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Carba-cyclophellitols Are Neutral Retaining-Glucosidase Inhibitors

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Supporting Information

ABSTRACT: The conformational analysis of glycosidases affords a route to their specific inhibition through transition-state mimicry. Inspired by the rapid reaction rates of cyclophellitol and cyclophellitol aziridine—both covalent retaining β -glucosidase inhibitors—we postulated that the corresponding carba “cyclopropyl” analogue would be a potent retaining β -glucosidase inhibitor for those enzymes reacting through the 4H_3 transition-state conformation. *Ab initio* metadynamics simulations of the conformational free energy landscape for the cyclopropyl inhibitors show a strong bias for the 4H_3 conformation, and carba-cyclophellitol, with an *N*-(4-azidobutyl)-carboxamide moiety, proved to be a potent inhibitor ($K_i = 8.2$ nM) of the *Thermotoga maritima* TmGH1 β -glucosidase. 3-D structural analysis and comparison with unreacted epoxides show that this compound indeed binds in the 4H_3 conformation, suggesting that conformational strain induced through a cyclopropyl unit may add to the armory of tight-binding inhibitor designs.

The diverse conformational pathways of glycosidases^{1,2} (for example, Figure 1A) coupled to their phenomenal transition-state stabilization³ offer a powerful route to selective enzyme inhibition. One of the main goals of the field—very rarely achieved—is to design and apply conformationally restricted inhibitors in order to provide both potency and specificity; conformationally biased inhibitors that target specific classes of glycoside hydrolase (GH) would be of considerable use as cellular and mechanistic probes with potential as starting points for therapeutic compounds. Cyclophellitol (**1**, Figure 1), isolated in 1990 from the mushroom *Phellinus* sp.,⁴ is a potent mechanism-based inhibitor of retaining β -glucosidases. It finds primary use as a covalent inactivator of β -glucosidases.⁵ Cyclophellitol is a configurational analogue of β -glucopyranose, but its conformational behavior is different. Whereas β -glucopyranoses prefer to adopt a 4C_1 conformation, the epoxide annulation in **1** likely enforces a preferred 4H_3 half-chair conformation onto the cyclitol moiety.

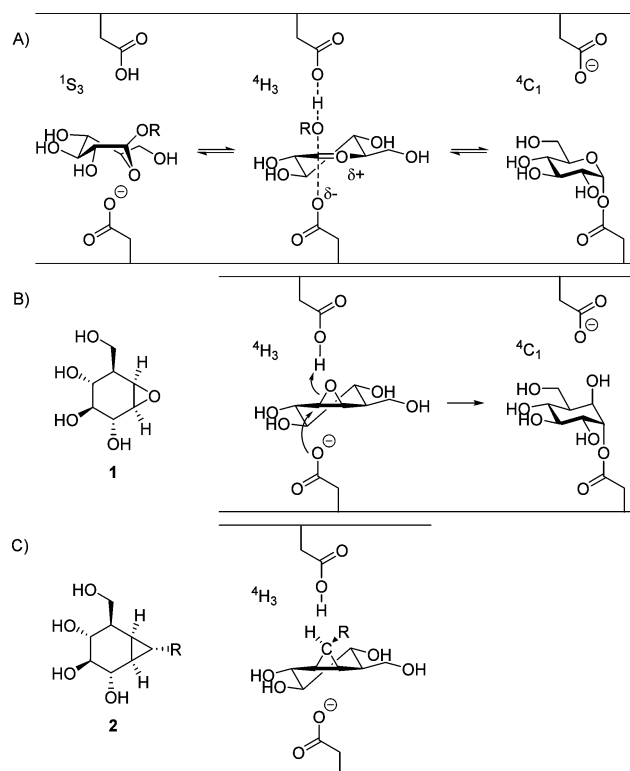


Figure 1. (A) Mechanistic itinerary of retaining β -glucosidases. (B) Structure of cyclophellitol (**1**) adopting a 4H_3 conformation and its proposed mechanism of binding. (C) Structure of carba-cyclophellitol (**2**) in 4H_3 conformation.

