Pergamon

Tetrahedron Letters 42 (2001) 6141–6145

TETRAHEDRON LETTERS

Solid-phase lipid synthesis (SPLS)-2: incidental discovery of organogelators based on artificial glycolipids

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Received 23 April 2001; revised 4 June 2001; accepted 8 June 2001

Abstract—Here we report a new solid-phase (glyco)lipid synthesis (SPLS), which gives traceless glycolipids using an acetal linker. During the synthesis, we incidentally found some of the artificial glycolipids act as good organogelators, the property of which is greatly dependent on the modular saccharide structure.

Saccharide-based molecular assembly has recently become attractive in supramolecular chemistry because of its intrinsic biocompatibility and environmental benignity.[1] However, their structural complexity has prevented rational design of sophisticated molecular materials. To construct the design principle, more systematic investigation using a large combinatorial library of glycosylated compounds is greatly required. We

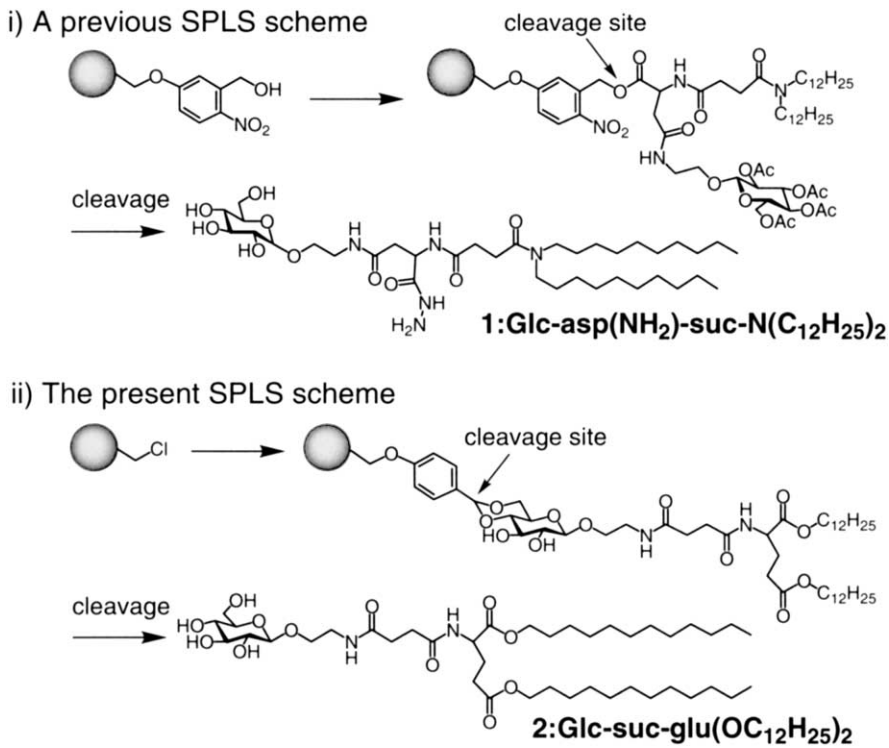

Figure 1. Typical examples of SPLS: (i) the glycolipids are abbreviated as '**1: sugar–connector(charge)–tail**'; (ii) the glycolipids are abbreviated as '**2: sugar–spacer–tail**'.

Keywords: glycolipids; organogels; solid-phase synthesis.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01013-9

recently reported a simple method for solid-phase (glyco)lipid synthesis (SPLS)[2] based on a module combination strategy.[3] Because of employing a benzylester linker and sugars protected by acetyl groups, the artificial lipids should not have any ester bonds within the core framework. In addition, a carboxylic acid derivative such as carbohydrazide inevitably remained as an attachment trace in the lipid molecules after cleavage (see Fig. 1). Here we describe a new SPLS using an acetal linker to overcome these drawbacks. During the synthetic experiments, we incidentally discovered that some artificial lipids act as gelators for organic solvents (i.e. organogelator). It is interesting that the gelation property is strongly dependent on the modular structure of the glycolipids.

