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Gelation Behavior of 2*H*-Chromene *N*-Acylamino Acid Conjugates

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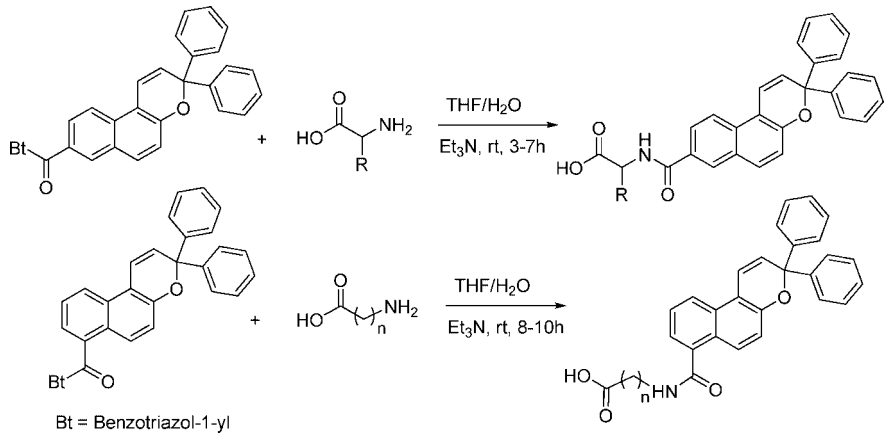

2*H*-Chromene-based conjugates of *N*-acyl-1,*ω*-amino acids (**5**, **9a**−**f**, **14a**−**f**) of natural amino acids (**10a**,**b**) and of dipeptide (**10c**) are prepared (60−97%) by *N*-acylbenzotriazole methodology in aqueous media at 20 °C. Gelation properties of the corresponding sodium salts in DMF and DMSO are generalized with respect to an increase or decrease in the chain length of the spacer.

Introduction

Gels are an example of nanoscale functional materials for which various synthetic protocols have been developed. Low molecular weight amphiphiles can self-assemble into nanoscale fibers that entangle to form 3D fibrous networks which organize liquids to solid or semisolid gels.[1,2] Supramolecular gels can form various exotic nanoaggregates such as fibers, thin sheets, helical and lamellar structures.[3] Such gels are used in templated materials[4] for drug delivery, cosmetics, separations, and biomimetics.[5] Supramolecular gel formation occurs when various structurally diverse low molecular weight organic molecules involving amidic, carbamate, urea, or oxalamide groups and long aliphatic chains or aromatic groups with a large surface are dispersed in organic solvents.[6] "Smart gels" (i.e., gels whose properties can be controlled reversibly or irreversibly in response to changes in external chemical, photochemical, thermal, or sonic stimuli) are organogelator materials of particular interest.[7−9]

Thermoreversible physical gels generated from relatively low molecular mass organic molecules represent a new class of self-assembling organic materials of potential interest as nanostructured materials and devices.[10−13] Control of the gelation process by external stimuli through addressable functions introduced into the supramolecular units (for example, organic photochromes) could allow light to modify the self-assembly process of individual molecules and the resulting supramolecular

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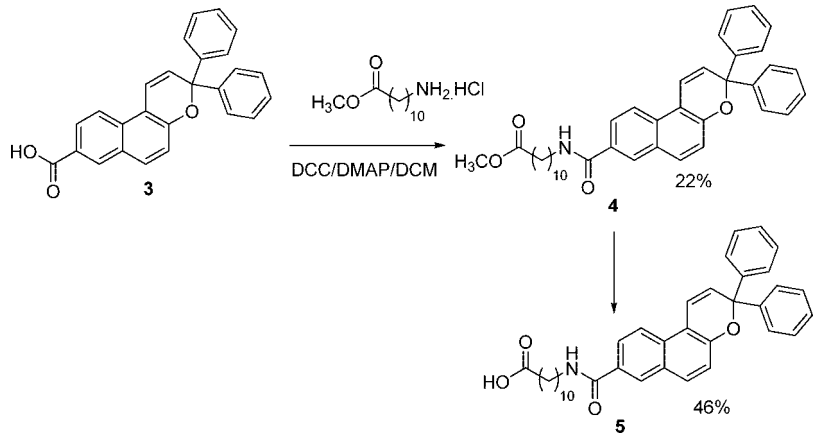
SCHEME 1



network.[11] Spiropyrans, spirooxazines, naphthopyrans, diarylethenes, and azobenzenes are all photochromic systems that display two molecular states with different absorption spectra.[11,13] Interestingly, light-induced transformation can cause reversibly important structural and physicochemical changes as depicted in 2*H*-chromene[13] (Figure 1).

