benzyloxy)urethane side chains render these molecules inadequate for gelation even in solvents such as EtOAc or hexane or in their mixtures.

2.6.4. Role of Secondary Amide Linkage. We then wondered whether replacement of the primary amide type of linkage between the hydrocarbon chain and the L-phenylalanine (NHCO) with a secondary amide link ($N(CH_3)CO$) would affect the gelation process. To probe this, we prepared *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-methyl-*N*-octadecylamide, **8**. This molecule did not aggregate at all in any of the above-mentioned solvents to form any fibrous networks and a gel. The material showed only platelets devoid of any fibrous microstructures. Clearly the prevention of N−H···O═C type of intermolecular hydrogen-bonding association in **8** inhibit the aggregation of **8** in any organic solvent in a manner conducive to gel formation.

2.6.5. Chirality. From all of the above observations we conclude that the *N*-(benzyloxy)carbonyl group actively participates in the hydrogen-bonding interactions with its neighboring molecules and the urethane moiety present in the (benzyloxy)carbonyl group is quite important. In addition, the presence of primary amide group (−CONH−) and the optimization of the chain length of the alkyl residues and the chiral nature of the amino acid core are essential for these systems to self-assemble effectively and to form a fibrous networks to exhibit pronounced gelation behavior.

To understand the significance of chirality on the gelation behavior of **1**, we also synthesized a racemic phenylalanine derivative such as (±)-**1**. Importantly the racemic derivative did not exhibit any gelation in the above solvents. The racemic compounds probably form planar aggregates that are not being conducive for gelation. It is possible that for the formation of gel, a chiral aggregate is also necessary. The packing densities of amphiphiles in an aggregate with racemic and pure enantiomeric headgroups are quite different. Thus when the amino acid core is in a pure enantiomeric form, it can also provide a sense of handedness to the resulting self-assembly. Then the intermolecular hydrogen bonding and aromatic stacking interactions reinforce the formation of nonplanar aggregates.

It would be perhaps instructive to put these results in perspective with related gel-forming molecules where chirality plays an important role in effecting gelation. For instance *N*-[(benzyloxy)carbonyl]-L-alanine-4-hexadecanoyl-2-nitrophenyl ester has earlier been shown to gelate in solvents such as MeOH and cyclohexane.[12] Intermolecular hydrogen bonds between N−H and C═O residues of the urethane group in addition to the existence of dipole−dipole interactions between $-NO_2$ and >C═O units as well as van der Waals contacts between the long alkyl chains are believed to contribute significantly to aggregation in this example.

As mentioned earlier, the presence of chirality often determines the efficiency of the amino acid based gelators.[13] Thus, while the pure enantiomeric derivatives afforded organogels, the corresponding racemic derivatives formed platelets and did not gelate effectively. Recently, Hanabusa et al. described[14] gelation from the bis-octadecylurea derivatives based on 1,2-bis-(amine)cyclohexane. Interestingly only the *trans*-(*R,R*) derivative exhibited gelation as opposed to the *cis*-(*R,S*) derivative, indicating the nature of physical gelation to be diastereospecific. However, instances are also known where racemic mixtures of optically active compounds form effective gels in aqueous media.[15] Therefore it appears that the presence of chirality is an important criterion for the gelating systems that are based on amino acid backbones such as the one described herein.

2.6.6. Effect of Dimerization. Recently, organic gelators based on dimeric, bolaform amides derived from *N*-protected L-valine or L-isoleucine units have been described.[16] These compounds were reported to form fibrous assemblies which are held together by hydrogen-bonded networks. In view of this report, we also prepared the corresponding dimeric L-Phe derivatives to examine the role of dimerization on gelation. Consequently we synthesized the L-Phe derivatives, **9**−**12**.

(12) Hanabusa, K.; Okui, K.; Kanako, K.; Koyama, T.; Shirai, H. *J. Chem. Soc. Chem. Commun.* **1992**, 1371.
(13) Hikada, S.; Murata, M.; Onai, T. *J. Chem. Soc., Chem. Commun.* **1984**, 562.
(14) Hanabusa, K.; Shimura, K.; Hirose, K.; Yamada, M.; Shirai, H. *Chem. Lett.* **1996**, 885.
(15) Fuhrhop, J.-H.; Demoulin, C.; Rosenberg, J.; Boettcher, C. *J. Am. Chem. Soc.* **1990**, *112*, 2827 and references therein.
(16) Hanabusa, K.; Tanaka, R.; Suzuki, M.; Kimura, M.; Shirai, H. *Adv. Mater.* **1997**, *9*, 1095.

