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Development of Low-Molecular-Mass Organogelators: Synthesis and Physical Properties of *N*-Linear Saturated Fatty Acyl-GABAs and Their Ester Derivatives

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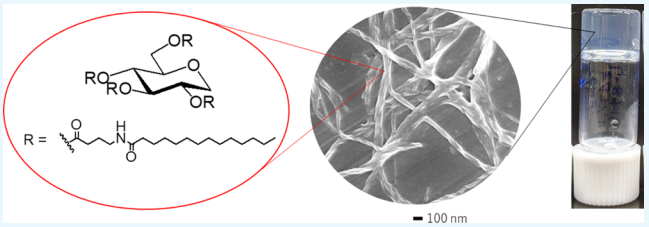
ABSTRACT: We determined that compounds in which γ-aminobutyric acid (GABA) and linear saturated fatty acids of various lengths are amide-bonded, as found in the human brain, have the ability to gelate organic solvents. We also synthesized compounds of these GABA derivatives attached to 1,5-anhydro-D-glucitol (1,5-AG) or D-glucopyranose (Glc) via ester linkages, and these compounds were also found to be able to gelate organic solvents. From the comparative experiments of gelation using various lengths of *N*-linear saturated fatty acyl-GABAs and their ester derivatives, it was determined that the compound of *N*-tetradecanoic acyl-GABA bonded to 1,5-AG via ester linkage (C_{14}GABA-AG) had a particularly high gel hardness and could gelate various organic solvents. Furthermore, field-emission scanning electron microscopy observations revealed the formation of a fibrous structure, which encapsulates the organic solvent and forms a gel. A variable-temperature Fourier transform infrared spectroscopy analysis revealed that the alkyl chains of *N*-linear saturated fatty acyl-GABAs are packed with an all-*trans* conformation, whereas the alkyl chains of the ester compounds attached to 1,5-AG or Glc are slightly skewed from the all-*trans* conformation due to the intermolecular hydrogen bonding of the amide groups. Here, we report the synthesis and analysis of *N*-linear saturated fatty acyl-GABA derivatives and the gelation mechanism.



1. INTRODUCTION

Low-molecular-mass organogelators can gelate organic solvents at as little as 1 wt % and are used in a variety of fields.[1−3] We recently determined that C16AG, a fully palmitoylated 1,5-anhydro-D-glucitol, can gelate a variety of organic solvents[4] and investigated its gelation mechanism.[5,6] The gelation mechanism was found to be caused by the formation of van der Waals interactions between alkyl chains as well as weak hydrogen bonds between the C−H groups of alkyl chains and the carbonyl groups. Due to these very weak intermolecular interactions, the C16AG gel was fragile to external physical force. 1,5-Anhydro-D-glucitol (1,5-AG)[7−9] was successfully derived from starch-derived 1,5-anhydro-D-fructose and had a structure in which the hydroxy group at the anomeric position of D-glucopyranose (Glc) is deoxygenated. Because there is no hydroxy group at the anomeric position, which is the most reactive position, it has excellent stability in acidic, alkaline, and high-temperature conditions. Therefore, it is suitable for industrial use as cyclic and chiral alcohols. Additionally, it is present in humans and has a high safety profile.[10]

On the other hand, compounds in which γ-aminobutyric acid (GABA) and linear saturated fatty acids of various lengths are amide bonded, especially 4-[(1-oxohexadecyl)amino]-butanoic acid (C_{16}GABA) and 4-[(1-oxooctadecyl)amino]-butanoic acid (C_{18}GABA), have been found in the human brain.[11] From the investigation of the effect of apomorphine on homophilic behavior in rats, high doses of C_{16}GABA and C_{18}GABA were found to antagonize locomotor activity and motor stereotypies and reported to act on the basal ganglia and nucleus accumbens.[12]

In the process of analyzing the physical properties of C16AG in detail, in which palmitic acid is introduced into 1,5-AG by ester bonds, we hypothesized that a stronger intermolecular hydrogen bond induces a stronger gelation of organic solvents, and we synthesized various compounds with amide groups introduced into fatty acids to test their gelation ability. We synthesized compounds in which linear saturated fatty acids [dodecanoic acid, tetradecanoic acid (myristic acid), hexadecanoic acid (palmitic acid), and octadecanoic acid (stearic acid)] were bonded to the amino group of GABA, a functional substance found in the human brain, and found that these simple compounds could gelate liquid paraffin. Furthermore, we synthesized a novel compound in which *N*-linear saturated fatty acyl-GABA was introduced into 1,5-AG or Glc by an ester bond and determined that these compounds can also gelate a

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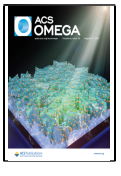

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variety of organic solvents. We analyzed the difference in the gelation ability depending on the length of the linear saturated fatty acid. The gelation ability of the compounds was also compared with that of C16AG. The gelation mechanism and the packing state for each molecule were also speculated.

2. RESULTS AND DISCUSSIONS

2.1. Synthesis of Organogelators. To observe the gelation property due to the difference in the length of fatty acids, dodecanoyl chloride (12 carbons), myristoyl chloride (14 carbons), palmitoyl chloride (16 carbons), and stearoyl chloride (18 carbons) were reacted with GABA in 1 M KOH at 0 °C[13] (Figure 1). The structures of these four GABA

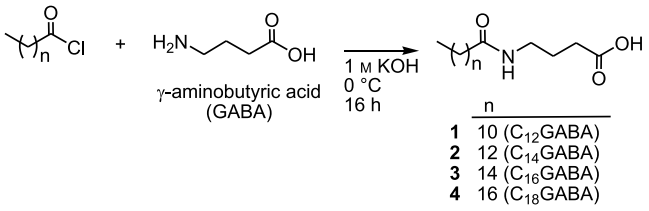

Figure 1. Coupling of different lengths of linear saturated fatty acyl chloride and GABA.

derivatives were confirmed via NMR after purification by column chromatography. These four compounds were introduced into 1,5-AG via ester linkages. DIC (*N*,*N*′-diisopropylcarbodiimide) was used as the condensing agent, DMAP [4-(dimethylamino)pyridine] was used as the base, and 1,2-dichloroethane was used as the solvent[14] (Figure 2).

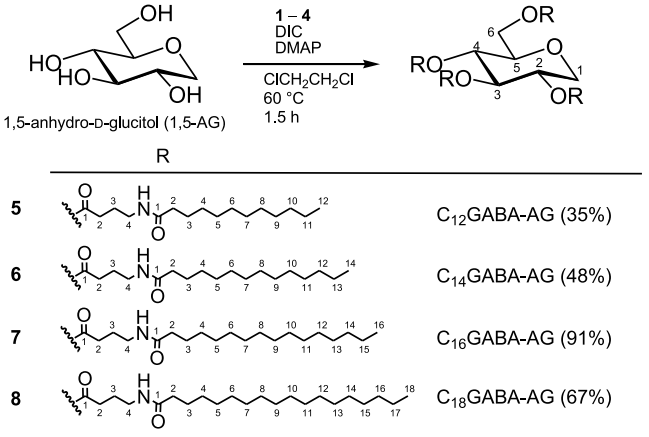

Figure 2. Preparation of 1,5-AG protected with *N*-linear saturated fatty acyl-GABA.

Because 1,5-AG in its crystalline state is quite insoluble in nonpolar solvents, we first dissolved it in a very small amount of water and then dried it well in a vacuum line to change to an amorphous form. After 1.5 h of reaction at 60 °C, methanol was added to quench the reaction and crystallize the product. Compound **5** did not crystallize, so column purification was performed. The obtained yields were 35% (compound **5**), 48% (compound **6**), 91% (compound **7**), and 67% (compound **8**). ^{1}H NMR showed compound **5** to be δ 4.08 (dd, H-6), 4.14 (dd, H-1 *eq*), 4.32 (dd, H-6′), 4.99−5.05 (m, H-2), 5.03 (t, H-4), and 5.18 (t, H-3) ppm, compound **6** was obtained as δ 4.10 (broad d, H-6), 4.13 (dd, H-1 *eq*), 4.29 (dd, H-6′), 4.98−5.03 (m, H-2), 5.02 (t, H-4), and 5.19 (t, H-3) ppm, compound **7** was δ 4.08 (dd, H-6), 4.14 (dd, H-1 *eq*), 4.32 (dd, H-6′), 4.99−5.05 (m, H-2), 5.03 (t, H-4), and 5.18 (t, H-3) ppm, and compound **8** was δ 4.11 (dd, H-6), 4.13 (dd, H-1 *eq*), 4.28 (dd, H-6′), 4.98−5.05 (m, H-2), 5.02 (t, H-4), and 5.21 (t, H-3) ppm, confirming that all the hydroxy groups were esterified. For comparison, Glc was used instead of 1,5-AG, and *N*-linear saturated fatty acyl-GABAs were introduced in the same way (Figure 3). Similarly, after 1.5 h of reaction at 60 °C, the

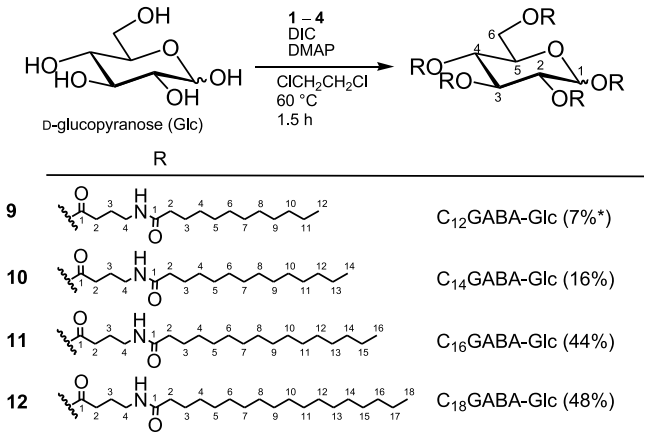

Figure 3. Preparation of Glc protected with *N*-linear saturated fatty acyl-GABA. *The yield increased to 44% under room temperature conditions.