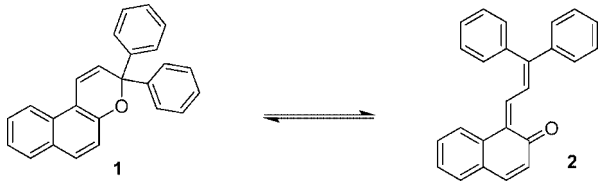


FIGURE 1. Photochromism in chromenes.

Ahmed et al. recently reported organogelators based on 2*H*-chromene and *N*-acyl-1,ω-amino acids that induce gelation of organic fluids such as DMF or DMSO,[11,14] demonstrating that while incorporation of a photoresponsive unit into the sodium *N*-acyl-11-aminoundecanoate scaffold does not suppress its gelation ability, the formation of supramolecular aggregates by intermolecular hydrogen bonds is strongly affected by photo-induced structural changes of the photochromic subunit. Such multiaddressable self-assembling organogelators are potential building blocks for the development of functional materials and devices. The methyl ester **4** of 2*H*-chromene-8-carbonyl amino acid was previously prepared[11] (22%) from 3,3-diphenyl-3*H*-benzo[*f*]chromene-8-carboxylic acid (**3**) and methyl 11-aminoundecanoate hydrochloride by coupling with DCC/DMAP followed by alkaline hydrolysis of **4** to give the expected chromene-2*H* amino acid conjugate (**5**, 46%; Scheme 1), but this methodology required anhydrous reaction conditions and tedious workup.[11]

The gelation abilities of *N*-acyl-1,ω-amino acids conjugate in organic solvents,[15] and the formation of fibrous molecular assemblies and gels from *N*-acyl derivatives of natural amino acids such as alanine or aspartic acid have also been studied.[16−18] However, no generalization of the effect of chain length on the gelation of chromene-2*H*-ω-amino acids conjugates and the corresponding natural amino acid analogues has appeared. Herein we report an efficient *N*-acylbenzotriazole-mediated preparation of 2*H*-chromene-based *N*-acyl-1,ω-amino acid (**5**, **9a**−**f**, **14a**−**f**) and natural amino acids and dipeptide (**10a**−**c**) conjugates with 60−97% yields in aqueous media at 20 °C, in order to investigate the trends in the gelation properties of the sodium salts of these chromene-2*H* natural and ω-amino acid conjugates in DMF and DMSO with chain length.

Results and Discussion

3,3-Diphenyl-3*H*-benzo[*f*]chromene-8-carboxylic acid (**3**) was prepared from 6-hydroxynaphthalene-2-carboxylic acid (**6**) and 1,1-diphenylprop-2-ynol (**7**): modifying the literature,[11] the cyclization was accomplished in toluene using a Dean−Stark trap during 6−8 h, and the product was recrystallized from acetonitrile, thus avoiding chromatography. Carboxylic acid (**3**) was converted into *N*-acylbenzotriazole derivative **8** (89%) following our published procedure.[19] *N*-Acylbenzotriazole (**8**) was coupled with various natural and ω-amino acids in aqueous THF/triethylamine at 20 °C for 4−10 h. Our approach allows the use of unprotected natural and ω-amino acids and provides yields of 60−97% (Scheme 2 and Table 1).

3,3-Diphenyl-3*H*-benzo[*f*]chromene-7-carboxylic acid (**12**) was prepared similarly (74%) from 6-hydroxynaphthalene-1-carboxylic acid (**11**) and 1,1-diphenylprop-2-ynol (**7**). Acid **12** was converted into the *N*-acylbenzotriazole derivative **13** (72%), which was also coupled with various ω-amino acids to give the corresponding 7-substituted 2*H*-chromene amino acid conjugates **14a**−**f** (Scheme 3 and Table 2).

The gelation behaviors of the sodium salts of **9a**−**f**, **5**, **10a**−**c**, and **14a**−**f** were investigated in DMF and DMSO with a concentration of 2 and 5 wt%/v via the inverted test tube method[20] (Table 3).