First 1,12-diaminododecane was coupled to *N*-[(benzyloxy)carbonyl]-L-phenylalanine on either of its amine ends to form a bolaamphiphile type molecule **9**. This self-assembled in a mixture of hexane and EtOAc (70−30% v/v) to form a stable macroscopic aggregate, containing bundles of thin and brittle braided tapes as evident from the SEM pictures (Figure 2e) similar to those observed with **1**−**3**. But, when the preparation of a gel from $CHCl_3$ was attempted, a very highly viscous and transparent gel with very long (>6 months) shelf life was produced. When a thin layer of this sticky mass was coated on appropriate surfaces such as glass or metal plates, the two surfaces were found to adhere very tightly. We believe that this observation is significant and will address this in detail in near future.

2.6.7. Role of N-(Benzyloxy)carbonyl group in Dimeric molecules. The (benzyloxy)urethane part was found to be indispensable for gelation in the case of monopolar compounds such as **1**−**3**. To ascertain the role of this moiety in bipolar derivatives, we also prepared the corresponding deprotected diamine, **10** upon hydrogenolysis of **9**. Importantly **10** showed no indication of gel formation from the above solvent mixtures, and the solid did not exhibit any characteristic microstructure irrespective of the solvents from which the solid was obtained.

2.6.8. Role of Rigid Spacer in Dimeric Molecules. To assess the contribution made by the spacer chain (flexible vs rigid) in the dimeric molecules toward aggregation and gelation, we compared the properties of the dimeric L-Phe-amides connected through a polymethylene chain **9** with the one that contained a rigid spacer such as 4,4′-diaminodiphenylmethane unit **11**. Notably this molecule, **11**, did not gelate at all in the above-mentioned organic solvents as was observed with **9**. Energy-minimization studies indicated that the two aromatic rings of the diaminodiphenylmethane in **11** remain in a conformation perpendicular to each other (Figure 4). In this situation, they go out of plane from each other and in this conformation there exists no aromatic π-stacking interactions between the phenyl rings a necessary prerequisite for achieving significant intermolecular hydrogen bonding interactions. Therefore, the lack of pronounced noncovalent intermolecular interactions with the incorporation of rigidity in the spacer make the aggregation and gelation impossible with **11**.

2.7. DSC Studies. The thermal stability of the solid aggregates produced from **1** in different solvents was also examined by differential scanning calorimetry (DSC 2, Perkin-Elmer Model). Solid samples generated upon drying of a solution of **1** in MeOH showed a melting endotherm at ∼98 °C. However, the corresponding solid sample generated upon drying of a gel slice produced from hexane−EtOAc mixture showed a melting only at ∼123 °C. Similarly, while the solid **3** prepared from its solution in MeOH melted at ∼92 °C, the dried sample obtained upon drying of the fibrous gel samples melted at ∼146 °C. Similar differences were also noticed with bipolar **9**. Thus while the solid produced from viscous gels of **9** melted at ∼167 °C, the corresponding solid formed from evaporation of a methanolic solution of **9** melted into a liquid at ∼127 °C. Taken together these variations in the thermal properties of the aggregates in their solid state produced from the same molecules from specific protic and aprotic solvents suggest that their aggregation and organization in the solid state are influenced by the environment of solvent molecules from which samples are generated.

2.8. Powder XRD Studies. To discern the nature of the solid aggregates produced from different solvents from the same molecule, samples were examined by powder X-ray diffraction. A sample of **1**, which formed a gel in hexane/EtOAc was kept in a tube. Compound **1** was also dissolved in MeOH in another tube. These two samples thus prepared in two different solvents were dried and powdered, and their powder XRD pattern was recorded. Notably, the powder XRD patterns of the same compound dried from two different solvents, i.e., a nonhydroxylic solvent such as, EtOAc and a protic solvent such as MeOH were quite different from each other (not shown). Protic solvent molecules compete with the intergelator molecular hydrogen-bonding interactions and thus hinder the process of self-assembly of the gelator molecules in MeOH. Because of this competition, these gelator molecules did not gelate in *hydroxylic* solvents. In contrast the aprotic solvents provide favorable environment for the hydrogen bonding interactions between the gelator molecules **1**, **2**, and **3**.