For the traceless synthesis of artificial glycolipids displayed in Fig. 1, we employed an acetal group consisting of the 4,6-hydroxyl group of a glycoside module to connect the module to the resin. Scheme 1 shows a synthetic route of SPLS-2. An acetal-protected azidoethylglycoside (2-azidoethyl 4,6-*O*-*p*-hydroxybenzylidene-β-D-glycopyranoside)[4] is attached to the chloromethyl resin by a Williamson reaction. The azide group is reduced by a Staudinger reaction in the presence of triphenylphosphine,[5] followed by ring opening amidation using succinic anhydride.[6] The carboxylic acid terminal thus generated is condensed with corresponding amines (as a hydrophobic tail) in the presence of diphenylphosphorylazide (DPPA),[8] giving a framework of artificial glycolipids. When we employ glutamate derivatives as a tail module, there are two routes at the condensation process. In the case of symmetric glutamates (path-A), lipids having a symmetric tail are straightforwardly synthesized. For the introduction of an asymmetric tail, a monoallyl–monoalkyl glutamate is used (path-B). The allyl ester is removed by a Pd(0) catalyst[9] and subsequently another tail unit such as pyrenyl alcohol is condensed in the presence of diisopropylcarbodiimide (DIC). The acid-catalyzed cleavage of the lipid from the resin is successfully achieved using a trifluoroacetic acid (TFA)/dichloromethane mixture in the presence of a few drops of water,[10] affording target compounds by purification through the silica gel column chromatography (as a typical eluent: $CHCl_3$/MeOH). The overall yields were in the range of 53–71% for path-A, and 25–29% for path-B.[11,12] The new SPLS is clearly suitable to provide artificial glycolipids with structural diversity.

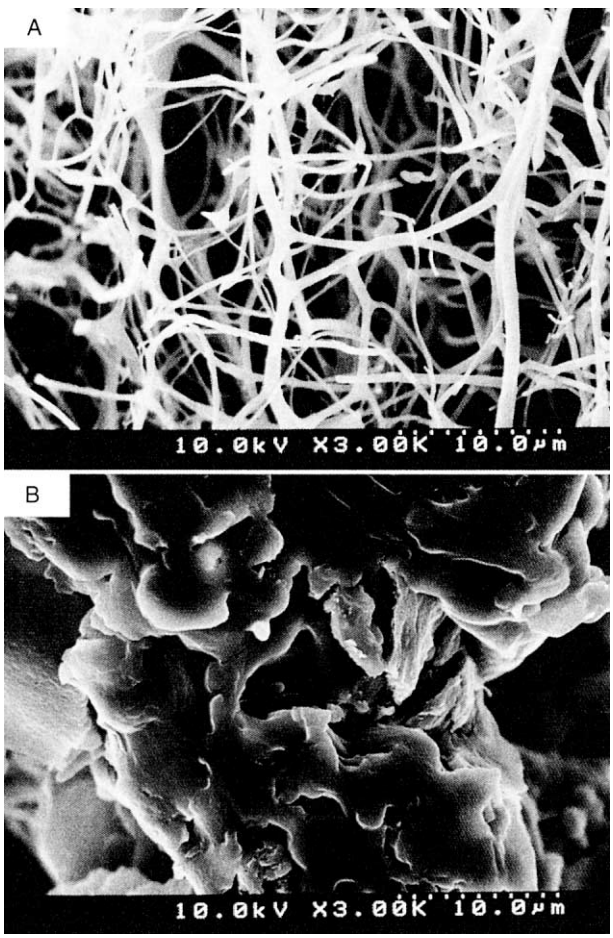
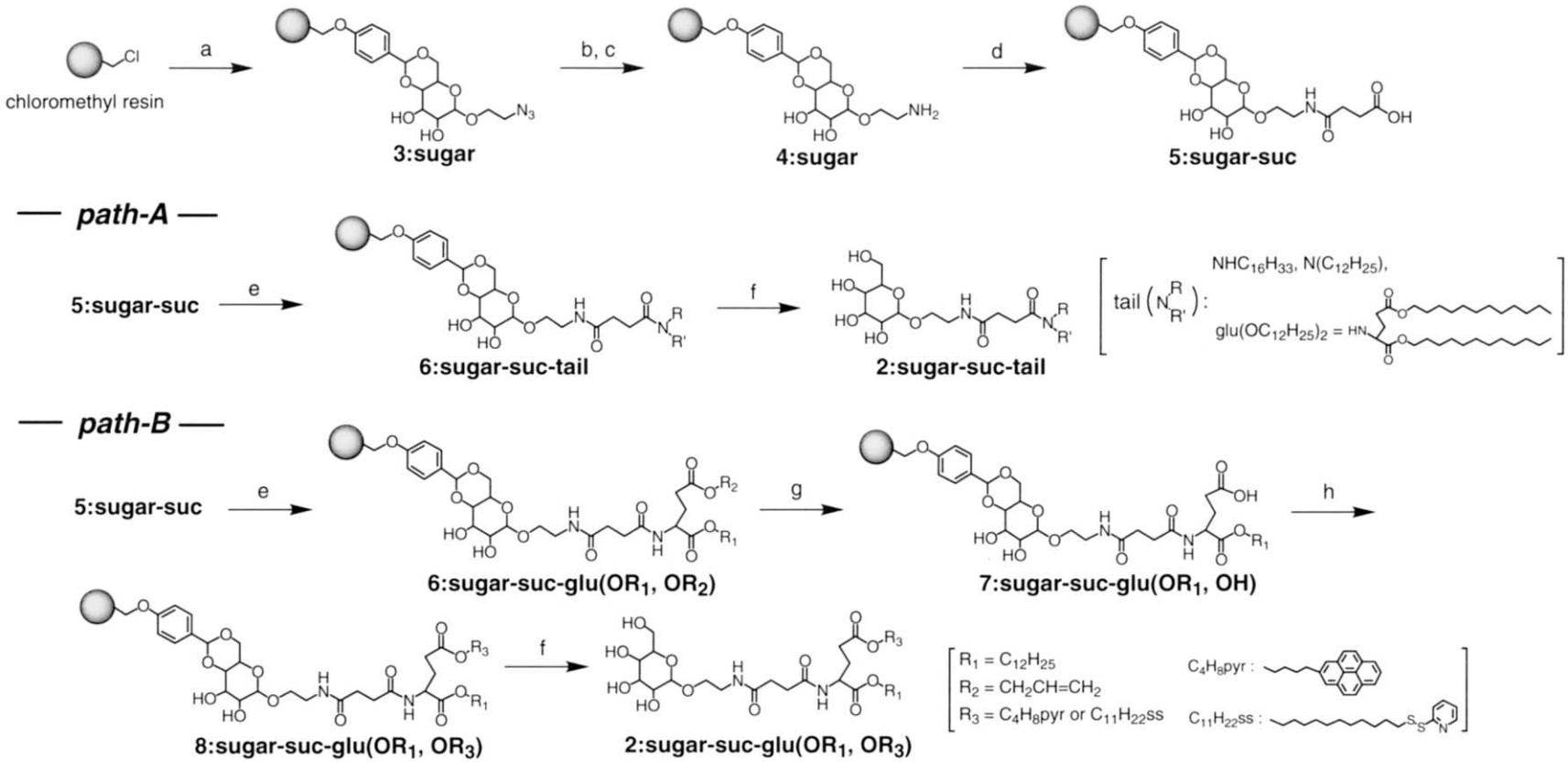