Thus we demonstrated that incorporation of ω-amino acids to 2*H*-chromene 8-carboxylic derivative with chain lengths of 11 and 12 (**5** and **9f**) strongly gelates (noted as G) in DMF and DMSO as the gels formed by them upon cooling are stable at room temperature for months. The conjugates with chain lengths of 6, 7, and 8 (**9c**, **9d**, and **9e**) gelatinized DMF at low

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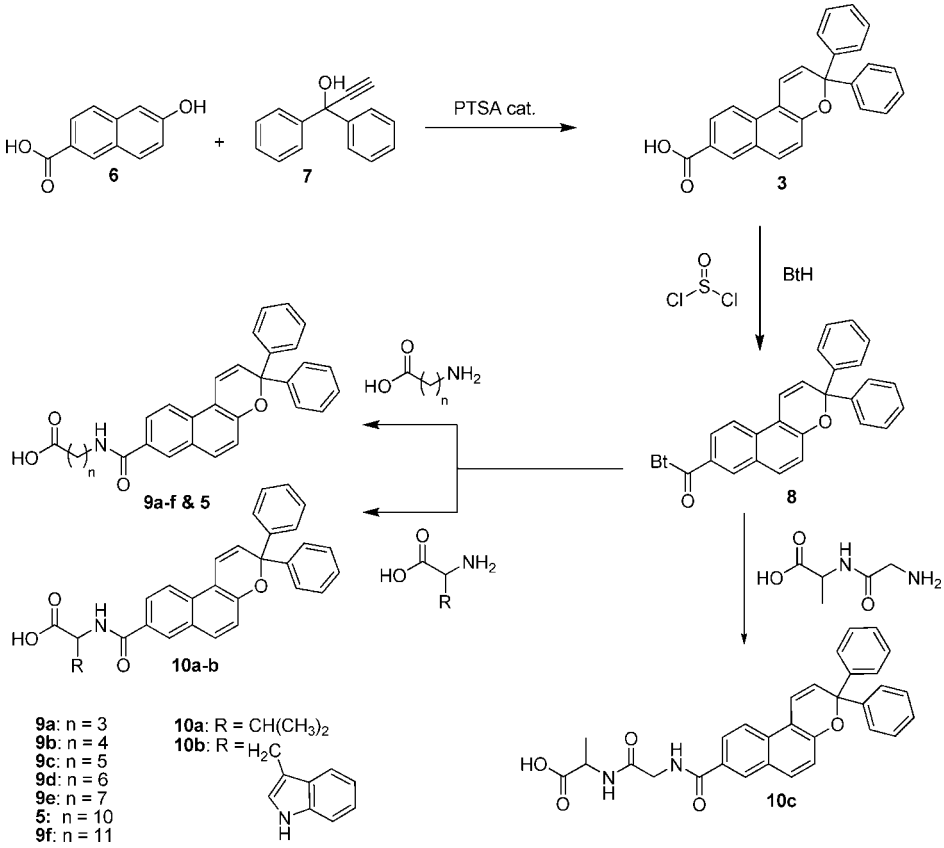
SCHEME 2



SCHEME 3

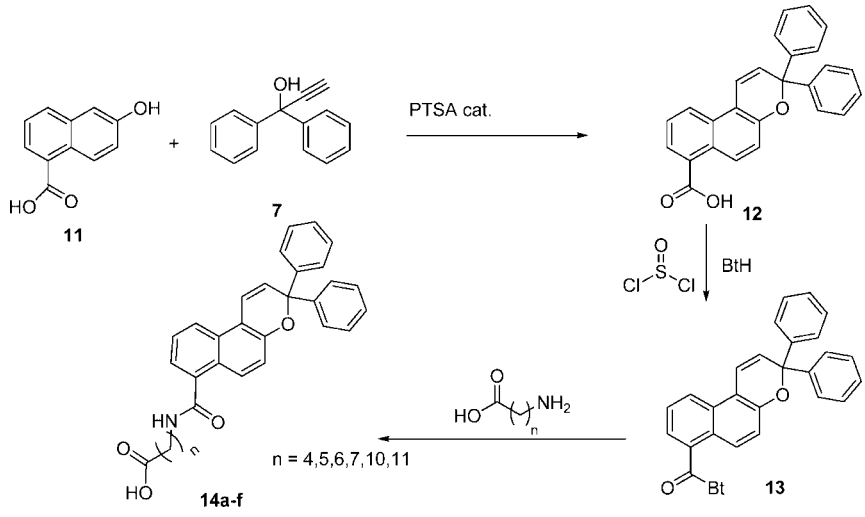


TABLE 1. Preparation of 2*H*-Chromene Amino Acid Conjugates (9a−f, 5, and 10a−c)

entry	time (h)	target compounds	yield (%)	mp (lit. mp (°C) decomp.)
1	6	**9a**	81	212−213
2	6	**9b**	85	216−218
3	5	**9c**	66	195−197
4	4	**9d**	97	176−178
5	4	**9e**	91	202−204
6	5	**5**	60	145−146(147)
7	3	**9f**	62	121−122
8	7	**10a**	91	198.5−200.5
9	5	**10b**	82	147−148
10	6	**10c**	92	110−112