Thus with the aid of the X-ray data, it was demonstrated that representative molecules **1**−**3** are polymorphous. In all the instances where powder diffraction data were obtained with each of **1**−**3**, the morphs for samples from MeOH were found to be different from those obtained from hexane−EtOAc. However, these data did not provide critical information pertaining to the unit cell dimensions.

2.9. Infrared Studies. Aggregation of **1** in $CHCl_3$ was studied by infrared spectroscopy (FT-IR). At low concentration (∼10 mM) of **1** when it remained in the form of a solution, single sharp bands were observed in the −NH stretch region (3332 cm^{-1}) and also at the carbonyl amide I (1668 cm^{-1}) and the amide II (1544 cm^{-1}) regions. Increasing the concentration of **1** in $CHCl_3$ to ∼25 mM (above the minimum concentration necessary for gelation) led to significant shifts of both the NH and amide I bands to 3301 and 1649 cm^{-1}, respectively, while the amide II band moved up to 1561 cm^{-1}. These concentration-dependent spectral changes clearly suggest the formation of intermolecular hydrogen-bonded supramolecular arrays in the gelated samples. We also found that the spectrum of the KBr pellet of **1** was similar to that of the gel sample, suggesting that the pattern of hydrogen bonding in the gel was quite similar to that in the solid state.

In contrast, when similar experiments were performed using samples of **1** in MeOH, concentration variation showed band broadening, implying the participation and competition of the MeOH molecules in the hydrogen bonding with the individual molecules of **1**, inhibiting an effective intermolecular association, a necessary prerequisite for gelation.

2.10. Effect of Using a Polymerizable Spacer. Instances of gelators are known where polymerization has been attempted in the gel phase. Recently Weiss et al. examined[17] the properties of organogels before and

(17) Gu, W.; Lu, L.; Chapman, G. B.; Weiss, R. G. *Chem. Commun.* **1997**, 543.

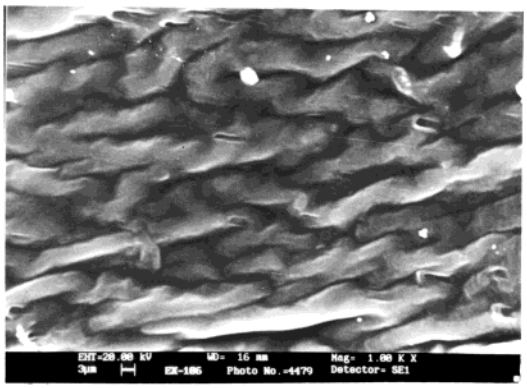


Figure 5. Scanning electron micrograph of the polymerized gel formed from **12** in hexane−EtOAc (70:30 v/v).

after the polymerization involving methyl methacrylate or styrene in the presence of tetraoctadecylammonium bromide (TOAB). Interestingly, TOAB, the gelator, could be removed leaving the polymerized matrix with vacant submicrometer cross-sectional channels.

In an alternative approach, to examine the role of polymerization in a gelated environment, we appended two core gel-forming units with an alkanediyl type spacer containing a polymerizable diacetylene group in the middle. For this purpose we used 1,22-diaminodocos-10,12-diyne which was synthesized by Glaser oxidative coupling from appropriate precursors. The idea of preparing this molecule was to study the aggregation and gelation behavior of this system before and after polymerization. In particular the polymerization of gels prepared from prepolymerizable molecules offer the possibility of engineering various properties such as stability and enhanced optical characteristics. The bolaamphiphiles containing diacetylene units polymerize normally upon UV irradiation. The reactive group in the polymethylene spacer could be conveniently "stitched" via intermolecular covalent connection in the middle portion of the spacer. The polymer is formed by 1,4-addition of the diacetylenic monomers, initiated by UV irradiation. We found that the molecules of **12** aggregate to form a white translucent gel in hexane−EtOAc (70:30, v/v) before polymerization. However, the same sample gradually turns purple upon exposure to daylight and becomes phase separated from the solvents in which it exists as gel. Once polymerized, the resulting solid can no longer exhibit the property of gelation as the same is virtually insoluble in most of the organic solvents. The resulting polymer was found to be intensely colored, in the case of **12** being deep purple. SEM examination of this purple-colored sample has revealed the presence of thick fibrous network made of polymerized fibers of thickness ~4.5 μM (Figure 5).