reaction was quenched by adding methanol, and the product was crystallized. However, compound **9** did not crystallize, so column purification was performed. The desired product was obtained at 7% (compound **9**), 16% (compound **10**), 44% (compound **11**), and 48% (compound **12**) yields. From ^{1}H NMR, compound **9** was determined to be δ 4.10 (dd, H-6), 4.34 (dd, H-6′), 5.09 (m, H-4), 5.11 (dd, H-2), 5.26 (t, H-3 β), 5.43 (t, H-3 α), 5.72 (d, H-1 β), and 6.33 (d, H-1 α) ppm, compound **10** was δ 4.07−4.16 (m, H-6), 4.28−4.38 (m, H-6′), 5.07−5.14 (m, H-4), 5.07−5.14 (m, H-2), 5.25 (t, H-3 β), 5.43 (t, H-3 α), 5.71 (d, H-1 β), and 6.33 (d, H-1 α) ppm, compound **11** was δ 4.04−4.14 (m, H-6), 4.33−4.40 (m, H-6′), 5.07−5.15 (m, H-4), 5.07−5.15 (m, H-2), 5.23 (t, H-3 β), 5.44 (t, H-3 α), 5.70 (d, H-1 β), and 6.34 (d, H-1 α) ppm, and compound **12** was δ 4.06−4.14 (m, H-6), 4.31−4.37 (m, H-6′), 5.06−5.14 (m, H-4), 5.06−5.14 (m, H-2), 5.25 (t, H-3 β), 5.43 (t, H-3 α), 5.71 (d, H-1 β), and 6.33 (d, H-1 α) ppm, indicating that all the hydroxy groups were esterified. The yield of compound **9** was very low (7%) but when the reaction was conducted under similar conditions at room temperature, the yield was increased to 44%. Because AG or Glc and *N*-linear saturated fatty acyl-GABA dissolved at a relatively high temperature of 60 °C, the reaction was carried out at this temperature. On the other hand, the condensing agent, DIC, is usually used below room temperature. When the reaction at 60 °C was followed by thin-layer chromatography (TLC), the reaction stopped before the *N*-linear saturated fatty acyl-GABA was introduced into all the hydroxy groups, resulting in a lower yield. On the other hand, when compound **9** was suspended and reacted at room temperature, if it dissolved, the reaction would proceed to the end, which is why we assume that this improvement in yield was observed. If we can create good suspension conditions for other compounds as well, we expect to be able to carry out the reaction at room temperature and improve the yield.

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2.2. Gelation Test of Each Compound. Compounds **1**−**12** were added to liquid paraffin #350 (LP #350) or triethylhexanoin [1,2,3-propanetriyl tris(2-ethylhexanoate); TIO] to 1 wt % and dissolved on a hot plate at 100 to 150 °C. The resulting solution was left at room temperature for at least 12 h, and then the formation of the gel was observed. An actual photograph of the upside-down screw tube bottles is shown in Figure 4. Gels of C16AG **13** are also shown for comparison. The hardness and relative turbidity of the formed gels are shown in Figure 5. From Figure 4, it can be seen that the LP #350 solution of C_{12}GABA-Glc (a-**9**) and the TIO solution of C_{18}GABA-Glc (b-**12**) did not form a gel, while the TIO solution of C_{12}GABA-Glc (b-**9**) formed a half gel and the other formed a gel. C_{14}GABA (**2**) is already known as an organogelator,[15] but other *N*-linear saturated fatty acyl-GABAs, such as C_{12}GABA (**1**), C_{16}GABA (**3**), and C_{18}GABA (**4**), were also found to be good organogelators. Figures 4 and 5 also show that the gels formed by the 1,5-AG derivatives **5**−**8** have a particularly high hardness and transparency. Some of them were also harder and more transparent than the existing C16AG gels (**13**). Among them, the C_{14}GABA-AG (**6**) gels had a high hardness and transparency against these two solvents. Interestingly, the gels of 1,5-AG derivatives **5**−**8** increased in hardness as the length of the fatty acids increased from 12 to 14 but conversely decreased as the length of the fatty acids increased further from 14 to 16 and 18. Similarly, we have already reported that the hardness of C16AG gels increases up to 16 carbons and decreases with further extension from 16.[4] Unfortunately, the cause of these decreases has not yet been clarified. The difference between Glc and 1,5-AG is the presence of an anomeric hydroxy group. The anomeric hydroxy groups α and β can be connected with *N*-linear saturated fatty acyl-GABA to give two different compounds. In fact, the α/β ratios were compound **9** (α/β = 0.13:0.87), compound **10** (α/β = 0.15:0.85), compound **11** (α/β = 0.48:0.52), and compound **12** (α/β = 0.51:0.49). This makes it difficult to create a uniform three-dimensional structure. Therefore, it was speculated that the gel hardness was low. On the other hand, 1,5-AG has no hydroxy group in the anomeric position, and no isomers exist. Therefore, there is only one type of compound with *N*-linear saturated fatty acyl-GABA, and it is possible to create a uniform three-dimensional structure, which is easily formed by the strong stacking of molecules, and it is assumed that the gel hardness is high.

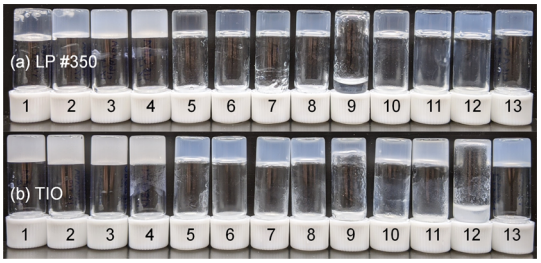

Figure 4. Actual photographs of the formed gels of each sample. (a) 1 wt % gel of each sample in LP #350. (b) 1 wt % gel of each sample in TIO. (1) C_{12}GABA, (2) C_{14}GABA, (3) C_{16}GABA, (4) C_{18}GABA, (5) C_{12}GABA-AG, (6) C_{14}GABA-AG, (7) C_{16}GABA-AG, (8) C_{18}GABA-AG, (9) C_{12}GABA-Glc, (10) C_{14}GABA-Glc, (11) C_{16}GABA-Glc, (12) C_{18}GABA-Glc, and (13) C16AG.

2.3. Field-Emission Scanning Electron Microscopy Observation. The xerogels were prepared by removing the organic solvent from the various gels prepared in Section 2.1 by soaking them in *n*-hexane for 2 days at room temperature. Field-emission scanning electron microscopy (FE-SEM) observations were performed after the osmium coating of the obtained xerogels. Figure 6 shows the FE-SEM images of various xerogels. Compounds **1**−**3**, which are GABA with linear saturated fatty acids, formed a needle-like structure, while compound **4** formed a plate-like structure. Comparing the solvents LP #350 and TIO, LP #350 produced finer structures. On the other hand, all the 1,5-AG derivatives (**5**−**8**) formed a right-handed helix with diameters less than 50 nm. In particular, there was no significant difference in the spiral structure due to the difference in the solvents LP #350 and TIO. Compounds **9**−**12**, Glc derivatives, had a varied structure, with spherical (a-**9**, a-**10**, and b-**12**), left-handed helix (a-**11**, a-**12**), and flaky (b-**9**, b-**10**, b-**11**) forms. We speculate that this is due to the loss of regularity in the formation of a macroscopic structure due to the presence of both α and β isomers. The 1,5-AG derivatives, compounds **5**−**8**, were thinner than the other compounds and formed a spiral structure, suggesting that the stacking of the molecules was stronger than the others, forming a stable fiber. If the fibers formed by the stacking of molecules are stable, they can exist stably even if they are not clustered together. We speculate that this is the reason for the high transparency and hardness of the gel.

In our previous work, we reported that C16AG, a palmitic acid bound to 1,5-AG, is a good organogelator.[4] This showed that the chiral compound 1,5-AG can sterically fix the position

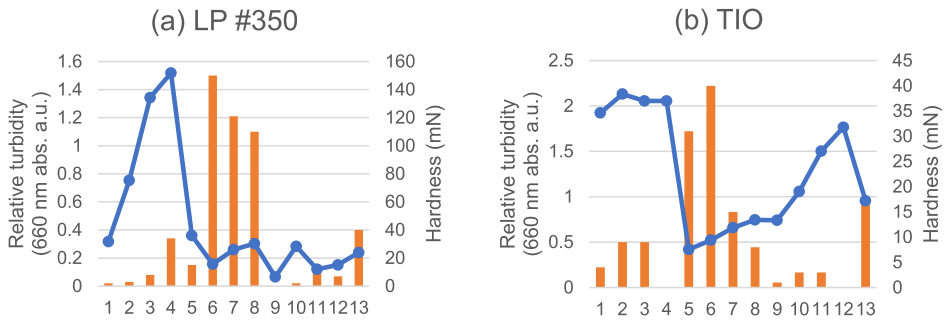

Figure 5. Relative turbidity and hardness of the 1 wt % formed gels. (a) 1 wt % gel of each sample in LP #350. (b) 1 wt % gel of each sample in TIO. The line graph shows the relative turbidity, and the bar graph shows hardness. (1) C_{12}GABA, (2) C_{14}GABA, (3) C_{16}GABA, (4) C_{18}GABA, (5) C_{12}GABA-AG, (6) C_{14}GABA-AG, (7) C_{16}GABA-AG, (8) C_{18}GABA-AG, (9) C_{12}GABA-Glc, (10) C_{14}GABA-Glc, (11) C_{16}GABA-Glc, (12) C_{18}GABA-Glc, and (13) C16AG.

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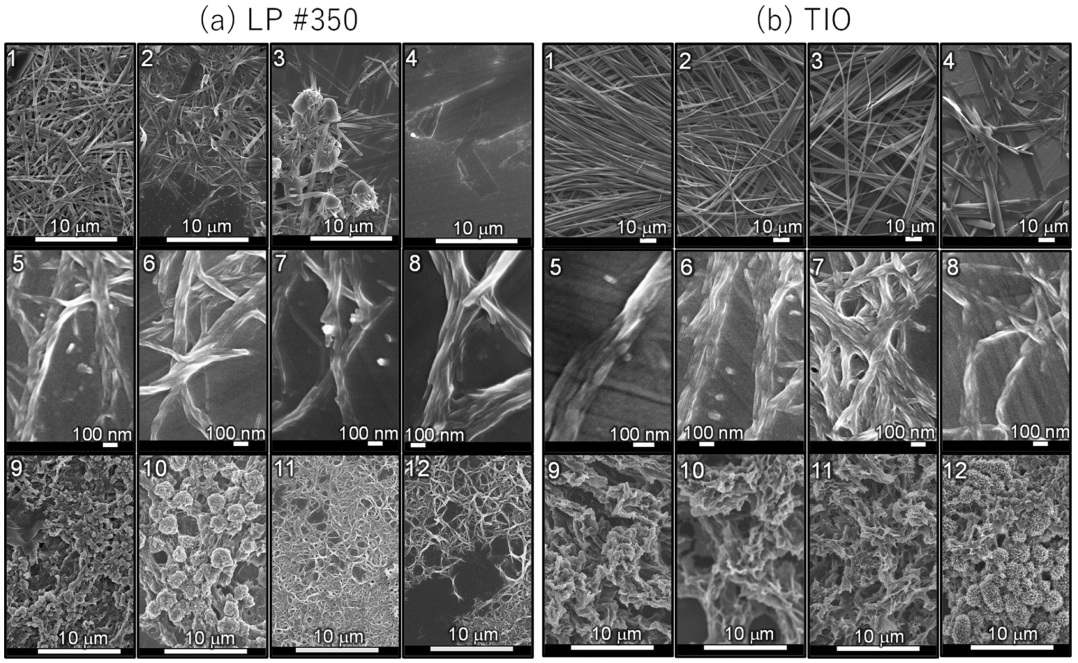

Figure 6. FE-SEM image of the xerogels of each sample. (a) Xerogel from a 1 wt % gel of each sample in LP #350. (b) Xerogel from 1 wt % gel of each sample in TIO. The bars in FE-SEM images 1 to 4 and 9 to 12 indicate 10 μm. The bars in FE-SEM images 5 to 8 indicate 100 nm. (1) C_{12}GABA, (2) C_{14}GABA, (3) C_{16}GABA, (4) C_{18}GABA, (5) C_{12}GABA-AG, (6) C_{14}GABA-AG, (7) C_{16}GABA-AG, (8) C_{18}GABA-AG, (9) C_{12}GABA-Glc, (10) C_{14}GABA-Glc, (11) C_{16}GABA-Glc, and (12) C_{18}GABA-Glc.

