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Cyclopropanecarboxylic Acid Esters as Potential Prodrugs with Enhanced Hydrolytic Stability

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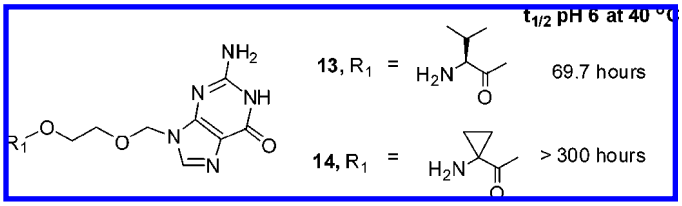
ABSTRACT



Esters of cyclopropanecarboxylic acid demonstrate a substantial increase in stability under both acid- and base-catalyzed hydrolytic conditions. Comparison of the stability of valacyclovir 13 with the cyclopropane analogue 14 shows that at 40 °C and pH 6 the half-life of 14 is >300 h while the value for 13 is 69.7 h. CBS-QB3 calculations on isodesmic reactions for transfer of groups from an alkane to an ester show that a cyclopropyl group provides hyperconjugative stabilization.

Prodrugs with ester functionalities have the significant potential to increase the oral availability of otherwise potent orally unavailable therapeutics.[1,2] For example, the antiviral agent valacyclovir (Valtrex) is the L-valine ester of the parent compound acyclovir. The ester has increased the oral bioavailability of this drug by 5-fold relative to acyclovir via recognition and active transport by the human peptide transporter hPepT1.[3] This type of prodrug strategy has also been employed with nucleosides, and there are currently 20 such drugs reported in the literature.[4,5] One such example is Hoe-961, which is an orally active acetate prodrug of a novel antiviral agent for the treatment of HSV.[6]

We have found that cyclopropanecarboxylic acid esters can be used as prodrugs that can provide increased stability in the acidic environment of the stomach and the alkaline conditions present in the intestine. Increased stability should result in better absorption of the intact prodrug into the plasma. The cyclopropyl group has unique conjugating properties that make it similar to a carbon−carbon double bond in its interaction with adjacent π-electron systems.[7] This

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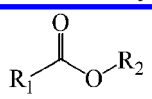
can provide increased stability to hydrolytic conditions without the disadvantages of benzoate esters.[2b] While the hydrolysis and transport properties of cyclopropyl esters of β adrenergic receptor blockers have been reported, the utility of these compounds as prodrugs is based on the higher permeability of the esters as compared to the parent molecules.[8]

We have found that esters of cyclopropanecarboxylic acid demonstrate a substantial increase in stability under both acid- and base-catalyzed hydrolytic conditions relative to related esters. The increase in the stability of some cyclopropanecarboxylic acid esters under the physiological conditions were reported earlier by Bodor.[9] Table 1 shows the

Table 1. Half-lives for the Hydrolysis of Esters



a, $R_2 = CH_2Ph$
b, $R_2 = CH_3$

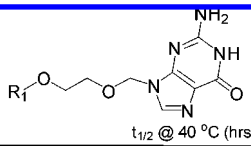
$t_{1/2}$ @ 40 °C (hrs)

ester	R_1	0.1 N HCl	pH 10
1a		180.2	78.7
2a	CH_3	14.2	8.7
3a	i-Pr	32.1	40.0
4a		14.1	16.0
5a		26.3	43.1
6a		52.4	87.0
7a	Ph	>300	55.4
8a	t-Bu	125.7	142.4
9a	$PhCH_2$	36.1	12.0
10a		267.5	192.0
11a		>300	43.1
12a		>300	7.8

half-lives determined here for benzyl cyclopropanecarboxylate esters **1a**, **10a**, and **11a** in 0.1 N HCl and pH 10 buffers at 40 °C compared to several other related esters. Benzyl cyclopropanecarboxylate **1a** is substantially (six times) more stable than the open-chain isopropyl analogue **3a** in 0.1 N HCl at 40 °C ($t_{1/2}$ = 180.2 h vs 32.1 h) and almost twice as stable in pH 10 buffer ($t_{1/2}$ = 78.7 h vs 40.0 h). This cyclopropanecarboxylic acid ester is similarly more stable than cyclopentanecarboxylic acid ester, **5a**. The contrast is even greater for the cyclobutane analogue **4a**, where the $t_{1/2}$ is only 14.1 h in 0.1 N HCl and 16.0 h in pH 10 buffer. While the benzoate ester **7a** is less stable in pH 10 buffer than the cyclopropanecarboxylic acid ester **1a** ($t_{1/2}$ = 55.4 h vs 78.7 h, respectively), it is more stable in 0.1 N HCl. The cyclohexanecarboxylate ester **6a** is slightly more stable than **1a** in pH 10 buffer (87 h vs 78.7 h). Comparing the more sterically hindered pivalic acid ester **8a**, with 1-methylcyclopropanecarboxylic acid benzyl ester **10a**, the cyclopropane ester is more than twice as stable in acid ($t_{1/2}$ = 267.5 h vs 125.7 h) and 1.3 times more stable in pH 10 buffer. This trend holds for amino acid derivatives **11a** vs **12a** as well. Both amino acids are stable under acidic conditions, but the cyclopropane analog **11a** is almost six times more stable ($t_{1/2}$ = 7.8 h vs 43.1 h) in pH 10 buffer.