In the case of amphiphiles containing a diacetylene group to polymerize, the amphiphiles must organize into the correct packing and orientation to undergo 1,4-addition to the conjugated polymer backbone. Therefore, the polymerization reaction itself and the optical detection of the pink color provide indirect evidence of the formation of an ordered assembly. In other words, the formation of the colored polymer can be used as a quick "benchtop" test of pronounced self-organization. Interestingly, gel samples of **12** underwent polymerization upon exposure to daylight. This may be because **12** must be forming a stable, self-assembled aggregate in which the diacetylene units of the neighboring molecules are ideally positioned for polymerization

3. Conclusions

From the present study it appears that the following structural features are necessary for the formation of gels from these low molecular weight *N*-[(benzyloxy)-carbonyl]-L-phenylalanine-*N*-alkyl amides. First, there should be a certain minimum alkyl chain length below which gelation is ineffective. Second, the urethane group arising from the *N*-(benzyloxy)carbonyl functionality must be present in order to attain the required geometry for optimal intermolecular packing. Third, the presence of intermolecular association through primary alkyl amide group (NH−CO) is also essential for the stabilization of the assembly. Fourth, and perhaps most intriguing, is necessity that the core amino acid should be enantiomerically pure. This structural requirement appears to be necessary for the gelation where the array of self-assembled molecules of **1** manifest the formation of a twisted, nonplanar aggregate due to the presence of chirality. In such an aggregate, the packing of amphiphiles must be very different from that of a planar aggregate such that the solvent molecules could be retained in the former. The molecular fidelity observed during the aggregation process is in good agreement with the reversible assembly processes postulated by Whitesides and co-workers.[18] Clearly the present study demonstrates how self-assembly involves association by many weak, reversible interactions that result in a final structure driven by the respective thermodynamic minima.

In conclusion, *N*-[(benzyloxy)carbonyl]-L-phenylalanine-*N*-hexadecylamide has been shown to form excellent thermoreversible gels in a number of organic solvents or in their mixtures. The formation of gel was found to depend on the concentration of the gelling agent, solvents, and the temperature. The SEM and TEM studies suggest the formation of intertwined threads and fibers juxtaposed by slender filaments, which also produce a network with pores, which probably hold solvent molecules due to surface tension in the gel. The specific role played by each structural subunits in inducing gelation from **1** was examined in detail. Clearly, the hydrogen-bonding interactions between the N−H and C═O of the urethane as well as the amide connector, the interaromatic π-stacking interactions, and the van der Waals interactions of the long hydrocarbon segments are essential driving forces for gelation and its mechanical stability. In addition to the monomeric systems, the effects of attaching *N*-(benzyloxy)carbonyl-protected L-phenylalanine at the chain termini of few bipolar systems were also studied. The bipolar molecule, **9**, shows strong adhesive property in addition to the gelation, while the corresponding bipolar system with a polymerizable residue in the alkanediyl spacer chain also exhibited gelation behavior prior to polymerization. It is notable that the gel formed from **12** could be conveniently polymerized when exposed even to daylight, which confirms the existence of

(18) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312.

pronounced order in the supramolecular arrays formed in the gels of **12**.

The phenylalanine compounds presented herein have many properties that are common with other gelator systems described in recent literature. The presently described molecules are, however, rather easy to prepare and amenable to wide structural alterations. These should therefore be excellent starting materials for the design of functional gels. Efforts are underway toward this direction in our laboratory.

4. Experimental Section

4.1. General Methods. All reagents and compounds were purchased either from Aldrich or Fluka and were used without further purification. Silica gel (Merck) 60−120 mesh was used for column chromatography. ^{1}H NMR spectra were recorded at either 90 or 300 MHz. Chemical shifts are given in parts per million downfield from an internal standard (tetramethylsilane, TMS). Mass spectra were recorded on a JEOL GCMS mass spectrometer. Optical rotations were run at 589 nm on a JASCO DIP-370. FTIR experiments were carried out on a SHIMADZU instrument model FTIR-8101 equipped with a DR-8001 workstation. XRD studies were conducted on an STOE/STADI-P powder X-ray diffractometer. SEM studies were carried out on a JEOL stereoscan S-360 scanning electron microscope and TEM studies were performed on a JEOL 200 CX transmission electron microscope. Melting points were recorded in open capillaries and are uncorrected. Descriptions of other instruments used for various characterizations have been published.[8a,b]