Cyclophellitol (**1**) is thus a potential conformational analogue of the oxocarbenium ion transition-state during β -glucosidase-mediated hydrolysis of a β -glucosidic linkage.

Although the mode of action of **1** is covalent (Figure 1B), its potency and specificity as a retaining β -glucosidase inhibitor

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and its mode of action (entering the enzyme active site as a 4H_3 half-chair transition-state analogue followed by S_N2 displacement of the epoxide heteroatom) led us to consider whether the corresponding carba analogue (that is, substitution of the oxygen for carbon) would result in competitive inhibitors in which potency and potentially specificity would be accrued by virtue of partial transition-state mimicry (Figure 1C).

To test this hypothesis, a set of carba-cyclophellitols was designed. Here we present the synthesis of carba-cyclophellitols 3–5 (Figure 2), the quantum mechanical analysis of their

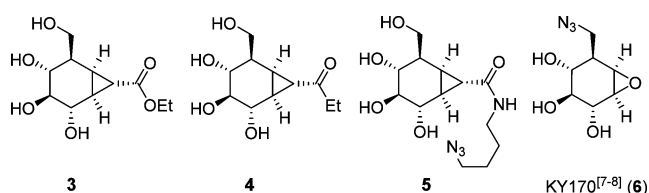


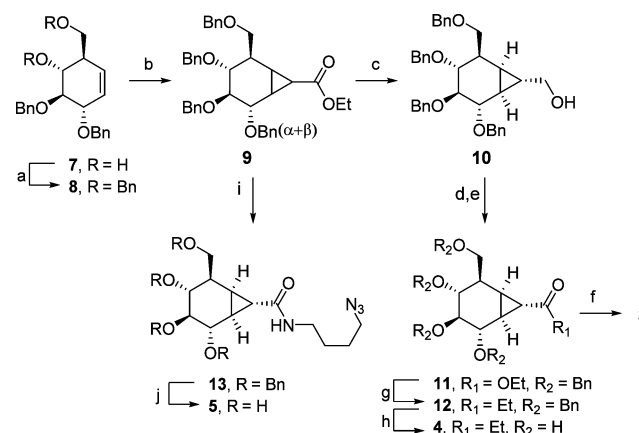
Figure 2. Structures of carba-cyclophellitols 3–5 and 8-azidocyclophellitol (6, KY170^{7,8}).

favorable conformation, and their structural and inhibitory dissection toward β -glucosidases. Carba-cyclophellitols are shown to be low μ M inhibitors. Furthermore, exploiting the possibility of incorporating pseudoaxial R groups—consistent with the catalytic itinerary—that bearing a hydrophobic moiety at the terminal cyclopropyl carbon (5) was indeed a potent (low nM) inhibitor of a classical model β -glucosidase, namely *Thermotoga maritima* TmGH1.^{5,6} The crystal structure of TmGH1 containing carba-cyclophellitol 5 was determined and compared with that of an unreacted cyclophellitol derivative; as predicted, both bind in 4H_3 conformation, which is the presumed transition-state conformation during the TmGH1-catalyzed hydrolysis of β -glucosidic linkages.

The synthesis of compounds 3–5 commenced with the easy access of key intermediate 7, which was obtained via the synthetic procedure described by the group of Madsen⁹ and optimized in our laboratory (Scheme 1).⁸ Global benzylation of 7 gave cyclohexene 8, and cyclopropanation with ethyl diazoacetate (EDA)^{10,11} under the agency of Cu(acac)₂ resulted in the formation of product 9 as a mixture of α - and β -isomers (α/β , 2:1). After the reduction step¹² the β -isomer could be isolated by column chromatography to give alcohol 10, which was oxidized, and ensuing esterification yielded enantiomerically pure β -ester 11. Sequential one-pot formation and Grignard addition onto the Weinreb amide yielded β -ketone 12. Both benzyl-protected ester 11 and ketone 12 were subjected to palladium-catalyzed hydrogenolysis conditions in ethyl acetate and acetic acid (11) or in methanol (12) to obtain target compounds 3 and 4. The mixture of α - and β -esters 9 was saponified, and the resulting carboxylates were condensed with 4-azidobutan-1-amine (see Supporting Information (SI)). The mixture of α - and β -amides was separated by preparative HPLC purification. Finally, the benzyl groups were removed in the presence of the azide with anhydrous BCl₃ in dichloromethane to afford β -amide 5.