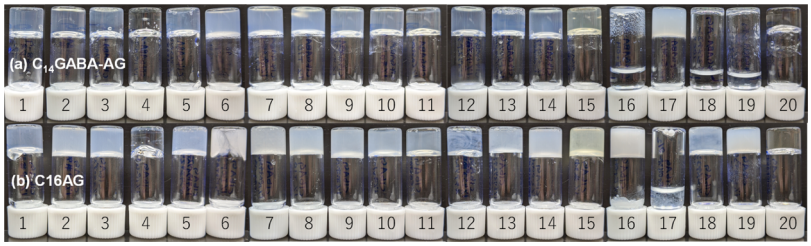

Figure 7. Actual photographs of the formed gels of each solvent. (a) 1 wt % gel of **6** (C_{14}GABA-AG) in various organic solvents. (b) 1 wt % gel of C16AG in various organic solvents. The solvents of each gel were as follows: (1) liquid paraffin #350, (2) liquid paraffin #70, (3) olive squalene, (4) hydrogenated polyisobutene (kinetic viscosity 300 mm^2/s), (5) pentaerythrityl tetraisostearate, (6) isopropyl myristate, (7) ethylhexyl palmitate, (8) triethylhexanoin, (9) jojoba oil, (10) canola oil, (11) castor oil, (12) diisostearyl malate, (13) polyglyceryl-2 triisostearate, (14) 2-octyl-1-dodecanol, (15) rice bran oil, (16) ethanol (99.5), (17) ethanol/H_2O v/v 8:2, (18) dimethylone (viscosity 10 mm^2/s), (19) cyclopentasiloxane, and (20) diphenylsiloxy phenyl trimethicone.

of the palmitic acid and strongly induce stacking between molecules to form a fibrous structure. In compounds **5**−**8**, we speculate that the hydrogen bonding of the amide group in the alkyl chain strongly induces intermolecular stacking. Therefore, it may form finer fibers and have a higher hardness than C16AG without the amide group.

2.4. Gelation Test with Various Organic Solvents Using C_{14}GABA-AG and a Comparison with Existing C16AG. From the above results, it was determined that the gels of compound **6** (C_{14}GABA-AG) formed a thin fibrous structure with high hardness and transparency. Next, we examined the difference in the gelation ability of this compound depending on the kinds of solvent and compared its gelation ability with that of the existing organogelator, C16AG, for 20 different solvents. The following solvents with different physical properties were selected. Hydrocarbon solvents [1: liquid paraffin #350, 2: liquid paraffin #70, 3: olive squalene, 4: hydrogenated polyisobutene (kinetic viscosity 300 mm^2/s)]; ester solvents (5: pentaerythrityl tetraisostearate, 6: isopropyl myristate, 7: ethylhexyl palmitate, 8: triethylhexanoin, 9: jojoba oil, 10: canola oil, 11: castor oil, 12: diisostearyl malate, 13: polyglyceryl-2 triisostearate, 15: rice bran oil); alcohol solvents [14: 2-octyl-1-dodecanol, 16: ethanol (99.5), 17: ethanol/H_2O v/v 8:2]; and silicone solvents [18: dimethicone (viscosity 10 mm^2/s), 19: cyclopentasiloxane, 20: diphenylsiloxy phenyl trimethicone]. For the existing organogelators, there are certain solvents that can be used for gelation depending on the type of the organogelator. This is the so-called "personality" of the organogelator, and for the future development of applications, it is necessary to conduct gelation tests on various organic solvents to know the range of application of the organogelator. We conducted gelation tests on 20 different organic solvents with different physical properties and decided to investigate in detail what physical properties of the developed compound C_{14}GABA-AG can and cannot be applied to the organic solvents. Figure 7 shows the actual photographs, and Figure 8 shows the relative turbidity and hardness of each solvent. From Figure 7, it is determined that compound **6** (C_{14}GABA-AG) has almost the same gelation ability to the various kinds of solvents as

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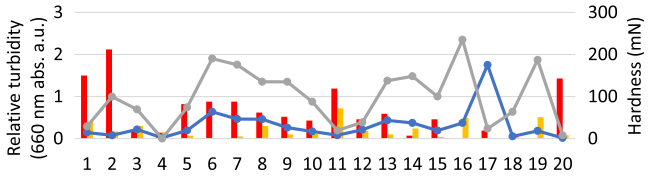

Figure 8. Relative turbidity and the hardness of the 1 wt % formed gel of each solvent. The red and yellow bar graphs show the hardness of gel **6** (C_{14}GABA-AG) and the C16AG gel, respectively. The blue and gray line graphs show the relative turbidity of **6** (C14GABA-AG) and C16AG gel, respectively. The solvents of each gel were as follows: (1) liquid paraffin #350, (2) liquid paraffin #70, (3) olive squalene, (4) hydrogenated polyisobutene (kinetic viscosity 300 mm^2/s), (5) pentaerythrityl tetraisostearate, (6) isopropyl myristate, (7) ethylhexyl palmitate, (8) triethylhexanoin, (9) jojoba oil, (10) canola oil, (11) castor oil, (12) diisostearyl malate, (13) polyglyceryl-2 triisostearate, (14) 2-octyl-1-dodecanol, (15) rice bran oil, (16) ethanol (99.5), (17) ethanol/H_2O v/v 8:2, (18) dimethylicone (viscosity 10 mm^2/s), (19) cyclopentasolone, and (20) diphenylsiloxy phenyl trimethicone.

C16AG, indicating that it can be applied to a wide range of solvent systems. Interestingly, C16AG gelled against ethanol (99.5), while C_{14}GABA-AG did not (entry 16). On the other hand, in ethanol/H_2O v/v 8:2, C16AG did not gel but C_{14}GABA-AG did (entry 17). TLC observations indicated that C_{14}GABA-AG was more polar than C16AG. We speculate that this difference in polarity may be related to the gelation ability to hydrous ethanol. Similarly, for isopropyl myristate in entry 6, C16AG was fluid but C_{14}GABA-AG gelled. In silicone solvents (entries 18−20), C_{14}GABA-AG gelled against diphenylsiloxy phenyl trimethicone in entry 20 but not dimethicone (entry 18) or cyclopentasiloxane (entry 19). In general, it was found that C_{14}GABA-AG is not well suited for silicon-based solvents but it has a high gelation ability in other solvents and tends to be more transparent than C16AG gels.

The relative turbidity at 660 nm from Figure 8 shows that the blue line (C_{14}GABA-AG) is lower than the gray line (C16AG) for all but entry 17. This means that C_{14}GABA-AG gels are more transparent than C16AG gels. In entry 17, the solution of C16AG is more transparent because it does not gel. Furthermore, C_{14}GABA-AG gels were harder than the C16AG gels in all but entries 14, 16, 18, and 19. In entries 16, 18, and 19, the C_{14}GABA-AG solution had a lower hardness because it did not gel. Thus, the gels of C_{14}GABA-AG were determined to have a lower turbidity and higher hardness for various organic solvents than the existing gels of C16AG. We speculate that this is due to the intermolecular hydrogen bonding of the amide groups in the alkyl chains, which results in stronger molecular stacking and thus the formation of similarly thin fibers with mechanical strength against various solvents.

2.5. X-ray Diffraction Analysis. To determine the molecular arrangement, an X-ray diffraction (XRD) analysis of compounds **1**−**8** was performed. Clear diffraction peaks were obtained for compounds **1**−**4** (Figure 9), and these profiles suggest that they are in a lamellar crystalline state (Table 1). Two lamellar structures were observed for compounds **3** and **4**. The molecular lengths of ideal straight and all-*trans* conformations calculated by Chem3D software (Cambridge Soft) are **1**: 2.24 nm, **2**: 2.51 nm, **3**: 2.60 nm, and **4**: 2.85 nm, respectively. The XRD results show that 5.26 nm (compound **3**) and 5.59 nm (compound **4**) are lamellar structures with two molecules aligned vertically. On the other hand, shorter lamellar structures of 3.78 nm (compound **1**), 4.17 nm (compound **2**), 4.55 nm (compound **3**), and 4.91 nm (compound **4**) were observed for each compound via XRD, which is consistent with the lamellar structure obtained when the two molecules are aligned at angles of approximately 57, 56, 61, and 59° with the horizontal plane.

On the other hand, compounds **5**−**8** did not show any peaks in the apparatus used in this study. Because a fibrous structure is observed from the FE-SEM observation, the existence of a lamellar structure is highly probable. We speculate that the reason why no peaks were observed is that the lamellar structure is not thick enough to produce diffraction peaks of sufficient intensity in this system.