TABLE 2. Preparation of 2*H*-Chromene Amino Acid Conjugates (14a−f)

entry	time (h)	target compounds	yield (%)	mp ((°C) decomp.)
1	8	**14a**	86	99−101
2	10	**14b**	83	114−116
3	8	**14c**	72	207−209
4	8	**14d**	79	146−148
5	8	**14e**	86	85−87
6	8	**14f**	71	86−88

temperature, but the gels formed are not stable at room temperature and hence are noted as Gs. Their corresponding solutions in DMSO are clear (noted as S) and hence classified

TABLE 3. Gelation Properties of the Sodium Salt of 2H-Chromene Amino Acid Conjugate (Na-9a−f, Na-5, Na-10a−c, Na-14a−f)[a]

compound	DMF	DMSO	compound	DMF	DMSO
9a	I	S	**10b**	S	S
9b	S	S	**10c**	Gs	S
9c	Gs	S	**14a**	I	S
9d	Gs	S	**14b**	S	S
9e	Gs	Gs	**14c**	Gs	S
5	G	G	**14d**	Gs	Gs
9f	G	G	**14e**	Gs	Gs
10a	S	S	**14f**	Gs	Gs

[a] G = Gel formed when cooled at 2−20°C and stable at room temperature. Gs = Gel formed but turned into solution at room temperature. S = Gel not formed, compound soluble at rt. I = compound insoluble even on heating.

as nongelators with respect to DMSO. With further decrease in the chain length to 4 and 5 (**9a** and **9b**), the gelation ability is completely eliminated in both DMF and DMSO. The same trend in the gelation behavior was not observed for the new 2*H*-chromene 7-carboxylic derivative with varying the chain lengths from 5 to 12 (**14a**−**f**). The derivatives with C-7, C-8, C-11, and C-12 chains (**14c**−**f**) partially gelatinized DMF and DMSO only at low temperatures, while the derivatives with C-5 and C-6 chains (**14a**,**b**) are nongelators in either of the two solvents. Our studies also showed that the natural amino acid 2*H*-chromene conjugates (**10a**,**b**) are nongelators, while the dipeptide 2*H*-chromene glycyl-DL-alanine conjugate (**10c**) gelatinized DMF only at low temperature, but not DMSO, and thus is noted as Gs. Although the chain length in this dipeptide is small, the presence of two peptide bonds may account for its partial gelation behavior.

Conclusion

2*H*-Chromene-based conjugates of *N*-acyl-1,ω-amino acids, natural amino acids, and dipeptide were prepared (60−97%) by benzotriazole methodology in aqueous media at 20 °C, and the gelation properties of their sodium salts in DMF and DMSO were generalized with respect to an increase or decrease in the chain length of the spacer.

Experimental Section

Preparation of 3,3-Diphenyl-3*H*-benzo[*f*]chromene-8-carboxylic acid (3). A mixture of 6-hydroxynaphthalene-2-carboxylic acid (0.94 g, 5 mmol) (**6**) and 1,1-diphenylpropyn-1-ol (1.04 g, 5 mmol) (**7**) was dissolved in dry acetonitrile (150 mL). A catalytic amount of *p*-toluenesulfonic acid (100 mg) was added, and the reaction mixture was stirred for 2 days. The precipitate thus obtained was filtered; the filtrate was concentrated to half its volume, and newly precipitated solid was again filtered. The combined solids were recrystallized from acetonitrile to give 1.36 g (72%) of 3,3-diphenyl-3*H*-benzo[*f*]chromene-8-carboxylic acid (**3**) as colorless crystals: mp 305−306 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 6.62 (d, J =10.2 Hz, 1H), 7.22−7.27 (m, 2H), 7.31−7.41 (m, 5H), 7.47−7.50 (m, 5H), 7.96−8.01 (m, 2H), 8.17 (d, J = 9.0 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 82.1, 114.0, 119.1, 119.1, 122.0, 126.0, 126.3, 127.6, 128.1, 128.3, 128.7, 131.2, 131.4, 131.6, 144.5, 151.8, 167.4. Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79. Found: C, 82.15; H, 4.80.