Having carba-cyclopropane 3–5 in hand, we studied their inhibition potency in comparison with deoxynojirimycin (DNJ), a known competitive TmGH1 inhibitor and AMP-DNM (MZ-21), a known human retaining β -glucosidase inhibitor.¹³ Initial binding constant (K_i) values were determined on TmGH1 by monitoring the UV absorbance of *p*-nitrophenolate from *p*-nitrophenyl β -D-glucopyranoside using

Scheme 1. The synthesis of carba-cyclophellitols 3–5^a



^aReagents and conditions: (a) BnBr, NaH, TBAI, DMF, 0 °C to rt, 24 h, 94%; (b) EDA, Cu(acac)₂, EtOAc, (35%, 2:1, as a mixture of α/β); (c) DIBAL, THF, 30 min at 0 °C and then 1 h at rt, 13%; (d) Jones reagent, acetone, 0 °C, 3 h, 53%; (e) EtOH, *N,N'*-diisopropylcarbodiimide, 4-dimethylaminopyridine, toluene, rt, 4 h, 62%; (f) Pd(OH)₂/C, H₂, EtOAc, AcOH, rt, overnight, 81%; (g) *N,O*-dimethylhydroxylamine hydrochloride, EtMgBr, THF, 48%; (h) Pd(OH)₂/C, H₂, MeOH, rt, overnight, (58%); (i) i) LiOH, MeOH, H₂O, rt, overnight; ii) 4-azidobutan-1-amine (see SI), DIPEA, HCTU, CH₂Cl₂, rt, overnight; (j) BCl₃, DCM, 99%.

the Lineweaver–Burk method. Carba-cyclophellitol 3 and 4 showed micromolar inhibition, consistent with our design strategy and similar to that displayed by the charged species DNJ, whereas 5 proved to be a strong reversible binding TmGH1 inhibitor with a K_i value of 8.2 nM, much more potent than DNJ¹⁴ and AMP-DNM (low micromolar) (Table 1 and

Table 1. Apparent IC₅₀ Values and Inhibitory Constants (K_i) for *in Vitro* Inhibition of α - and β -Glucosidase Activity by Compounds 3–5, DNJ, and AMP-DNM

compound	K_i^a	app IC ₅₀	
	TmGH1 ^b	GBA1 ^c	GAA ^c
3	22.3 μ M	>150 μ M	>150 μ M
4	88.9 μ M	>150 μ M	>150 μ M
5	8.20 nM	99 \pm 1.9 μ M	>150 μ M
DNJ	2.50 μ M ^d	109 \pm 1.0 μ M ^e	1.5 μ M ^g
AMP-DNM (MZ-21)	4.97 μ M	156 \pm 16 nM ^f	0.4 μ M ^g

^a K_m TmGH1 = 0.24 mM. ^bThe assay was performed with *p*-NPG as substrate. ^cThe assay was performed with 2,4-DNPG as substrate. Values in agreement with literature. ^d K_i DNJ = 3.8 μ M in TmGH1.¹⁴ ^eIC₅₀ DNJ = 250 μ M in GBA1.¹⁵ ^fIC₅₀ AMP-DNM = 100–200 nM in GBA1.^{15,16} ^gValues from ref 17. App: apparent.