2.6. FT-IR Analysis. Variable-temperature Fourier transform infrared spectroscopy (FT-IR) was measured to understand the behavior of intermolecular hydrogen bonding and diagnose the alkyl chain arrangement (Figures 10 and 11). As a result of the FT-IR measurements before and after the melting point, changes in the FT-IR spectra were observed for all the compounds. Usually, the methylene antisymmetric [$\nu_{as}(CH_2)$] and symmetric [$\nu_s(CH_2)$] stretching vibrations of the alkyl chains are strongly absorbed at approximately 2918−2928 and

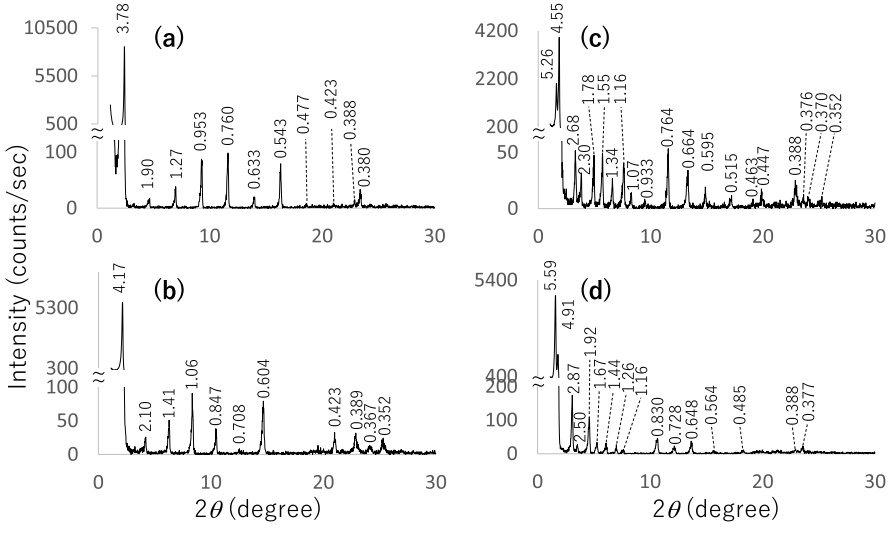

Figure 9. XRD patterns of (a) **1**: C_{12}GABA, (b) **2**: C_{14}GABA, (c) **3**: C_{16}GABA, and (d) **4**: C_{18}GABA. The numbers indicate *d* spacings (nm).

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Table 1. Distance (nm) and Reflection Attributions Calculated from Bragg's Law from the XRD Pattern of Neat Powders for Compounds 1−4

	small-angle diffractions							
compound	001	002	003	004	005	006	007	wide-angle diffractions
1: C_{12}GABA	3.78	1.90	1.27	0.953	0.760	0.633	0.543	0.477, 0.423, 0.388, 0.380
2: C_{14}GABA	4.17	2.10	1.41	1.06	0.847	0.708	0.604	0.423, 0.389, 0.367, 0.352
3: C_{16}GABA	5.26	2.68	1.78	1.34	1.07			0.764, 0.664, 0.595, 0.515, 0.463, 0.447, 0.388, 0.376, 0.370, 0.352
	4.55	2.30	1.55	1.16	0.933			
4: C_{18}GABA	5.59	2.87	1.92	1.44	1.16			0.830, 0.728, 0.648, 0.564, 0.485, 0.388, 0.377
	4.91	2.50	1.67	1.26				

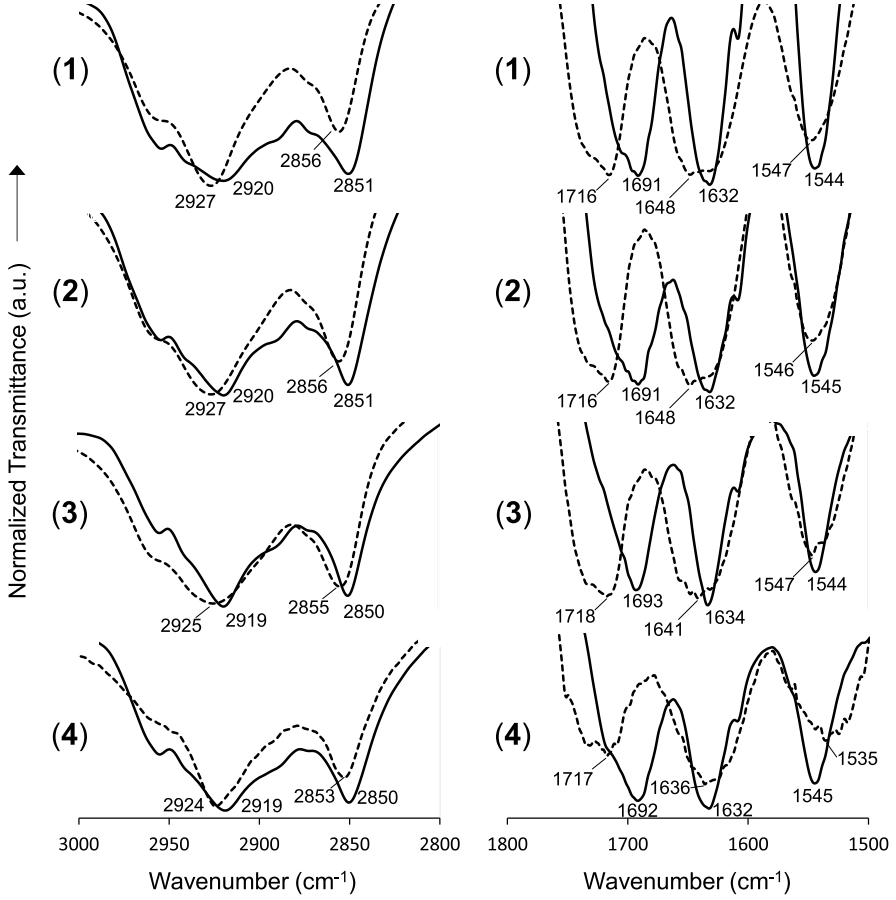

Figure 10. Variable-temperature FT-IR spectra. Left column: methylene antisymmetric [$\nu_{as}(CH_2)$] and symmetric [$\nu_s(CH_2)$] stretching regions. Right column: carbonyl [ν(C═O)] ester and amide (amide-I) stretching regions and amide [δ(N−H)] (amide-II) bending regions. (**1**): C_{12}GABA, (**2**): C_{14}GABA, (**3**): C_{16}GABA, and (**4**): C_{18}GABA, measured at 80, 80, 80, and 80 °C (solid lines), respectively, and at 100, 110, 110, and 120 °C (dotted lines, above the melting point), respectively.

2850−2860 cm^{-1}, respectively, while the all-*trans* structure is absorbed at approximately 2917−2920 and 2848−2851 cm^{-1}, and the *gauche*-including structure is absorbed at approximately 2923−2928 and 2852−2860 cm^{-1}, respectively.[16−19] Additionally, it has been determined that the stretching vibrations of $\nu_{as}(CH_2)$ and $\nu_s(CH_2)$ increase the absorption wavenumber by approximately 6 cm^{-1} when the all-*trans* conformation is converted to the *gauche*-including conformation.[18] Below the melting point, $\nu_{as}(CH_2)$ and $\nu_s(CH_2)$ stretching vibrations of *N*-linear saturated fatty acyl-GABAs (compounds **1**−**4**) were observed at 2919−2920 and 2850−2851 cm^{-1}, indicating that they are all-*trans* conformations (Figure 10). Above the melting point, these stretching vibrations are 2924−2927 and 2853−2856 cm^{-1}, respectively, indicating that the alkyl chains change to *gauche*-including structures. Each increase in the absorption wavenumber of the stretching vibration is also close to the typical value of 6 cm^{-1}. On the other hand, generally the stretching vibration of the proton-accepting group, C═O, decreases and the angular vibration of the proton-donating group, N−H, increases when the intermolecular hydrogen bonds are formed.[20] Here, we compare the stretching vibration of the C═O of the carboxy group and the amide group (amide-I) and the angular vibration of amide-II of compounds **1** to **3** before and after the melting point, which are 1716−1718, 1641−1648, and 1546−1547 cm^{-1} above the melting point, respectively, while below the melting point they were 1691−1693, 1632−1634, and 1544−1545 cm^{-1}. The decrease in the stretching vibration of C═O of the carboxy group and the amide group (amide-I) indicates the formation of the intermolecular hydrogen bond.

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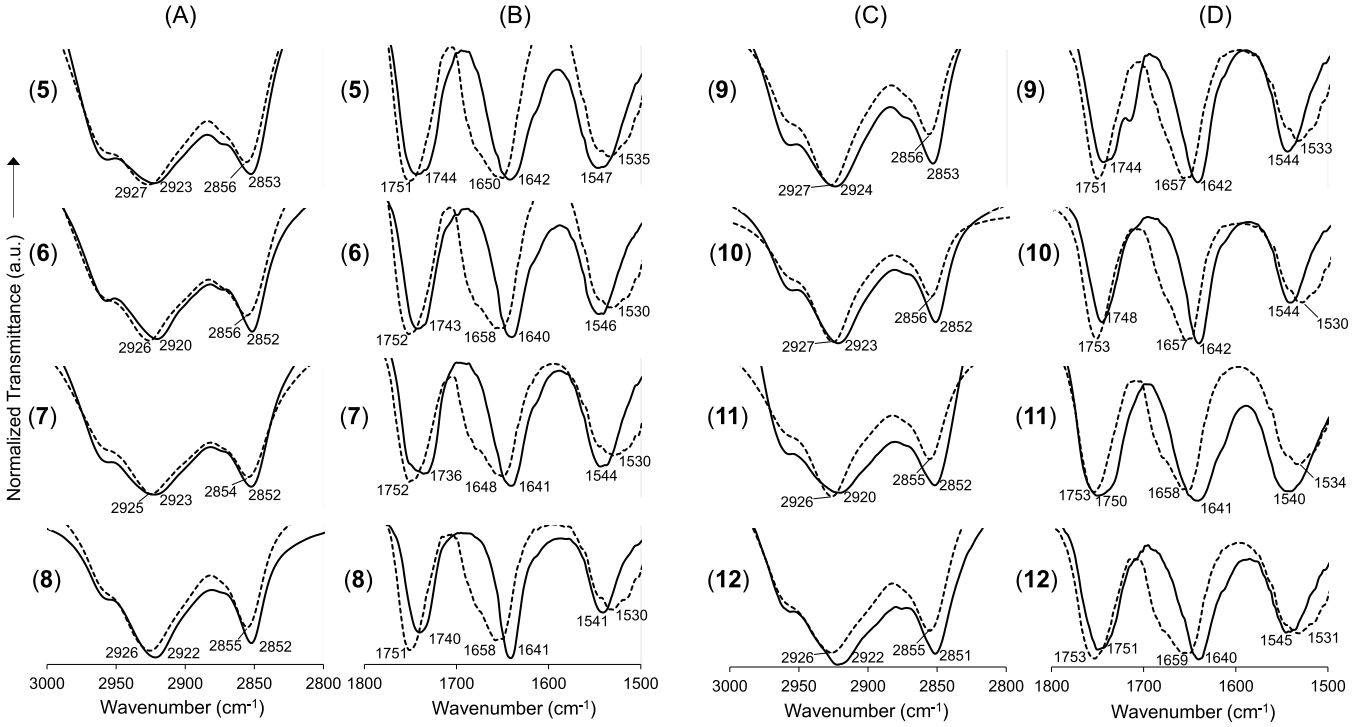

Figure 11. Variable-temperature FT-IR spectra. (A,C): methylene antisymmetric [$\nu_{as}(CH_2)$] and symmetric [$\nu_s(CH_2)$] stretching regions. (B,D): carbonyl [ν(C═O)] ester and amide (amide-I) stretching regions and amide [δ(N−H)] (amide-II) bending regions. (**5**): C_{12}GABA-AG, (**6**): C_{14}GABA-AG, (**7**): C_{16}GABA-AG, and (**8**): C_{18}GABA-AG, measured at 80, 80, 100, and 110 °C (solid lines), respectively, and at 140, 150, 150, and 150 °C (dotted lines, above the melting point), respectively. (**9**): C_{12}GABA-Glc, (**10**): C_{14}GABA-Glc, (**11**): C_{16}GABA-Glc, and (**12**): C_{18}GABA-Glc, measured at 120, 120, 120, and 120 °C (solid lines), respectively, and at 160, 160, 150, and 150 °C (dotted lines, above the melting point), respectively.