Preparation of (1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(3,3-diphenyl-3*H*-benzo[*f*]chromen-8-yl)methanone (8). To a solution of 1*H*-benzotriazole (1.95 g, 16.40 mmol) in CH_2Cl_2 (20 mL) was added dropwise thionyl chloride (0.59 g, 4.92 mmol). After 2 h stirring at room temperature, 3,3-diphenyl-3*H*-benzo[*f*]chromene-8-carboxylic acid (**3**) (1.55 g, 4.10 mmol) was added and the mixture was stirred for an additional hour. The precipitate was filtrered and the organic filtrate diluted with CH_2Cl_2 (20 mL) and washed with saturated Na_2CO_3 solution (20 mL × 3). The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuum to afford a yellow solid, which was recrystallized from DCM/hexane to give pure product as 1.74 g (89%) of yellow crystals: mp 206−207 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 6.33 (d, J = 9.9 Hz, 1H), 7.25−7.37 (m, 8H), 7.47−7.50 (m, 4H), 7.54 (t, 1H), 7.70 (t, 1H), 7.84 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.16−8.22 (m, 2H), 8.40 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 83.2, 114.0, 114.8, 118.9, 119.6, 120.1, 121.7, 126.1, 126.2, 127.0, 127.6, 127.7, 128.0, 128.2, 128.3, 130.3, 131.9, 132.4, 132.5, 135.1, 144.4, 145.7, 153.3, 166.4. Anal. Calcd for $C_{32}H_{21}N_3O_2$: C, 80.15; H, 4.41; N, 8.76. Found: C, 79.90; H, 4.33; N, 8.79.

General Procedure for Preparation of 2*H*-Chromene Amino Acid Conjugates (5, 9a−f, 10a−c, 14a−f). A mixture of (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(3,3-diphenyl-3*H*-benzo[*f*]chromen-8-yl)methanone (**8** or **13**) (1 equiv) and amino acid (1 equiv) was dissolved in THF/H_2O (10 mL, 6 + 4). After addition of triethylamine (2 equiv), the reaction was stirred for 4−10 h. The course of the reaction was monitored by TLC (MeOH/DCM, 2:98). For workup, THF was removed under reduced pressure and 4 N HCl was added dropwise to yield a precipitate which was filtered and washed with water to furnish excellent yields of the desired compounds. Pure products were obtained by recrystallization from THF/H_2O or acetonitrile.

6-(3,3-Diphenyl-3*H*-benzo[*f*]chromene-8-carboxamido)hexanoic acid (9c): ^{1}H NMR (DMSO-d_6) δ 1.32−1.35 (m, 2H), 1.54 (br s, 4H), 2.21 (t, J = 7.2 Hz, 2H), 3.29 (m, 2H), 6.63 (d, J = 9.9 Hz, 1H), 7.24−7.29 (m, 2H), 7.33−7.39 (m, 5H), 7.49−7.54 (m, 5H), 7.91 (t, J = 9.0 Hz, 2H), 8.17 (d, J = 9.0 Hz, 1H), 8.35 (s, 1H), 8.57 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 24.2, 26.0, 28.8, 33.5, 81.6, 113.8, 118.8, 119.1, 121.6, 125.0, 126.2, 127.4, 128.0, 128.1, 128.5, 129.8, 130.3, 130.9, 144.5, 151.0, 165.7, 174.4. Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; N, 2.85. Found: C, 77.99; H, 6.00; N, 3.00.

General Procedure for Preparation of Sodium Salts of 2*H*-Chromene Amino Acid Conjugates (Na-5, Na-9a−f, Na-10a−c, Na-14a−f). A mixture of 2*H*-chromene amino acid conjugates (**5**, **9a**−**f**, **10a**−**c**, **14a**−**f**) (1 equiv) and 1 N NaOH solution (1.2 equiv) was stirred in methanol at room temperature for 3−4 h. The solvent was then removed under vacuum. The product was washed with diethyl ether (×2) and dried under vacuum to yield fluffy crystalline solids, which were used as such for the gelation experiments by the inverted test tube method.[20]

Gelation Experiments "Inverted Test Tube Method": In a typical gelation experiment, a weighed amount of sodium salt of the chromene amino acid conjugate (**Na-5**, **Na-9a**−**f**, **Na-10a**−**c**, **Na-14a**−**f**) and 1 mL or organic solvent (DMF or DMSO) were placed in a septum-capped sample tube (generally 2 and 5 wt%/v). The sample tube was heated under agitation until the solid had dissolved. The solution was cooled in an ice bath and set aside at 25 °C for 6−8 h. The gelation behaviors as G, Gs, S, and I of these conjugates are summarized in Table 3.

Supporting Information Available: Compound characterization data for **9a**,**b**, **9d**,**e**, **5**, **9f**, **10a**−**c**, and **14a**−**f**. Copies of ^{1}H and ^{13}C spectra of **3**, **8**, **12**, **13**, **9a**−**e**, **5**, **9f**, **10a**−**c**, and **14a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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