Figure S4). We then explored the activity of compound 5 in human lysosomal retaining β -glucosidase, GBA1 (deficiency of which is causative of the human lysosomal storage disorder, Gaucher disease) with an apparent IC₅₀ \approx 100 μ M. No apparent inhibition of the human lysosomal α -glucosidase, GAA (deficient in the human glycogen storage disease, Pompe disease) was observed at final concentrations of 5 up to 150 μ M. Thus, although less potent for GBA1 than for the bacterial enzyme tested, compound 5 appears to have selectivity for the human lysosomal β -glucosidase over the human lysosomal α -glucosidase, which is opposite of the selectivity observed for DNJ (Table 1).

Inspired by the low μM to nM inhibition of *TmGH1* by the carba-cyclopropanes, we sought to determine whether the cyclopropyl moiety indeed biased the conformation to ${}^4\text{H}_3$. We calculated the conformational free energy landscape (FEL) for generic cyclopropyl (**2**, $\text{R} = \text{H}$) by *ab initio* metadynamics (see SI), and the Cremer–Pople puckering coordinates θ and ϕ were used as collective variables, yielding a Mercator representation for the FEL (as used previously for diverse glycosidase inhibitors^{18–20}), Figure 3A. Compound **2** clearly

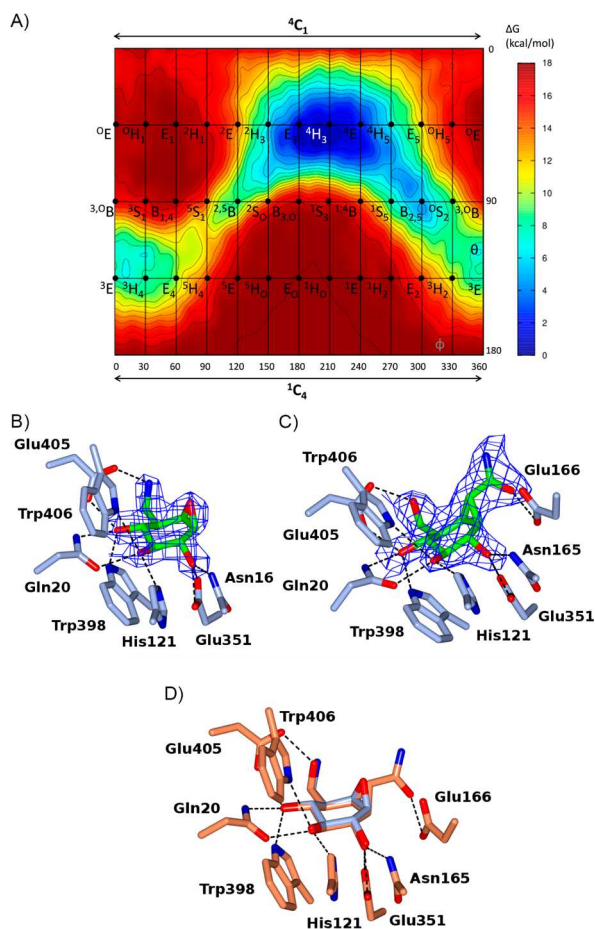


Figure 3. (A) A mercator representation for the computed free energy landscape (FEL) of cyclopropyl (**2**, $\text{R} = \text{H}$) (θ and ϕ are given in degrees). (B) Crystal structure of *TmGH1* in complex with unreacted **6**, KY170. (C) Crystal structure of *TmGH1* in complex with carba-cyclophellitol **5**, showing the carba-cyclophellitol CO–NH group. Electron density maps for both (B) and (C) are maximum likelihood/ σ_A weighted $2F_{\text{obs}} - F_{\text{calc}}$ syntheses contoured at 1.4σ . (D) Overlay of (B) in ice blue on (C) in coral.

favors the ${}^4\text{H}_3$ conformation *in vacuo*, with the flipped ${}^3\text{H}_4$ form in another local energy minimum. Subsequent to FEL calculation, we compared the experimental J values of several (cyclohexane) ring protons of compound **4** with their calculated counterparts, in which calculations were performed on compound **4** in the ${}^4\text{H}_3$ conformation. Both sets of values are in good agreement, which underscores the notion that compound **4**, and by extension also the other compounds subject of this Communication (whose ${}^1\text{H}$ NMR spectra give broadened signals due to the amide present—see SI) do indeed adopt the ${}^4\text{H}_3$ conformation in solution.