However, the angular vibration of amide-II was decreased. On the other hand, for compound **4**, C_{18}GABA, above the melting point, the vibrations were 1717, 1636, and 1535 cm^{-1}, but below the melting point, they were 1692, 1632, and 1545, indicating that the stretching vibration of the proton-accepting group C═O decreased and the angular vibration of the proton-donating group N−H increased, as predicted by theory. In other words, the formation of intermolecular hydrogen bonds between each substituent in the solid state was suggested.

The methylene antisymmetric [$\nu_{as}(CH_2)$] and symmetric [$\nu_s(CH_2)$] stretching vibrations of various 1,5-AG derivatives (compounds **5**−**8**) were 2920−2923 and 2852−2853 cm^{-1}, indicating that the alkyl chains are slightly skewed from the all-*trans* conformation. Above the melting point they are 2925−2927 and 2854−2856 cm^{-1}, respectively, indicating that the alkyl chains are *gauche*-including structures (Figure 11). Additionally, the increase in the wavenumber in the stretching vibration of $\nu_{as}(CH_2)$ and $\nu_s(CH_2)$ when the all-*trans* conformation converted to the *gauche*-including structure is small, averaging 3.5 cm^{-1}, again suggesting that the alkyl chains are slightly skewed from the all-*trans* conformation in the solid-state. In addition, the stretching vibrations of both C═O for the ester and amide (amide-I) and N−H for the angular vibration of the amide (amide-II) were 1736−1744, 1640−1642, and 1541−1547, respectively, indicating that they have intermolecular hydrogen bonds, whereas above the melting point they are 1751−1752, 1648−1658, and 1530−1535 cm^{-1}, indicating the disappearance of intermolecular hydrogen bonds. For Glc derivatives, similar to 1,5-AG derivatives, in the solid-state the alkyl chains have a slightly skewed structure from the all-*trans* conformation, and the C═O (ester and amide) and N−H groups are involved in an intermolecular hydrogen bond. The C═O (ester and amide) and N−H groups involved in the intermolecular hydrogen bonding are spatially fixed in both the 1,5-AG and Glc derivatives, we speculated that the affected alkyl chains are expected to be packed slightly skewed from the all-*trans* conformation.

Compounds **9**−**12**, which introduced *N*-linear saturated fatty acyl-GABA into Glc derivatives, are mixtures of anomeric configurations α and β, respectively, with different ratios. They are α/β = 0.13:0.87, 0.15:0.85, 0.48:0.52, and 0.51:0.49, respectively. However, the significant difference was not seen from the variable-temperature FT-IR spectra. On the other hand, the SEM observation of compounds **9**−**12** shows that various 3D structures are generated, and we speculate that very small differences in the intermolecular environment, which cannot be detected by variable-temperature FT-IR, may appear in the differences in the 3D structures.

3. MATERIALS AND METHODS

3.1. General Methods. $^1H-^1H$ COSY, HMBC, HSQC, ^1H NMR, and ^{13}C NMR spectra were obtained in $CDCl_3$ or $CDCl_3/CD_3OD$ on Bruker BioSpin spectrometers (AV 400, Bruker Corporation, Madison, MA, USA). Chemical shifts are given in ppm (parts per million) and referenced to Me_4Si (δ 0.00). To characterize the signals, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and dd = doublet of doublets. ESI-Orbitrap-MS spectra were recorded on a Thermo Fisher Scientific instrument (VELOS PRO, Thermo Fisher Scientific Inc., Waltham, MA, USA). Optical rotations were determined in $CHCl_3$/MeOH 10:1 on a

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Jasco instrument (P-1020-GT, Jasco Corp., Tokyo, Japan) at an ambient temperature. The melting point was measured while observing the sample on the temperature controller (FP82 hot stage linked to an FP90 with an accuracy of ±0.4 °C, Mettler Toledo, Columbus, OH, USA) under a microscope (BX51, Olympus Corp., Tokyo, Japan). Liquid paraffins #350 and #70 were products of Yamakei Sangyo (Osaka, Japan). Olive squalene, jojoba oil, and canola oil were products of Tree of Life Co., Ltd. (Tokyo, Japan). Hydrogenated polyisobutene (kinetic viscosity 300 mm^2/s) was obtained from the NOF Corporation (Tokyo, Japan). Pentaerythrityl tetraisostearate, triethylhexanoin, diisostearyl malate, and polyglyceryl-2 triisostearate were products of The Nisshin Oillio Group, Ltd. (Tokyo, Japan). Isopropyl myristate was obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Ethylhexyl palmitate was obtained from Nikko Chemicals Co., Ltd. (Tokyo, Japan). Castor oil and ethanol (99.5) were products of FUJIFILM Wako Pure Chemical Corp. (Osaka, Japan). 2-Octyl-1-dodecanol was obtained from Sigma-Aldrich Co. LLC (St. Louis, MO, USA). Rice bran oil was a product of Boso oil and fat Co., Ltd. (Tokyo, Japan). Dimethicone (viscosity 10 mm^2/s), cyclopentasiloxane, and diphenylsiloxy phenyl trimethicone were products of Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). All the reagents and solvents were of reagent grade.

3.2. Preparation of Per-*O*-saturated Linear Fatty Acyl-GABA-protected 1,5-AG. *3.2.1. 1,5-Anhydro-2,3,4,6-tetra-O-{4-[(1-oxododecyl)amino]butanoyl}-D-glucitol (**5**: C_{12}GABA-AG).* Crystals of 1,5-AG (24 mg, 0.146 mmol) were dissolved in water (100 μL), and the water was evaporated using an oil rotary vacuum pump to obtain dry amorphous 1,5-AG. C_{12}GABA (**1**: 250 mg, 0.876 mmol), DMAP (214 mg, 1.75 mmol), and 1,2-dichloroethane (20 mL) were added and dissolved at 60 °C. DIC (275 μL, 1.76 mmol) was added to this solution, and the mixture was stirred at 60 °C for 1.5 h. After confirming the completion of the reaction, methanol (60 mL) was added and stirred at room temperature for 1.5 h. After stirring, the reaction was incubated at 6 °C for 12 h. Unfortunately, no crystals were obtained. Therefore, the reaction solution was concentrated, and the compound was isolated and purified via silica gel column chromatography (chloroform/methanol 20:1). It was further recrystallized with methanol and water at an 8:2 ratio to obtain pure compound **5** (63.81 mg, 35%). $[\alpha]_D^{25}$ +14.8 (*c* 0.3, $CHCl_3$/MeOH 10:1); mp (°C) 135−138; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 12H, J_{CH_3,CH_2} 7.0 Hz, −C(=O)$CH_2CH_2(CH_2)_8C\underline{H}_3$), 1.26−1.28 (m, 64H, −C(=O)$CH_2CH_2(C\underline{H}_2)_8CH_3$), 1.60−1.63 (m, 8H, −C(=O)$CH_2C\underline{H}_2(CH_2)_8CH_3$), 1.73−1.86 (m, 8H, −C(=O)$CH_2C\underline{H}_2CH_2NH$), 2.13−2.18 (m, 8H, −C(=O)-$C\underline{H}_2CH_2(CH_2)_8CH_3$), 2.30−2.43 (m, 8H, −C(=O)-$C\underline{H}_2CH_2CH_2NH$), 3.18−3.35 (m, 9H, −C(=O)-$CH_2CH_2C\underline{H}_2$NH and H-1*ax*), 3.59 (ddd, 1H, $J_{4,5}$ 10.0 Hz, $J_{5,6'}$ 4.2 Hz, $J_{5,6}$ 2.2 Hz, H-5), 4.08 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6}$ 2.1 Hz, H-6), 4.14 (dd, 1H, J_{gem} 11.3 Hz, $J_{1eq,2}$ 5.7 Hz, H-1 *eq*), 4.32 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6'}$ 4.3 Hz, H-6′), 4.99−5.05 (m, 1H, H-2), 5.03 (t, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 5.18 (t, 1H, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3), 5.82 (t, 1H, J_{NH,CH_2} 5.6 Hz, NH), 5.99 (t, 1H, J_{NH,CH_2} 5.8 Hz, NH), 6.21 (t, 1H, J_{NH,CH_2} 5.8 Hz, NH), 6.22 (t, 1H, J_{NH,CH_2} 5.9 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11 (C_{lipid}-12), 22.69 (C_{lipid}-11), 24.49 (C_{GABA}-3), 24.52 (C_{GABA}-3), 24.60 (C_{GABA}-3), 24.68 (C_{GABA}-3), 25.80 (C_{lipid}-3), 25.81 (C_{lipid}-3), 25.82 (C_{lipid}-3), 29.35−29.67 (−C(=O)-$CH_2CH_2(\underline{C}H_2)_6CH_2CH_2CH_3$), 31.07 ($C_{GABA}$-2), 31.19 ($C_{GABA}$-2), 31.38 ($C_{GABA}$-2), 31.41 ($C_{GABA}$-2), 31.92 ($C_{lipid}$-10), 36.74 ($C_{lipid}$-2), 36.77 ($C_{lipid}$-2), 36.83 ($C_{lipid}$-2), 38.47 ($C_{GABA}$-4), 38.62 ($C_{GABA}$-4), 38.65 ($C_{GABA}$-4), 38.67 ($C_{GABA}$-4), 61.97 (C-6), 66.97 (C-1), 68.21 (C-4), 68.99 (C-2), 73.89 (C-3), 76.54 (C-5), 171.95 (OC=O), 172.09 (OC=O), 172.51 (OC=O), 172.90 (OC=O), 173.35 (NC=O), 173.50 (NC=O), 173.60 (NC=O), and 173.65 (NC=O); ESI-Orbitrap-MS, calculated for $C_{70}H_{129}N_4O_{13}^+$ $(M + H)^+$: 1233.9551; found, 1233.9585.