Figure 2. SEM pictures of freeze-dried samples of (A): organogel of **2: Gal-suc-glu($OC_{12}H_{25}$)$_2$** and benzene, (B): homogeneous solution of **2: Man-suc-glu($OC_{12}H_{25}$)$_2$** and benzene.

It is unexpectedly found that some organic solvents form into gels just by dissolving the artificial lipids during the purification process, suggesting a unique possibility of new gelators based on the glycolipids. Thus, we decided to investigate the gelation ability of the present small glycolipid library. Table 1 summarizes the gelation assay data of the lipids against various organic solvents. It is clear that some glycolipids show good gelation capability for a variety of organic solvents. We observed additional features as follows. (i) Among lipids with an identical β-glucoside head module, the tail bearing a double chain (e.g. N($C_{12}H_{25}$)$_2$ or glu(O $C_{12}H_{25}$)$_2$) has better gelation ability, since the single chain derivative is not satisfactorily soluble in any organic solvents. (ii) More interestingly, the structure of the sugar head sensitively affects the gelation ability. Galactoside and glucoside derivative are excellent gelators for hexane, benzene, toluene, ethyl acetate, and acetone or acetonitrile, whereas mannoside derivative is a poor gelator for all of those solvents. Mannoside derivative is too soluble in nonpolar solvents such as hexane, benzene and toluene to act as a gelator and concurrently is scarcely soluble in polar nonprotic solvents such as acetonitrile and ethyl acetate. (iii) An asymmetric tail structure seems to lessen the gelation capability. (iv) The lipids synthesized by the previous SPLS scheme are not good gelators.

