Tetrahedron: *Asymmetry* 28 (2017) 1435–1443

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Verification study for an empirical rule in diverse helical conformational behaviors of asymmetric 1,2-diacyl-*sn*-glycerols in the solution state

Yoshihiro Nishida [a,*], Yuan Mengfei [a], Kaito Fujisawa [a], Sakura Kitagawa [a], Hirofumi Dohi [a], Hirotaka Uzawa [b]

[a] *Molecular Chirality Research Center, Graduate School of Advanced Integration Science, Chiba University, Matsudo 271-8510, Chiba, Japan*
[b] *Nanomaterials Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), 1-1-1 Higashi, Tsukuba 305-8565, Japan*

ARTICLE INFO

Article history:
Received 31 July 2017
Revised 23 September 2017
Accepted 28 September 2017
Available online 23 October 2017

Dedicated to the memory of Dr. Howard Flack

ABSTRACT

Cell-membrane glycerophospholipids and glycolipids have a common asymmetric skeleton of 1,2-diacyl-*sn*-glycerols. The 1,2-diacyl moiety in solutions permits a rapid equilibrium among three helical conformers, namely gt(+), gg(−), and tg, to display diverse conformational properties. The conformational property changes variably not only by head groups at the *sn*-3 position, but also by the solvent conditions applied. Recently, we came across an empirical rule in the conformational diversity in the solution state when we assumed the term of 'helical disparity' for the equilibrium between gt(+) and gg(−) conformers with reversed helical signs for each other. The sign and magnitude of the helical disparity (%) governs the (+)- or (−)-chirality around the lipid tail and corresponds to the magnitude of the exciton couplet CD (circular dichroism) bands. The empirical rule expresses that the disparity (%) changes linearly by the function of gt(+) population (%). Herein, the rule was verified by ^{1}H NMR spectroscopy using different types of 1,2-diacyl-*sn*-glycerols as model compounds. The present paper describes that the rule is formulated with a general equation (Eq-1): 'helical disparity (%)' = [gt(+)−gg(−)] (%) = A[gt(+)−B], in which A and B are constants taking values around 1.3 and 38, respectively. This rule is maintained regardless of the 1,2-diacyl and *sn*-3 substituent groups as far as examined here, while affording several exceptions. With Eq-1 (A = 1.3, B = 38), a conformational diagram can be obtained. This allows us to overview the diverse helical conformational properties of the asymmetric 1,2-diacyl-*sn*-glycerols in the solutions state.

1. Introduction

The glycerol-types of phospholipids and glycolipids serve as the major elements of cytoplasm membranes. They have a common asymmetric skeleton of 1,2-diacyl-*sn*-glycerol bearing polar head groups at the *sn*-3 position.[1] They self-assemble under physiological conditions to construct fluid bilayer membranes together with cholesterol. The chirality[2] in the asymmetric *sn*-glycerol skeleton should play an important role in their biological functions essential in our cell lives.

The asymmetric *sn*-glycerol skeleton is also of interest in terms of its stereochemistry; it furnishes several conformers by free rotation along each of the *sn*-1,2 and *sn*-2,3 C–C single bonds.[3] For example, the 1,2-diacyl moiety in the solution state permits a rapid equilibration among three helical conformers, namely gt(+), gg(−), and tg (Fig. 1). The gt(+) and gg(−) are *gauche* conformers with reversed helicities around vicinal oxygens, while the tg is another rotamer aligning the two oxygens in an antiperiplanar relationship.

Thanks to extensive stereochemical studies on glycerophospholipids,[4–8] we know that the 1,2-diacyl moiety favors gt(+) and gg(−) conformers in both solution and in the liquid crystalline state. This trend is also observed among α-glycosyl glycerophospholipids (α GGPLs) in *Mycoplasma cytoplasmic membranes*.[9] According to our results based on ^{1}H NMR and circular dichroism (CD) spectroscopy,[10–12] the 1,2-diacyl moiety maintains a regular rule; the three conformers are distributed in the relative order as gt(+) ≥ gg(−) > tg (%) in the solution state. In particular, *sn*-3 phosphates and α-glycosyl linkages display notable effects; they increase the population of the gt(+) conformer and amplify the (+)-chirality around the 1,2-diacyl moiety.[13] We also encountered another rule, which may be worthy of discussion and verification. Herein the new rule is verified in our ^{1}H NMR spectroscopic analyses for those

* Corresponding author.
E-mail address: tdn_nishida@msn.com (Y. Nishida).

https://doi.org/10.1016/j.tetasy.2017.09.021
0957-4166/

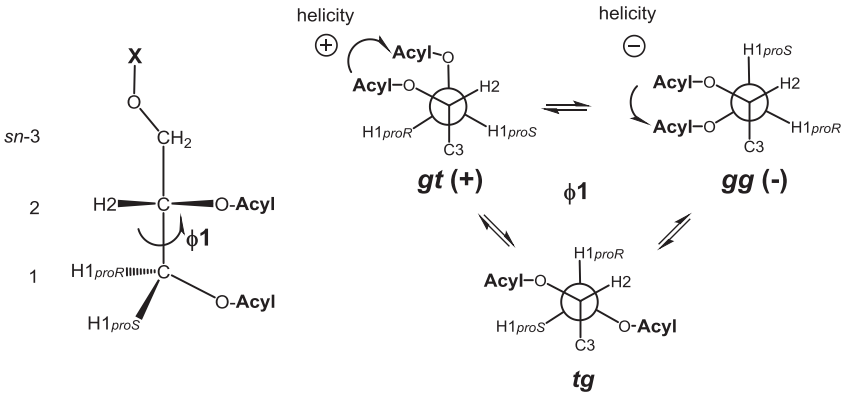

Fig. 1. Structures of asymmetric 1,2-diacyl-*sn*-glycerols and their helical conformational properties around 1,2-diacyl moiety.