*3.2.2. 1,5-Anhydro-2,3,4,6-tetra-O-{4-[(1-oxotetradecyl)-amino]butanoyl}-D-glucitol (**6**: C_{14}GABA-AG).* This reaction was conducted in the same way as the synthesis of compound **5**, except using C_{14}GABA (**2**: 275 mg, 0.877 mmol). This compound was not purified via column chromatography because crystals were deposited in methanol (60 mL) that was added at the end of the reaction. The crystals were filtered and washed with methanol to yield compound **6** (94.20 mg, 48%). $[\alpha]_D^{25}$ +15.6 (*c* 0.3, $CHCl_3$/MeOH 10:1); mp (°C) 140−143; ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ 0.88 (t, 12H, J_{CH_3,CH_2} 6.5 Hz, −C(=O)$CH_2CH_2(CH_2)_{10}C\underline{H}_3$), 1.26−1.29 (m, 80H, −C(=O)$CH_2CH_2(C\underline{H}_2)_{10}CH_3$), 1.60 (broad s, 8H, −C(=O)$CH_2C\underline{H}_2(CH_2)_{10}CH_3$), 1.73−1.85 (m, 8H, −C(=O)$CH_2C\underline{H}_2CH_2NH$), 2.15−2.18 (m, 8H, −C(=O)-$C\underline{H}_2CH_2(CH_2)_{10}CH_3$), 2.29−2.42 (m, 8H, −C(=O)-$C\underline{H}_2CH_2CH_2NH$), 3.15−3.28 (m, 8H, −C(=O)-$CH_2CH_2C\underline{H}_2$NH), 3.32−3.37 (m, 1H, H-1*ax*), 3.61−3.64 (m, 1H, H-5), 4.10 (broad d, 1H, *J* 10.7 Hz, H-6), 4.13 (dd, 1H, J_{gem} 11.8 Hz, $J_{1eq,2}$ 5.7 Hz, H-1 *eq*), 4.29 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6'}$ 4.1 Hz, H-6′), 4.98−5.03 (m, 1H, H-2), 5.02 (t, 1H, $J_{3,4} = J_{4,5}$ 9.6 Hz, H-4), 5.19 (t, 1H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): δ 14.14 (C_{lipid}-14), 22.79 (C_{lipid}-13), 24.47 (C_{GABA}-3), 24.57 (C_{GABA}-3), 24.62 (C_{GABA}-3), 25.98 (C_{lipid}-3), 26.00 (C_{lipid}-3), 29.48−29.77 (−C(=O)$CH_2CH_2(\underline{C}H_2)_8CH_2CH_2CH_3$), 31.25 ($C_{GABA}$-2), 31.32 ($C_{GABA}$-2), 31.43 ($C_{GABA}$-2), 31.50 ($C_{GABA}$-2), 32.04 ($C_{lipid}$-12), 36.64 ($C_{lipid}$-2), 36.70 ($C_{lipid}$-2), 38.53 ($C_{GABA}$-4), 38.58 ($C_{GABA}$-4), 38.64 ($C_{GABA}$-4), 62.22 (C-6), 66.96 (C-1), 68.43 (C-4), 69.16 (C-2), 74.05 (C-3), 76.55 (C-5), 172.28 (OC=O), 172.47 (OC=O), 172.86 (OC=O), 173.37 (OC=O), 174.56 (NC=O), 174.67 (NC=O), and 174.70 (NC=O); ESI-Orbitrap-MS, calculated for $C_{78}H_{145}N_4O_{13}^+$ $(M + H)^+$: 1346.0803; found, 1346.0805.

*3.2.3. 1,5-Anhydro-2,3,4,6-tetra-O-{4-[(1-oxohexadecyl)-amino]butanoyl}-D-glucitol (**7**: C_{16}GABA-AG).* This reaction was conducted in the same way as the synthesis of compound **6**, except C_{16}GABA (**3**: 300 mg, 0.878 mmol) was used to yield compound 7 (193.1 mg, 91%). $[\alpha]_D^{25}$ +12.5 (*c* 0.3, $CHCl_3$/MeOH 10:1); mp (°C) 141−143; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 12H, J_{CH_3,CH_2} 7.0 Hz, −C(=O)-$CH_2CH_2(CH_2)_{12}C\underline{H}_3$), 1.25−1.28 (m, 96H, −C(=O)-$CH_2CH_2(C\underline{H}_2)_{12}CH_3$), 1.61 (broad s, 8H, −C(=O)-$CH_2C\underline{H}_2(CH_2)_{12}CH_3$), 1.73−1.86 (m, 8H, −C(=O)-$CH_2C\underline{H}_2CH_2NH$), 2.16 (m, 8H, −C(=O)$C\underline{H}_2CH_2(CH_2)_{12}CH_3$), 2.30−2.43 (m, 8H, −C(=O)-$C\underline{H}_2CH_2CH_2NH$), 3.23 (m, 8H, −C(=O)$CH_2CH_2C\underline{H}_2$NH), 3.32 (m, 1H, H-1*ax*), 3.59 (ddd, 1H, $J_{4,5}$ 10.0 Hz, $J_{5,6'}$ 4.1 Hz, $J_{5,6}$ 2.2 Hz, H-5), 4.08 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6}$ 1.9 Hz, H-6), 4.14 (dd, 1H, J_{gem} 11.2 Hz, $J_{1eq,2}$ 5.6 Hz, H-1 *eq*), 4.32 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6'}$ 4.2 Hz, H-6′), 4.99−5.05 (m, 1H, H-2), 5.03 (t, 1H, $J_{3,4} = J_{4,5}$ 9.6 Hz, H-4), 5.18 (t, 1H, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3), 5.82 (t, 1H, J_{NH,CH_2} 5.8 Hz, NH), 6.00 (t, 1H, J_{NH,CH_2} 5.8

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Hz, NH), 6.21 (t, 1H, J_{NH,CH_2} 5.6 Hz, NH), 6.22 (t, 1H, J_{NH,CH_2} 5.4 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12 (C_{lipid}-16), 22.70 (C_{lipid}-15), 24.50 (C_{GABA}-3), 24.52 (C_{GABA}-3), 24.60 (C_{GABA}-3), 24.68 (C_{GABA}-3), 25.80 (C_{lipid}-3), 25.82 (C_{lipid}-3), 25.83 (C_{lipid}-3), 25.85 (C_{lipid}-3), 29.37−29.72 (−C(=O)-$CH_2CH_2(\underline{C}H_2)_{10}CH_2CH_2CH_3$), 31.07 ($C_{GABA}$-2), 31.19 ($C_{GABA}$-2), 31.38 ($C_{GABA}$-2), 31.41 ($C_{GABA}$-2), 31.94 ($C_{lipid}$-14), 36.74 ($C_{lipid}$-2), 36.77 ($C_{lipid}$-2), 36.82 ($C_{lipid}$-2), 38.47 ($C_{GABA}$-4), 38.61 ($C_{GABA}$-4), 38.65 ($C_{GABA}$-4), 38.67 ($C_{GABA}$-4), 61.97 (C-6), 66.97 (C-1), 68.20 (C-4), 68.99 (C-2), 73.89 (C-3), 76.55 (C-5), 171.94 (OC=O), 172.08 (OC=O), 172.50 (OC=O), 172.89 (OC=O), 173.33 (NC=O), 173.49 (NC=O), 173.58 (NC=O), and 173.63 (NC=O); ESI-Orbitrap-MS, calculated for $C_{86}H_{161}N_4O_{13}^+$ $(M + H)^+$: 1458.2055; found, 1458.2031.

*3.2.4. 1,5-Anhydro-2,3,4,6-tetra-O-{4-[(1-oxooctadecyl)-amino]butanoyl}-D-glucitol (**8**: C_{18}GABA-AG).* This reaction was conducted in the same way as the synthesis of compound **6**, except C_{18}GABA (**4**: 324 mg, 0.877 mmol) was used to yield compound **8** (154.84 mg, 67%). $[\alpha]_D^{25}$ +11.9 (*c* 0.3, $CHCl_3$/MeOH 10:1); mp (°C) 140−143; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 0.89 (t, 12H, J_{CH_3,CH_2} 7.0 Hz, −C(=O)$CH_2CH_2(CH_2)_{14}C\underline{H}_3$), 1.26−1.32 (m, 112H, −C(=O)-$CH_2CH_2(C\underline{H}_2)_{14}CH_3$), 1.60 (broad t, 8H, −C(=O)-$CH_2C\underline{H}_2(CH_2)_{14}CH_3$), 1.73−1.85 (m, 8H, −C(=O)-$CH_2C\underline{H}_2CH_2NH$), 2.17 (m, 8H, −C(=O)-$C\underline{H}_2CH_2(CH_2)_{14}CH_3$), 2.30−2.43 (m, 8H, −C(=O)$C\underline{H}_2CH_2CH_2NH$), 3.15−3.27 (m, 8H, −C(=O)-$CH_2CH_2C\underline{H}_2NH$), 3.36 (m, 1H, H-1*ax*), 3.64 (ddd, 1H, $J_{4,5}$ 9.9 Hz, $J_{5,6'}$ 4.5 Hz, $J_{5,6}$ 2.1 Hz, H-5), 4.11 (dd, 1H, $J_{5,6}$ 2.0 Hz, H-6), 4.13 (dd, 1H, J_{gem} 11.1 Hz, $J_{1eq,2}$ 5.8 Hz, H-1 *eq*), 4.28 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6'}$ 4.6 Hz, H-6′), 4.98−5.05 (m, 1H, H-2), 5.02 (t, 1H, $J_{3,4} = J_{4,5}$ 9.8 Hz, H-4), 5.21 (t, 1H, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3), 7.10−7.40 (m, NH); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): δ 14.19 (C_{lipid}-18), 22.90 (C_{lipid}-17), 24.59 (C_{GABA}-3), 24.67 (C_{GABA}-3), 24.72 (C_{GABA}-3), 26.16 (C_{lipid}-3), 29.59−29.93 (−C(=O)$CH_2CH_2(\underline{C}H_2)_{12}CH_2CH_2CH_3$), 31.38 ($C_{GABA}$-2), 31.44 ($C_{GABA}$-2), 31.52 ($C_{GABA}$-2), 31.61 ($C_{GABA}$-2), 32.16 ($C_{lipid}$-16), 36.69 ($C_{lipid}$-2), 36.73 ($C_{lipid}$-2), 38.67 ($C_{GABA}$-4), 38.76 ($C_{GABA}$-4), 62.36 (C-6), 67.03 (C-1), 68.60 (C-4), 69.33 (C-2), 74.19 (C-3), 76.68 (C-5), 172.44 (OC=O), 172.63 (OC=O), 173.00 (OC=O), 173.52 (OC=O), 174.97 (NC=O), and 175.04 (NC=O); ESI-Orbitrap-MS, calculated for $C_{94}H_{177}N_4O_{13}^+$ $(M + H)^+$: 1570.3307; found, 1570.3289.