4.2. Modeling Parameters. The modeling studies were conducted with BIOSYM software running on a Silicon Graphics Indigo workstation. The molecules were built using standard amino acid templates, bond lengths, angles, and side-chain dihedral angles. The atoms within each molecule were assigned their proper hybridization, charge, and bond order utilizing the Builder module of Insight (Version 2.3.5). The consistent valence force field (CVFF) provided by the Discover module was chosen for the minimization constraints. This force field was applied to the constructed amino acid derivative and evaluated with conjugate gradient method. The interaction number for the conjugate gradient method was 200. The derivative (or convergence criterion) was chosen as 0.001 kcal/(mol Å). The conformational preference of each molecule was determined in the following manner: the peptide underwent ∼1000 steps of a dynamic simulation at 300 K with a time interval of 1.0 fs. The resulting lowest energy conformation was selected as the minimum for this parameter set.

4.3. Optical Microscopy. A small piece of the wet gel was transferred onto a cover slip. Excess solvent was removed by blowing a gentle stream of nitrogen gas on it. The sample was then observed under an Olympus model BH2 optical microscope.

4.4. Scanning Electron Microscopy. A small slice of the wet gel was transferred on to a clean cover slip. Excess solvent from this was evaporated by blowing a gentle stream of nitrogen gas on it. The substrate was then sputter coated with gold. SEM photographs were then obtained for each specimen.

4.5. Transmission Electron Microscopy. A small portion of the "loose" gel was transferred on to a copper grid (400 mesh) and left for drying under vacuum. This substrate was then examined in a JEOL-TEM 200 CX Transmission Electron Microscope with an accelerating voltage of 120 keV for recording the micrographs.

4.6. Gelation Experiments. *4.6.1 Preparation of Gel.* In a typical gelation experiment an excess of the organic solvent (10 mL) was added to a weighed amount of a potential gelator (0.01 mmol) in a test tube, and the mixture was heated to give a clear solution which was then allowed to cool. On standing for 30 min, a viscoelastic mass in the tube starts to gelate, and it takes around ∼1 h to gelate completely. This gel formation can be also monitored by first observing the formation of fine white tapes, which increase in size with time.

4.6.2. Gelation Capacity Measurements. A typical procedure for measuring gelation capacity is as follows: a weighed sample of the gelator (0.01 mmol) was mixed with an organic liquid (10 mL) in a screw-capped vial, and the mixture was heated until the solid dissolved. The resulting solution was left to cool at 25 °C for an hour and then the gelation was checked visually. Once the gel is formed, a stable mass is produced such that the tube containing the gel can be inverted without changing the shape of the mass. The excess solvent from the gelated mass could be separated completely by merely holding (decanting) the tube upside down. Once all the excess solvent has been drained, the weight of vial containing the gel was then measured, and from this the weight of the solvent that participated in the gelation process was calculated.

4.7. Synthesis. *(S)-N-[(Benzyloxy)carbonyl]phenylalanine.* To a solution of L-phenylalanine (100 mmol, 16.52 g) in water (30 mL) was added 5 N NaOH (25 mL), and the stirred solution was cooled in an ice−water bath. A 50% solution of benzyl chloroformate in toluene (100 mmol, 15 mL) and 2 N NaOH (70 mL) were added alternatingly in 10 portions to the reaction mixture while the resulting mixture was vigorously stirred and the temperature was maintained at ∼10 °C. In about 1.5 h, the addition was completed. After continued stirring at room temperature for an additional 0.5 h, the alkalinity of the mixture was adjusted to pH ∼10 and the solution extracted with ether (4 × 100 mL). The aqueous layer was acidified to congo blue with 5 N HCl (50 mL), and the oil, which separated out, was extracted into ether (3 × 100 mL). All the organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo, to afford a thick liquid residue, which was taken up in ethyl acetate and kept in the refrigerator for a day. A white solid formed (21 g, 70%): mp = 87 °C (lit.[19] 89 °C), IR 3300 cm^{-1} (N−H stretch), 1680 cm^{-1} (amide C=O stretch), 1640 cm^{-1} (urethane stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.1−7.5 (m, 10H), 5.1 (s, 2H), 4.7 (br s, 1H), 3.12 (br t, tending toward a dd, 2H).