Fig. 2 shows typical SEM (scanning electron microscopy) photographs of a freeze-dried sample of the transparent gel consisting of **2: Gal-suc-glu($OC_{12}H_{25}$)$_2$** in benzene and a homogeneous benzene solution of **2: Man-suc-glu($OC_{12}H_{25}$)$_2$**. Clearly, the gelator forms a three dimensional network with 1–10 μm fibrils, indicating that the glycolipid self-assembles to form many microcavities which immobilize the solvent molecules. In contrast, the SEM photograph of the **2: Man-suc-glu($OC_{12}H_{25}$)$_2$** sample dose not show any net-



Scheme 1. *Reagents and conditions*: (a) 2-azidoethyl 4,6-*O*-*p*-hydroxybenzylidene-β-D-hexopyranoside (1.0 equiv.), Cs_2CO_3 (3.0 equiv.), TBAI (0.1 equiv.), DMF, 18 h, 80°C; (b) PPh_3 (3.0 equiv.), CH_2Cl_2, 4 h, reflux; (c) H_2O (excess), THF, 8 h, reflux; (d) succinic anhydride (adequate), DIEA (2.0 equiv.), CH_2Cl_2, rt; (e) NH(R)(R′) (2.0 equiv.), DPPA (2.0 equiv.), DIEA (4.0 equiv.), DMF, 12 h, rt; (f) 10% TFA, H_2O (a few drops), CH_2Cl_2, 1.5 h, rt; (g) $Pd^{II}(OAc)_2$ (0.08 equiv.), PPh_3 (2.0 equiv.), morpholine (3.0 equiv.), THF, 4 h, 40°C; (h) R_3-OH (6.0 equiv.), DIC (4.0 equiv.), HOBt·H_2O (4.0 equiv.), DMAP (4.0 equiv.), DMF, 12 h, rt.

Table 1. Synthetic yields and gelation ability of the artificial glycolipids prepared by SPLS

Glycolipid	Total yield (%)	Gelation ability									
		MeOH	EtOH	Acetone	CH_3CN	AcOEt	$CHCl_3$	CH_2Cl_2	Toluene	Benzene	Hexane
1: Glc-asp(NH_2)-suc-N($C_{10}H_{21}$)$_2$	81	H	H	H	I	P	H	H	**pG**	**pG**	**pWG**
1: Glc-asp(NH_2)-suc-N($C_{14}H_{29}$)$_2$	59	H	H	P	I	P	H	H	**G**	**pG**	**pWG**
2: Glc-suc-$NHC_{16}H_{33}$	60	H	H	I	I	I	I(G)	I(pG)	I(pG)	I(G)	I
2: Glc-suc-N($C_{12}H_{25}$)$_2$	53	H	H	**WG**	I	**WG**	H	H	**G**	**G**	**WG**
2: Glc-suc-glu($OC_{12}H_{25}$)$_2$	58	H	H	H	**pWG**	**pWG**	H	H	**pG**	**pG**	**WG**
2: Man-suc-glu($OC_{12}H_{25}$)$_2$	–[a]	H	H	H	P	P	H	H	H	H	H
2: Gal-suc-glu($OC_{12}H_{25}$)$_2$	71	H	H	**WG**	**WG**	**WG**	H	H	**G**	**pG**	**WG**
2: Gal-suc-glu($OC_{12}H_{25}$, OC_4H_8pyr)	25	H	H	H	I	**WG**	H	H	**G**	**G**	P
2: Gal-suc-glu($OC_{12}H_{25}$, $OC_{11}H_{22}$ss)	29	H	H	H	P	P	H	H	**pG**	**G**	P

H = homogeneous, I = insoluble, P = precipitation, pG = partial gel, WG = white gel, G = gel[glycolipid] = 25 mM, aging overnight at 25°C.

[a] This glycolipid was synthesized in solution phase.

work fibrils, but instead amorphous solid surfaces. This is in good agreement with the gelation ability.

The present results preliminarily suggest that the macroscopic gelation ability of the artificial glycolipids may greatly be affected by the modular saccharide structure. Very recently, low molecular weight gelators are being investigated as intriguing functional materials in many fields.[13–15] By the combinatorial SPLS approach, we are now exploring a super gelator based on an artificial glycolipid which is capable of forming a hydrogel, as well as an organogel.

Acknowledgements

Shigeki Kiyonaka is a JSPS fellow for Japanese Junior Scientist.