3.3. Preparation of Per-*O*-saturated Linear Fatty Acyl-GABA-protected Glc. *3.3.1. 1,2,3,4,6-Penta-O-{4-[(1-oxododecyl)amino]butanoyl}-D-glucopyranoside (**9**: C_{12}GABA-Glc).* Crystals of Glc (20 mg, 0.111 mmol) were dissolved in water (100 μL), and the water was evaporated using an oil rotary vacuum pump to obtain dry amorphous Glc. C_{12}GABA (**1**: 238 mg, 0.834 mmol), DMAP (203 mg, 1.66 mmol), and 1,2-dichloroethane (20 mL) were added and dissolved at 60 °C. DIC (261 μL, 1.67 mmol) was added to this solution, and the mixture was stirred at 60 °C for 3 h. After confirming the completion of the reaction, methanol (30 mL) was added and stirred at room temperature for 0.5 h. After stirring, water (7.5 mL) was added, and the reaction was incubated at 6 °C for 12 h. Unfortunately, no crystals were obtained. Therefore, the reaction solution was concentrated, and the compound was isolated and purified via silica gel column chromatography (chloroform/methanol 20:1). It was further recrystallized with methanol to obtain compound **9** (12.08 mg, 7%, α/β = 0.13:0.87). mp (°C) 152−154; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 0.88 (t, 15H, J_{CH_3,CH_2} 7.1 Hz, −C(=O)$CH_2CH_2(CH_2)_8C\underline{H}_3$), 1.26−1.28 (m, 80H, −C(=O)$CH_2CH_2(C\underline{H}_2)_8CH_3$), 1.60 (broad s, 10H, −C(=O)$CH_2C\underline{H}_2(CH_2)_8CH_3$), 1.71−1.84 (m, 10H, −C(=O)-$CH_2C\underline{H}_2CH_2NH$), 2.16 (m, 10H, −C(=O)-$C\underline{H}_2CH_2(CH_2)_8CH_3$), 2.27−2.43 (m, 10H, −C(=O)-$C\underline{H}_2CH_2CH_2NH$), 3.14−3.26 (m, 10H, −C(=O)-$CH_2CH_2C\underline{H}_2NH$), 3.88 (ddd, 0.87H, $J_{4,5}$ 10.0 Hz, $J_{5,6'}$ 4.3 Hz, $J_{5,6}$ 2.2 Hz, H-5 β), 4.10 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6}$ 1.8 Hz, H-6), 4.34 (dd, 1H, J_{gem} 12.4 Hz, $J_{5,6'}$ 4.5 Hz, H-6′), 5.09 (m, 1H, H-4), 5.11 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{1,2}$ 8.3 Hz, H-2), 5.26 (t, 0.87H, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3 β), 5.43 (t, 0.13H, $J_{2,3} = J_{3,4}$ 9.6 Hz, H-3 α), 5.72 (d, 0.87H, $J_{1,2}$ 8.3 Hz, H-1 β), 6.33 (d, 0.13H, $J_{1,2}$ 3.6 Hz, H-1 α), 6.90−7.21 (m, NH); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): δ 14.15 (C_{lipid}-12), 22.81 (C_{lipid}-11), 24.41 (C_{GABA}-3), 24.51 (C_{GABA}-3), 24.61 (C_{GABA}-3), 26.03 (C_{lipid}-3), 29.48−29.77 (−C(=O)$CH_2CH_2(\underline{C}H_2)_6CH_2CH_2CH_3$), 31.19 ($C_{GABA}$-2), 31.37 ($C_{GABA}$-2), 31.47 ($C_{GABA}$-2), 32.05 ($C_{lipid}$-10), 36.62 ($C_{lipid}$-2), 36.69 ($C_{lipid}$-2), 38.53 ($C_{GABA}$-4), 38.59 ($C_{GABA}$-4), 38.63 ($C_{GABA}$-4), 38.66 ($C_{GABA}$-4), 61.56 (C-6), 67.94 (C-4), 70.42 (C-2), 72.84 (C-5), 72.94 (C-3), 89.25 (C-1 α), 91.91 (C-1 β), 171.62 (OC=O), 171.98 (OC=O), 172.19 (OC=O), 172.60 (OC=O), 173.27 (OC=O), 174.68 (NC=O), 174.79 (NC=O), and 174.88 (NC=O); ESI-Orbitrap-MS, calculated for $C_{86}H_{158}N_5O_{16}^+$ $(M + H)^+$: 1517.1698; found, 1517.1712.

*3.3.2. 1,2,3,4,6-Penta-O-{4-[(1-oxotetradecyl)amino]-butanoyl}-D-glucopyranoside (**10**: C_{14}GABA-Glc).* This reaction was conducted in the same way as the synthesis of compound **9**, except using C_{14}GABA (**2**: 261 mg, 0.833 mmol). This compound was not purified via column chromatography because the crystals were deposited in methanol (30 mL)/water (7.5 mL) that was added at the end of the reaction. The crystals were filtered and washed with methanol/water at an 8:2 ratio to yield compound **10** (28.66 mg, 16%, α/β = 0.15:0.85). mp (°C) 151−153; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 0.88 (t, 15H, J_{CH_3,CH_2} 7.0 Hz, −C(=O)$CH_2CH_2(CH_2)_{10}C\underline{H}_3$), 1.26−1.28 (m, 100H, −C(=O)$CH_2CH_2(C\underline{H}_2)_{10}CH_3$), 1.59 (broad s, 10H, −C(=O)$CH_2C\underline{H}_2(CH_2)_{10}CH_3$), 1.70−1.84 (m, 10H, −C(=O)$CH_2C\underline{H}_2CH_2NH$), 2.16 (m, 10H, −C(=O)-$C\underline{H}_2CH_2(CH_2)_{10}CH_3$), 2.27−2.43 (m, 10H, −C(=O)-$C\underline{H}_2CH_2CH_2NH$), 3.14−3.28 (m, 10H, −C(=O)-$CH_2CH_2C\underline{H}_2NH$), 3.87 (m, 0.85H, H-5 β), 4.07−4.16 (m, 1.15H, H-6 α, H-6 β, and H-5 α), 4.28−4.37 (m, 1H, H-6′ α and H-6′ β), 5.07−5.14 (m, 2H, H-2 α, H-2 β, H-4 α, and H-4 β), 5.25 (t, 0.85H, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3 β), 5.43 (t, 0.15H, $J_{2,3} = J_{3,4}$ 9.6 Hz, H-3 α), 5.71 (d, 0.85H, $J_{1,2}$ 8.3 Hz, H-1 β), 6.33 (d, 0.15H, $J_{1,2}$ 3.6 Hz, H-1 α), 6.40−6.97 (m, NH); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): δ 14.13 (C_{lipid}-14), 22.75 (C_{lipid}-13), 24.40 (C_{GABA}-3), 24.42 (C_{GABA}-3), 24.46 (C_{GABA}-3), 24.57 (C_{GABA}-3), 25.96 (C_{lipid}-3), 29.43−29.73 (−C(=O)-$CH_2CH_2(\underline{C}H_2)_8CH_2CH_2CH_3$), 31.11 ($C_{GABA}$-2), 31.31 ($C_{GABA}$-2), 31.44 ($C_{GABA}$-2), 31.99 ($C_{lipid}$-12), 36.62 ($C_{lipid}$-2), 36.69 ($C_{lipid}$-2), 38.43 ($C_{GABA}$-4), 38.47 ($C_{GABA}$-4), 38.51 ($C_{GABA}$-4), 38.55 ($C_{GABA}$-4), 38.59 ($C_{GABA}$-4), 61.46 (C-6), 67.84 (C-4), 70.31 (C-2), 72.79 (C-3 or C-5), 72.84 (C-3 or C-5), 89.19 (C-1 α), 91.83 (C-1 β), 171.52 (OC=O), 171.87 (OC=O), 172.09 (OC=O), 172.50 (OC=O), 173.13 (OC=O), 174.31 (NC=O), 174.46 (NC=O), and 174.49

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(NC═O); ESI-Orbitrap-MS, calculated for $C_{96}H_{178}N_5O_{16}^+$ $(M + H)^+$: 1657.3263; found, 1657.3216.