*(S)-N-[(Benzyloxy)carbonyl]phenylalanine-N-hexadecylamide (**1**).* A solution of *N*-[(benzyloxy)carbonyl]-L-phenylalanine (0.6 g, 2 mmol) in dry $CHCl_3$ (10 mL) was added to a solution of 1-hexadecylamine (0.48 g, 2 mmol) in $CHCl_3$ (50 mL) and cooled to 0 °C. To this solution was added dicyclohexylcarbodiimide (DCC) (0.42 g, 2 mmol) in $CHCl_3$ (10 mL), and the ice bath was removed after an hour. The reaction was then left for stirring for 24 h. At the end of this period, TLC indicated completion of the reaction. The solid precipitated, dicyclohexylurea (DCU), was separated by filtration, and the filtrate was concentrated under reduced pressure to afford a white solid. This solid was then purified by repetitive column chromatography over silica gel using 10% ethyl acetate−hexane as eluent to ensure complete removal of dicyclohexylurea (0.86 g, 82%): mp = 98 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C=O stretch), 1650 (urethane C=O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (br m, 10H), 5.1 (s, 2H), 4.3 (dd, 1H), 2.9−3.1, (m, 4H), 1.3 (br m, 28 H), 0.87 (t, 3H); optical rotation $[\alpha]^{20}_D$ = 5.49 (*c* 5.1, $CHCl_3$). Anal. Calcd for $C_{33}H_{50}O_3N_2$: C, 75.82; H, 9.64; N, 5.36. Found: C, 76.04; H, 10.02; N, 5.36.

*(R,S)-N-[(Benzyloxy)carbonyl]phenylalanine-N-hexadecylamide (±**1**).* A similar procedure was followed for the synthesis of the racemic compound except that (*R,S*)-*N*-[(benzyloxy)-carbonyl]phenylalanine was employed in the place of (*S*) enantiomer (0.86 g, 82%): mp = 91 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C=O stretch), 1650 (urethane C=O stretch); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3 (br m, 10H), 5.1 (s, 2H), 4.3 (dd, 1H), 2.9−3.1 (m, 4H), 1.3 (br m, 28H), 0.87 (t, 3H). Anal. Calcd for $C_{33}H_{50}O_3N_2$: C, 75.82; H, 9.64; N, 5.36. Found: C, 76.11; H, 10.05; N, 5.41.

*(S)-N-[(Benzyloxy)carbonyl]phenylalanine-N-undec-10-yn-1-amide (**2**).* The same procedure was followed as that for **1** except that 1-aminoundec-10-yne was used in place of 1-hexadecylamine. A solid was obtained upon column chromatogra-

(19) *The Practice of Peptide Synthesis*; Bodanszky, M., Bodanszky, A., Eds.; Springer-Verlag: New York, 1984; pp 114.

phy over silica gel using 10% ethyl acetate−hexane as eluent (0.58 g, 65%): mp = 108 °C; IR (cm^{-1}) 3300 (N−H stretch), 2100 (C≡C), 1680 (amide C═O stretch), 1640 (urethane C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 10H), 5.9 (s, 2H), 4.3 (dd, 1H), 2.99−3.15 (m, 4H), 2.2 (m, 2H), 1.8 (m, 1H), 1.25 (br m, 14H), 0.85 (t, 3H); optical rotation $[\alpha]^{20}_D = 2.0.75$ (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}N_2O_3 \cdot 0.5H_2O$: C, 73.49; H, 8.15; N, 6.12; Found: C, 73.24; H, 8.1; N, 5.69.

*(S)-N-[(Benzyloxy)carbonyl]phenylalanine-N-butylamide (**3**).* The same procedure was followed as that for **1**, except that 1-aminobutane was used in place of 1-hexadecylamine. A solid was obtained upon column chromatography over silica gel using 10% ethyl acetate−hexane as eluent (0.6 g, 85%): mp = 92 °C; IR (cm^{-1}) 3300 (N−H stretch), 1680 (amide C═O stretch), 1640 (urethane C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (br m, 10H), 5.9 (s, 2H), 4.3 (dd, 1H), 2.99−3.15 (m, 4H), 1.25 (m, 4H), 0.85 (t, 3H); optical rotation $[\alpha]^{20}_D$ = 3.47 (*c* 2.4, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.39; N, 7.9. Found: C, 71.23; H, 7.8; N, 7.88.