sorts of asymmetric 1,2-diacyl-*sn*-glycerols, which include 1,2-dibenzoyl-*sn*-glycerols **1**–**12** (Chart 1).

2. Results and discussion

2.1. Definition of the helical conformational property of 1,2-diacyl-*sn*-glycerols with the 'helical disparity' and 'helical volume'

The 1,2-diacyl moiety gives two *gauche* conformers, namely gt(+) and gg(−), which have (+)- and (−)-helicity, respectively around the 1,2-diol esters. This gives another conformer, namely tg, which aligns the vicinal oxygens in an antiperiplanar relationship (Fig. 1). The helical conformational property is determined by the equilibrium position of the three helical conformers. In our preceding study[12], we introduced the terms of 'helical disparity (%)' and 'helical volume (%)'. The helical disparity (%) is defined as the difference in populations between gt(+) and gg(−) conformers, and the helical volume (%) as the sum of their populations. The helical disparity (%) informs us the sign and magnitude of chirality around the 1,2-diacyl moiety. The helical volume (%) informs us how far extents the two helical conformers occupy the conformational equilibrium around the 1,2-diacyl moiety. These parameters can be estimated precisely by using our ^{1}H NMR Karplus relationship, and the results are in good agreement with the exciton couplet CD bands of Nakanishi et al. and Harada et al.[14,15]

In the ^{1}H NMR analysis of 1,2-dipalmitoyl-*sn*-glycerols,[13] we plotted the helical disparities (%) against the populations of gt(+) conformer to afford a linear correlation. The following equation (Eq-1) expresses the linear relationship;

$$\text{Eq-1 : 'the helical disparity' } (\%) = [gt(+) - gg(-)]\ (\%) = A[gt(+) - B],$$

in which gt(+) and gg(−) are fractional distributions (%) and determined in our ^{1}H NMR Karplus analysis. A and B are constants with values of 1.34 and 37.9, respectively, estimated from the linear relationship.

We assume that the two constants (A and B) may vary due to several factors such as the acyl groups in the 1,2-moiety and the solvents applied. It is also possible that the linear relationship may be valid in only limited cases. Since we believe that the defined helical conformational property is of high significance for understanding the stereochemistry of cell-membrane 1,2-diacyl-*sn*-glycerols, we tried to evaluate the empirical rule using different types of 1,2-diacyl-*sn*-glycerols, which include the series of 1,2-dibenzoyl-*sn*-glycerols **1**–**12**.

2.2. Evaluation of Eq-1 using C2-symmetric triacylglycerols in $CDCl_3$ solutions

First, we evaluated Eq-1 using three types of *C2*-symmetric triacylglycerols bearing different acyl groups (Chart 2).

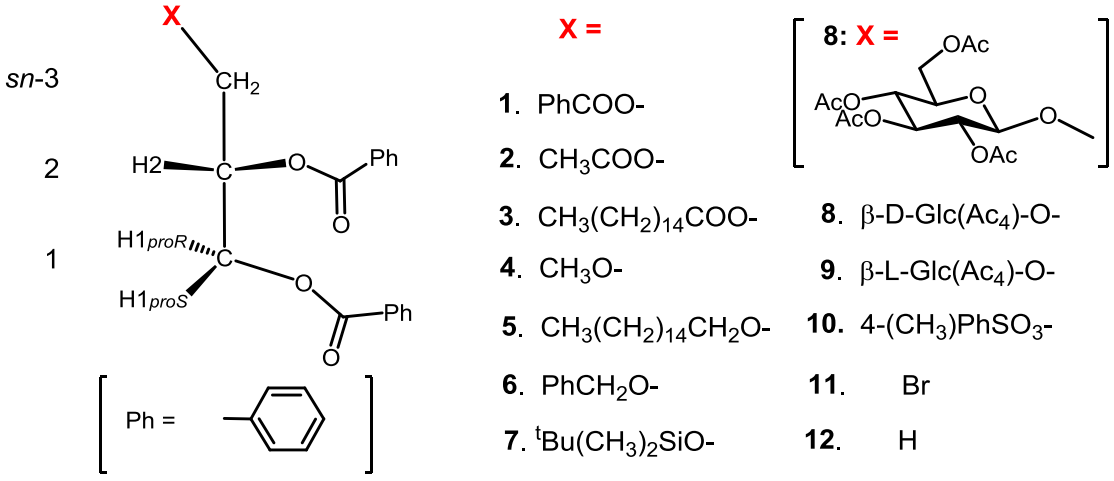

Chart 1. Structures of asymmetric 1,2-dibenzoyl-*sn*-glycerols 1–12.