3.3.3. 1,2,3,4,6-Penta-O-{4-[(1-oxohexadecyl)amino]-butanoyl}-D-glucopyranoside (11: C_{16}GABA-Glc). This reaction was conducted in the same way as the synthesis of compound **10**, except C_{16}GABA (**3**: 284 mg, 0.832 mmol) was used to yield compound **11** (87.67 mg, 44%, α/β = 0.48:0.52). mp (°C) 140−146; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 15H, J_{CH_3,CH_2} 7.0 Hz, −C(═O)$CH_2CH_2(CH_2)_{12}C\underline{H}_3$), 1.25−1.28 (m, 120H, −C(═O)$CH_2CH_2(C\underline{H}_2)_{12}CH_3$), 1.60 (broad s, 10H, −C(═O)$CH_2C\underline{H}_2(CH_2)_{12}CH_3$), 1.73−1.91 (m, 10H, −C(═O)$CH_2C\underline{H}_2CH_2NH$), 2.16 (m, 10H, −C(═O)-$C\underline{H}_2CH_2(CH_2)_{12}CH_3$), 2.28−2.51 (m, 10H, −C(═O)-$C\underline{H}_2CH_2CH_2NH$), 3.19−3.34 (m, 10H, −C(═O)-$CH_2CH_2C\underline{H}_2NH$), 3.84 (ddd, 0.52H, $J_{4,5}$ 10.1 Hz, $J_{5,6'}$ 4.3 Hz, $J_{5,6}$ 2.2 Hz, H-5 β), 4.04−4.14 (m, 1.48H, H-5 α, H-6 α, and H-6 β), 4.33−4.40 (m, 1H, H-6′ α and H-6′ β), 5.07−5.15 (m, 2H, H-2 α, H-2 β, H-4 α, and H-4 β), 5.23 (t, 0.52H, $J_{2,3}$ = $J_{3,4}$ 9.3 Hz, H-3 β), 5.44 (t, 0.48H, $J_{2,3}$ = $J_{3,4}$ 9.9 Hz, H-3 α), 5.70 (d, 0.52H, $J_{1,2}$ 8.2 Hz, H-1 β), 6.34 (d, 0.48H, $J_{1,2}$ 3.7 Hz, H-1 α); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12 (C_{lipid}-16), 22.70 (C_{lipid}-15), 24.47 (C_{GABA}-3), 24.53 (C_{GABA}-3), 24.57 (C_{GABA}-3), 24.68 (C_{GABA}-3), 24.82 (C_{GABA}-3), 25.83 (C_{lipid}-3), 29.38−29.72 (−C(═O)$CH_2CH_2(\underline{C}H_2)_{10}CH_2CH_2CH_3$), 31.00 ($C_{GABA}$-2), 31.05 ($C_{GABA}$-2), 31.23 ($C_{GABA}$-2), 31.35 ($C_{GABA}$-2), 31.44 ($C_{GABA}$-2), 31.56 ($C_{GABA}$-2), 31.94 ($C_{lipid}$-14), 36.70 ($C_{lipid}$-2), 36.77 ($C_{lipid}$-2), 38.31 ($C_{GABA}$-4), 38.35 ($C_{GABA}$-4), 38.45 ($C_{GABA}$-4), 61.29 (C-6 α or β), 61.45 (C-6 α or β), 67.74 (C-4 α and β), 69.38 (C-2 α), 69.84 (C-3 α), 70.11 (C-5 α), 70.23 (C-2 β), 72.79 (C-3 β and C-5 β), 89.14 (C-1 α), 91.77 (C-1 β), 171.18 (OC═O), 171.29 (OC═O), 171.60 (OC═O), 171.85 (OC═O), 172.26 (OC═O), 172.30 (OC═O), 172.78 (OC═O), 173.32 (NC═O), 173.48 (NC═O), 173.53 (NC═O), 173.56 (NC═O), and 173.59 (NC═O); ESI-Orbitrap-MS, calculated for $C_{106}H_{199}N_5O_{16}^{2+}$ $(M + 2H)^{2+}$: 899.2450; found, 899.2417.

3.3.4. 1,2,3,4,6-Penta-O-{4-[(1-oxooctadecyl)amino]-butanoyl}-D-glucopyranoside (12: C_{18}GABA-Glc). This reaction was conducted in the same way as the synthesis of compound **10**, except C_{18}GABA (**4**: 307 mg, 0.831 mmol) was used to yield compound **12** (103.48 mg, 48%, α/β = 0.51:0.49). mp (°C) 139−145; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 15H, J_{CH_3,CH_2} 7.0 Hz, −C(═O)-$CH_2CH_2(CH_2)_{14}C\underline{H}_3$), 1.26−1.29 (m, 140H, −C(═O)-$CH_2CH_2(C\underline{H}_2)_{14}CH_3$), 1.60 (broad s, 10H, −C(═O)-$CH_2C\underline{H}_2(CH_2)_{14}CH_3$), 1.70−1.89 (m, 10H, −C(═O)-$C\underline{H}_2C\underline{H}_2CH_2NH$), 2.16 (m, 10H, −C(═O)$C\underline{H}_2CH_2(CH_2)_{14}CH_3$), 2.27−2.51 (m, 10H, −C(═O)-$C\underline{H}_2CH_2CH_2NH$), 3.14−3.28 (m, 10H, −C(═O)-$CH_2CH_2C\underline{H}_2NH$), 3.87 (ddd, 0.49H, $J_{4,5}$ 10.1 Hz, $J_{5,6'}$ 4.2 Hz, $J_{5,6}$ 2.1 Hz, H-5 β), 4.06−4.14 (m, 1.51H, H-5 α, H-6 α, and H-6 β), 4.31−4.37 (m, 1H, H-6′ α and H-6′ β), 5.06−5.14 (m, 2H, H-2 α, H-2 β, H-4 α, and H-4 β), 5.25 (t, 0.49H, $J_{2,3}$ = $J_{3,4}$ 9.4 Hz, H-3 β), 5.43 (t, 0.51H, $J_{2,3}$ = $J_{3,4}$ 9.9 Hz, H-3 α), 5.71 (d, 0.49H, $J_{1,2}$ 8.3 Hz, H-1 β), 6.33 (d, 0.51H, $J_{1,2}$ 3.7 Hz, H-1 α); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14 (C_{lipid}-18), 22.76 (C_{lipid}-17), 24.48 (C_{GABA}-3), 24.57 (C_{GABA}-3), 24.61 (C_{GABA}-3), 24.71 (C_{GABA}-3), 25.94 (C_{lipid}-3), 25.97 (C_{lipid}-3), 29.44−29.79 (−C(═O)$CH_2CH_2(\underline{C}H_2)_{12}CH_2CH_2CH_3$), 31.12 ($C_{GABA}$-2), 31.16 ($C_{GABA}$-2), 31.30 ($C_{GABA}$-2), 31.39 ($C_{GABA}$-2), 31.44 ($C_{GABA}$-2), 31.57 ($C_{GABA}$-2), 32.01 ($C_{lipid}$-16), 36.62 ($C_{lipid}$-2), 36.69 ($C_{lipid}$-2), 38.48 ($C_{GABA}$-4), 38.56 ($C_{GABA}$-4), 38.59 ($C_{GABA}$-4), 61.46 (C-6 α or β), 61.59 (C-6 α or β), 67.84 (C-4 α and β), 69.49 (C-2 α), 69.95 (C-3 α), 70.10 (C-5 α), 70.32 (C-2 β), 72.79 (C-3 β or C-5 β), 72.84 (C-3 β or C-5 β), 89.19 (C-1 α), 91.83 (C-1 β), 171.47 (OC═O), 171.52 (OC═O), 171.88 (OC═O), 172.09 (OC═O), 172.15 (OC═O), 172.51 (OC═O), 172.56 (OC═O), 173.15 (OC═O), 174.34 (NC═O), and 174.51 (NC═O); ESI-Orbitrap-MS, calculated for $C_{116}H_{219}N_5O_{16}^{2+}$ $(M + 2H)^{2+}$: 969.3233; found, 969.3182.

3.4. Gelation Evaluation. Gelation evaluation was performed using a 2 mL screw-capped glass bottle. Each sample was accurately weighed into this bottle and then added to each oil with an accurate weighing. This was placed on a hot plate at 100 to 150 °C to dissolve the compounds and then left at room temperature for 12 h to obtain the gels. To determine the gelation ability, the glass bottle was gently inverted upside down and observed, and those that did not drip were judged to be gelled.

3.5. Hardness Measurements. The hardness of the obtained gels was measured using a RHEONER II (RE2-33005C, Yamaden Co., Ltd., Tokyo, Japan). A 5 mmφ spherical plunger was inserted into a gel in a 2 mL screw-capped glass bottle at a speed of 60 mm/min, and the maximum stress up to a 2.5 mm insertion was taken as the gel hardness.

3.6. Turbidity Measurements. Turbidity was measured by the absorbance at 660 nm using a spectrophotometer (DU650, Beckman Coulter Inc., Brea, CA, USA) directly from the gel in the above 2 mL screw-capped glass bottle. Water was measured as the blank and set to 0.

3.7. FE-SEM Observation. The various gels were soaked in *n*-hexane for 2 days at room temperature to remove the organic solvent and prepare the xerogels. The xerogel samples were then coated with osmium using an osmium coater from Filgen (OPC60A, Filgen Inc., Nagoya, Japan). FE-SEM observations were made using a JEOL instrument (JSM-7600F, JEOL Ltd., Tokyo, Japan).

3.8. XRD Analysis. The crystalline phases of the powder (compounds **1**−**8**) were inspected via XRD (RINT 2200VK/PC, Rigaku Corp., Tokyo, Japan) in the continuous scanning mode using monochromated Cu Kα radiation (40 kV, 40 mA) in the 2θ range between 1.1 and 30°.

3.9. Variable-Temperature FT-IR Spectroscopy. Variable-temperature FT-IR spectra were obtained on a Spectrum One FT-IR spectrometer (PerkinElmer, Inc., Waltham, MA, USA) operating at 4 cm^{-1} resolution. The temperature was controlled with a Mettler FP82 hot stage linked to a Mettler FP90 with an accuracy of ±0.4 °C.

4. CONCLUSIONS

We synthesized *N*-linear saturated fatty acyl-GABA present in the human brain and discovered that they are organogelators. In other words, even in the human brain they may be involved in gelation as a form of control of the physical properties of the oil components present in the brain. They formed a bimolecular layered structure (lamellar structure) tilted at 56−61° to the horizontal plane, and the alkyl chains were found to pack and stabilize in an all-*trans* conformation.

We also synthesized novel 1,5-AG and Glc derivatives, in which these *N*-linear saturated fatty acyl-GABA are ester bonded, and determined that they are also organogelators. They essentially formed a fibrous structure in organic solvents and gelled, but some compounds existed in spherical, flake, and

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plate forms. The length of the fatty acid also influenced the gelation, with C_{14}GABA-AG, a 1,5-AG derivative, having the highest gel hardness and transparency. Compared to the previously reported C16AG organogelator, C_{14}GABA-AG was harder and more transparent. This is because the intermolecular hydrogen bonding of the amide groups in the fatty acids stabilizes the fibrous structure in three dimensions and forms very thin fibers with a diameter of less than 50 nm to form the gel. The 1,5-AG and Glc derivatives synthesized here are formed by ester linkages. There are various esterases and lipases in the body, and it is expected that the 1,5-AG and Glc derivatives synthesized here will be degraded by these enzymes to release 1,5-AG, Glc, and *N*-linear saturated fatty acyl-GABA. Because the *N*-linked saturated fatty acyl-GABA released in this process has physiological functions, the 1,5-AG and Glc derivatives synthesized here may also have physiological functions as a source of *N*-linked saturated fatty acyl-GABA, and we plan to investigate the physiological function of these compounds in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02240.

^{1}H, ^{1}H−^{1}H COSY, ^{13}C, HSQC, and HMBC NMR charts of compounds **1**−**12** (PDF)

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Author Contributions

Conceptualization, S.K.; methodology, S.K.; validation, S.K. and R.I.; formal analysis, S.K. and R.I.; investigation, S.K.; resources, S.K.; data curation, S.K. and R.I.; writing—original draft preparation, S.K.; writing—review and editing, S.K.; visualization, S.K.; supervision, S.K.; project administration, S.K.; and funding acquisition, S.K. and R.I.

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Notes

The authors declare no competing financial interest.

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