*(S)-N-[(tert-Butyloxy)carbonyl]phenylalanine-N-hexadecylamide (**4**).* A solution of *N*-[(*tert*-butyloxy)carbonyl]-L-phenylalanine (0.53 g, 2 mmol) in dry $CHCl_3$ was added to a solution of 1-hexadecylamine (0.48 g, 2 mmol) in 50 mL $CHCl_3$ and cooled to 0 °C. To this solution was added DCC (0.42 g, 2 mmol) in 10 mL $CHCl_3$, and the ice bath was removed after 1 h and the reaction was left stirring for 24 h. At the end of this period a solid precipitated (DCU), which was filtered, and the clear solution was rotary evaporated to get a white solid, which was purified by column chromatography over silica gel using 10% EtOAc−hexane as eluent (0.63 g, 65%): mp = 82 °C; IR (cm^{-1}) 3300 (N−H str), 1690 (amide C═O stretch), 1650 (urethane C═O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5H), 4.3 (dd, 1H), 2.9−3.1 (br m, 4H), 1.45 (m, 28H), 1.25 (s, 9H), 0.88 (t, 3H); optical rotation $[\alpha]^{20}_D = 4.6$ (*c* 3, $CHCl_3$); MALDI mass spectrum expected *m/e* 488, base peak found *m/e* 488, an additional peak (511) due to $(M + Na)^+$ was also observed.

*(S)-N-Benzoylphenylalanine-N-hexadecylamide (**5**).* The same procedure was followed as that for **4** except that *N*-benzoyl-L-phenylalanine (0.54 g, 2 mmol) was employed in place of *N*-[(*tert*-butyloxy)carbonyl]-L-phenylalanine. A solution of *N*-benzoyl-L-phenylalanine (0.54 g, 2 mmol) in dry $CHCl_3$ was added to a solution of 1-hexadecylamine (0.48 g, 2 mmol) in 50 mL of $CHCl_3$ and cooled to 0 °C. A white solid was obtained upon column chromatography over silica gel using 10% ethyl acetate−hexane as eluent (0.59 g, 65%): mp = 114 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch), 1650 (urethane C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 10H), 4.3 (dd, 1H), 2.9−3.1 (m, 4H), 1.3 (br m, 28H), 0.87 (t, 3H); LRMS expected *m/e* 493, found *m/e* 493.

*(S)-N-Acetylphenylalanine-N-hexadecylamide (**6**).* The same procedure was followed as that for **4** except that *N*-acetyl-L-phenylalanine (0.42 g, 2 mmol) was employed in the place of *N*-[(*tert*-butyloxy)carbonyl]-L-phenylalanine. A solution of *N*-acetyl-L-phenylalanine (0.42 g, 2 mmol) in dry $CHCl_3$ was added to a solution of 1-hexadecylamine (0.48 g, 2 mmol) in 50 mL of $CHCl_3$ and cooled to 0 °C. A white solid was obtained by performing column chromatography over silica gel using 10% EtOAc−hexane as eluent (0.53 g, 60%): mp = 89 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 5H), 4.3 (dd, 1H), 2.9−3.1 (m, 4H), 2.2 (s, 3H), 1.3 (br m, 28 H), 0.87 (t, 3H); MALDI expected *m/e* 430, found 430, and an additional peak (453) due to $(M + Na^+)$ was also observed.

(S)-Phenylalanine-N-hexadecylamide (7). To a solution of **1** (0.52 g, 1 mmol) in EtOAc was added 0.02 g of 5% Pd in charcoal. The suspension was subjected to hydrogenation under a pressure of 40 psi over a period of 10 h. At the end of this period the suspension was filtered and the solvent from the filtrate was removed by evaporation. The solid that was obtained upon solvent removal was purified by column chromatography over silica gel using 20% EtOAc−hexane as eluent (0.68 g, 88%): mp = 65 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 5H), 4.3 (dd, 1H), 2.9−3.1 (m, 4H), 1.3 (br m, 28H), 0.87 (t, 3H). Anal. Calcd for $C_{25}H_{44}N_2O$: C, 75.82; H, 9.64; N, 5.36. Found: C, 76.09; H, 10.01; N, 5.41.