References

1. (a) Fuhrhop, J.-H. *Chem. Rev.* **1993**, *93*, 1565; (b) Hafkamp, R. J. H.; Kokke, B. P. A.; Danke, I. M.; Geurts, H. P. M.; Roman, A. E.; Feiters, M. C.; Nolte, R. J. M. *Chem. Commun.* **1997**, 545; (c) Shimizu, T.; Masuda, M. *J. Am. Chem. Soc.* **1997**, *119*, 2812; (d) Nakazawa, I.; Masuda, M.; Okada, Y.; Hanada, T.; Yase, K.; Asai, M.; Shimizu, T. *Langmuir* **1999**, *15*, 4757; (e) Yoza, K.; Ono, Y.; Yoshihara, K.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 907; (f) Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem. Eur. J.* **1999**, *5*, 2722; (g) Inoue, K.; Ono, Y.; Kanekiyo, Y.; Kiyonaka, S.; Hamachi, I.; Shinkai, S. *Chem. Lett.* **1999**, 225.
2. Hamachi, I.; Kiyonaka, S.; Shinkai, S. *Chem. Commun.* **2000**, 1281.
3. Kunitake, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 709 and references cited therein.
4. Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2394.
5. Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, *00*, 815.
6. In this reaction, succinic anhydride was added dropwise slowly to the reaction mixture until the Kaiser test[7] became negative.
7. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *32*, 595.
8. (a) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 849; (b) Tsuda, T.; Nishimura, S.-I. *Chem. Commun.* **1996**, 2779.
9. Guibé, F. *Tetrahedron* **1998**, *54*, 2967 and references cited therein.
10. Hanessian, S.; Huynh, H. K. *Synlett.* **1999**, 102.
11. Selected data for a typical example (**2: Glc-suc-glu($OC_{12}H_{25}$)$_2$**): ^{1}H NMR (600MHz, $CDCl_3$: CD_3OD = 5: 1): δ 4.59 (s, 2H, NH), 4.42 (m, 1H, CH), 4.28 (d, 1H, J = 7.7, H-1), 4.13–4.06 (m, 4H, $CH_3(CH_2)_{10}CH_2OCO$), 3.90 (m, 1H, $NHCH_2CH_2O$), 3.87 (dd, 1H, H-6), 3.67–3.65 (m, 2H, H-6, $NHCH_2CH_2O$), 3.43 (m, 1H, $NHCH_2CH_2O$), 3.38–3.35 (m, 2H, H-3, $NHCH_2CH_2O$), 3.31–3.27 (m, 2H, H-4, H-5), 3.21 (t, 1H, J = 8.3, H-2), 2.54–2.49 (m, 4H, $COCH_2CH_2CO$), 2.42 (t, 2H, J = 7.6, $CHCH_2CH_2COO$), 2.14, 1.94 (m, 2H, $CHCH_2CH_2COO$), 1.64 (m, 4H, $CH_3(CH_2)_9CH_2CH_2OCO$), 1.29 (m, 36H, $CH_3(CH_2)_9CH_2CH_2OCO$), 0.91 (t, 6H, J = 6.7, $CH_3(CH_2)_9CH_2$). MALDI-TOF-MS for $C_{41}H_{76}N_2O_{12}$ (M = 789.06): m/z = 813.12 $[M+Na]^+$, 829.05 $[M+K]^+$. Elemental anal. calcd for $C_{41}H_{76}N_2O_{12}$: C, 62.41; H, 9.71; N, 3.55. Found: C, 62.11; H, 9.76; N, 3.47%.
12. It was found by ^{1}H NMR and MALDI-TOF mass spectroscopies that major byproducts were due to the excess acylation of succinic anhydride with unprotected OH groups of the glycoside moiety.
13. (a) Carr, A. J.; Melendez, R.; Geib, S. J.; Hamilton, A. D. *Tetrahedron Lett.* **1998**, *39*, 7447; (b) Shi, C.; Huang, Z.; Kilic, S.; Xu, J.; Enick, R. M.; Beckman, E. J.; Carr, A. J.; Melendez, R. E.; Hamilton, A. D. *Science* **1999**, *286*, 1540; (c) Estroff, L. A.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 3447.
14. (a) Hanabusa, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949; (b) Kato, T.; Kondo, G.; Hanabusa, K. *Chem. Lett.* **1998**, 193; (c) Hanabusa, K.; Maesaka, Y.; Suzuki, M.; Kimura, M.; Shirai, H. *Chem. Lett.* **2000**, 1168; (d) de Loos, M.; van Esch, J.; Stokroos, I.; Kellogg, R. M.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 12675; (e) van Esch, J.; De Feyter, S.; Kellogg, R. M.; De Schryver, F.; Feringa, B. L. *Chem. Eur. J.* **1997**, *3*, 1238.
15. (a) Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679; (b) Bhattacharya, S.; Krishnan-Ghosh, Y. *Chem. Commun.* **2001**, 185.