Structural dissection of the inhibitory action of **5**, and the conceptual link through to cyclophellitol **1**, was achieved first by rapid soaking (as opposed to preincubation as used previously to trap the covalent adduct⁵) of crystals of *TmGH1* with cyclophellitol derivative KY170^{7,8} (**6**). Serendipitously, this indeed afforded the unreacted cyclophellitol KY170 in ${}^4\text{H}_3$ conformation, with the nucleophile poised to attack, Figure 3B, confirming our hypothesis that (unreacted) cyclophellitols adopt a transition-state like ${}^4\text{H}_3$ conformation. In order to dissect similar mimicry by carba-cyclopropane **5**, and confirm the FEL calculated by *ab initio* metadynamics, *TmGH1* crystals were soaked with carba-cyclophellitol **5** and the subsequently obtained structure was analyzed and solved with X-ray crystallography. The obtained electron density pattern clearly demonstrates the presence of carba-cyclophellitol **5** in the active site in ${}^4\text{H}_3$ conformation (Figure 3C; the butyl azide moiety is mobile and differently disordered in the structure and not shown for clarity).

Overlay of cyclophellitol derivative KY170 with carba-cyclophellitol **5** (Figure 3D) shows almost perfect coincidence of atomic positions, showing that, as suggested by the FEL, **5** is a permanent mimic of cyclophellitol posted in the active site prior to nucleophilic attack.

The improved binding of **5**, relative to **3** and **4** presumably stems from desolvation caused by the alkyl-azido “tail” sitting in the aglycone site. One of the design advantages of the carba-cyclopropanes is that any pendent R groups are disposed pseudoaxial to the sugar ring, consistent with the distortions seen during catalysis which presumably adds to their augmentation of binding. The 3-D structure with **5** confirms this and shows a lateral, antitrajectory interaction of the catalytic amino acid Glu166 with the pseudoaxially disposed amide of **5**. There are four molecules of *TmGH1* in the crystallographically observed asymmetric unit. While they all show the R group axial, they all show different degrees of disorder of this alkyl region itself. In one molecule, there is essentially no electron density for the tail, while in two molecules the chain passes through the aglycon region (that is flanked by Val169, Trp168, and Trp324), making nonspecific interactions with this region. In the fourth molecule of the AU, the alkyl azido chain appears to follow two separate routes along each hydrophobic flank of the substrate binding cleft.

Bicyclic cyclopropyl glucosidase inhibitors, with the bridge between the “C6” and “O5” atoms, were first proposed by Tanaka and co-workers²¹ and later developed in *galacto* configuration by Bennet and co-workers and found to be good α -glucosidase and galactosidase inhibitors, respectively.²² More recently, activated forms of these compounds have been used as covalent inhibitors.²³ In these cases the conformational restriction limits the accessible conformations to “off-pathway” ${}^3\text{H}_2$ and ${}^2\text{H}_3$ half-chairs²³ (or perhaps their related 1,4 boats) recently elegantly revealed by X-ray crystallography.²⁴ Further, Stick and Stubbs²⁵ synthesized a bicyclic cyclopropyl inhibitor with the bridge between the “anomeric” C1 carbon position and the “C2” atom with a millimolar K_i value. The carba-cyclophellitol derivatives presented here offer, by virtue of the advantage of their conformational restriction between the “O5” and “anomeric” C1 carbon positions, a potent inhibitor in which the conformational restraint is a glycosidase reaction coordinate relevant ${}^4\text{H}_3$. Given the large number of glycosidase inhibitors in medical use, including those being developed as pharmacological chaperones and as diagnostic tools, the harnessing of appropriate conformation restraint, coupled to

correct stereochemistry, should add greatly to the enzymological, cellular, and, ultimately, therapeutic toolbox.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01773.

Primary NMR data files for 3–5, 8, 10–14 (ZIP)

Experimental procedures, Figures S1–S5 and Table S1, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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