*(S)-N-[(Benzyloxy)carbonyl]phenylalanine-N-methyl-N-octadecylamide (**8**).* The same procedure was adopted as that for **1** except that *N*-methyl-*N*-octadecylamine was used in place of 1-aminohexadecane. The white solid obtained was purified by column chromatography over silica gel using 10% ethyl acetate−hexane as eluant (0.77 g, 68%): IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch), 1650 (urethane C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 10H), 5.1 (s, 2H), 4.3 (dd, 1H), 2.9−3.1 (m, 4H), 2.1 (s, 3H), 1.3 (br m, 24H), 0.87 (t, 3H); optical rotation $[\alpha]^{20}_D = 5.4$ (*c* 5.1 $CHCl_3$). Anal. Calcd for $C_{36}H_{56}O_3N_2$: C, 76.6; H, 9.92; N, 4.96. Found: C, 76.14; H, 10.08; N, 5.26.

*(S,S)-N-[(Benzyloxy)carbonyl]phenylalanine-(1,12)-N,N-dodecyldiamide (**9**).* The same procedure as that for **1** was followed except that 1,12-diaminododecane was used in place of 1-aminohexadecane. A solid was obtained after thorough purification of the crude product by repetitive column chromatography over silica gel using 15% ethyl acetate and hexane as eluent (1.1 g, 74%): mp = 149−152 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch), 1640 (urethane C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.4 (m, 20H), 5.1 (s, 4H), 4.3 (q, 2H), 3.0 (m, 8H), 1.2 (br m, 20H); optical rotation $[\alpha]^{20}_D = -35.71$ (*c* 0.43 g $CHCl_3$). Anal. Calcd. for $C_{46}H_{58}O_6N_4$: C, 72.41; H, 7.66; N, 7.34. Found: C, 72.71; H, 7.84; N, 7.4.

*(S,S)-Bisphenylalanine-(1,12)-N,N-dodecyldiamide (**10**).* The same procedure was adopted as that for **7** using a solution of **9** (0.38 g, 0.5 mmol) in EtOAc. A viscous material was obtained upon concentration after hydrogenation of this material. This was then purified by column chromatography over silica gel using 35% EtOAc−hexane as eluent (0.35 g, 71%): IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.3 (m, 10H), 4.3 (dd, 2H), 2.9−3.1 (m, 8H), 1.3 (br m, 20H); MALDI expected *m/e* 494, found *m/e* 494, and an additional peak (517) due to $(M + Na^+)$ was also observed.

*(S,S)-Bis[N-[(benzyloxy)carbonyl]phenylalanine]-4,4′-diaminodiphenylmethane (**11**).* The same procedure as that for **1** was followed for the synthesis of **11**, except that 4,4′-diaminodiphenylmethane was used in place of 1-aminohexadecane and 2 equiv of DCC was employed to accomplish amide coupling. This solid was purified by column chromatography over silica gel using 20% ethyl acetate/hexane as eluent (0.3 g, 40%): mp = 82 °C; IR (cm^{-1}) 3300 (N−H stretch), 1690 (amide C═O stretch), 1640 (urethane C═O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 28H), 5.1 (s, 4H), 4.3 (dd, 2H), 2.9−3.1 (m, 4H); MALDI expected *m/e* 760, found 760 and 783 $(M + Na^+)$.

*(S,S)-N-[(Benzyloxy)carbonyl]phenylalanine-1,22-docosa-9,-11-diynediamide (**12**).* To a solution of **2** (0.9 g, 2 mmol) in dry methanol (25 mL) were added $CuCl_2$ (0.1 g, 1 mmol) and dry pyridine (0.56 g, 7 mmol); a blue solution was obtained. Air was passed through this solution for 9 h, and the color of the solution changed to dark green. Removal of methanol from the reaction mixture gave a green residue which was digested with 2 N HCl and the pH was brought to 4. An off-white solid floating over the bulk of the reaction mixture was filtered off, and the residue was washed with water. This white solid was purified by column chromatography over silica gel using 25% ethyl acetate/hexane as eluent (0.63 g, 70%): IR (cm^{-1}) 3300 (N−H stretch), 2100 (C≡C), 1680 (amide C═O stretch), 1640 (urethane C═O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 20H), 5.9 (s, 4H), 4.3 (dd, 2H), 2.99−3.15 (m, 8H), 2.2 (m, 4H), 1.3 (br m, 28H); MALDI expected *m/e* 894, found *m/e* 894, 917.

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