The advantage of the increased stability of cyclopropane derivatives of amino acid esters under hydrolytic conditions for the design of a suitable prodrug is highlighted by comparing the stability of valacyclovir **13** with the cyclopropane analog **14** (Table 2). At 40 °C, the half-life of the

Table 2. Hydrolysis Rates of **13** and Cyclopropane Derivative **14**



$t_{1/2}$ @ 40 °C (hrs)

ester	R_1	0.1 N HCl	pH 2	pH 4	pH 6	pH 8	pH 10
13		>300	>300	>300	69.7	7.8	6.8
14		>300	>300	>300	>300	90.1	23.8

cyclopropane amino acid ester at pH 6 is >300 h while the value for valacyclovir is 69.7 h. This trend holds at pH 8 and pH 10 as well. The enhancement in chemical stability is very important in terms of drug development potential. Anand and co-workers[10] note that acyclovir would be a suitable drug for the treatment of herpes simplex keratitis, the leading cause of blindness in the United States,[10] but the corneal permeability is very low. Valacyclovir has much better permeability, but the half-life in aqueous buffer is unsatisfactory for an ophthalmic solution. This issue could be overcome with the cyclopropane prodrug **14**, where the half-life in pH 6 buffer at 5 °C is 352 days.[11]

We hypothesize that hyperconjugative stabilization of cyclopropanecarboxylic acid esters is responsible for the increased hydrolytic stability of these esters. In order to quantitate the stabilization of cyclopropanecarboxylic acid esters compared to other esters, the isodesmic reactions shown in Table 3 were computed at the CBS-QB3 level. Cyclopropanecarboxylic acid esters are stabilized by about

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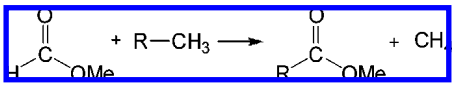
(11) Extrapolated from the Arrhenius plot; see the Supporting Information.

Table 3. Energies of Stabilization upon Replacement of H by R and Relative Energies of the *gem*-Diol Intermediates with Respect to Reactants and a Water Molecule



R	Δ*H*(CBS-QB3)	Δ*H*(B3LYP)	Δ*H*(B3LYP-*gem*-diol)
cyclopropyl	−12.6	−11.6	13.8
methyl	−10.2	−9.2	11.1
isopropyl	−9.2	−7.5	11.1
cyclobutyl	−10.1	−8.9	10.2
cyclopentyl	−10.4	−8.8	10.7
cyclohexyl	−10.0	−8.2	10.9
phenyl	−10.9	−9.4	14.3

2 kcal/mol more than other alkyl esters; this must arise by hyperconjugative donation from the cyclopropane group into the π^*_{CO} orbital. This is interrupted in the tetrahedral intermediate formed in the acid- and base-promoted hydrolysis reactions. This is consistent with the calculations on conjugation in cyclopropanecarboxylic acid ester derivatives.[7b] Stabilization has been attributed to the electrostatic stabilization of the carbonyl bond by the cyclopropyl group as well.[7c]

The activation free energies for base-promoted hydrolysis of cyclic esters **1b** and **4b**−**7b** were investigated with a combination of QM/MM/MC free energy perturbation (FEP) calculations and B3LYP/6-31+G(d) calculations.[12] Transition states (TS) TS1 and TS2 (Figure 1) were located with the

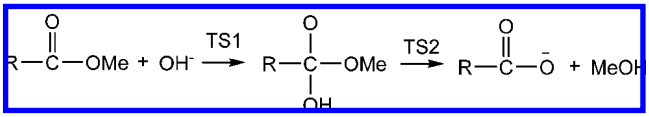


Figure 1. Schematic diagram of the competing reaction pathways.

FEP calculations in a box of 750 TIP4P water molecules from which one water molecule was removed for each heavy atom in the solutes to make space for the solutes. The QM region was described with the semiempirical PDDG/PM3 method, and the reaction coordinate was explored with 0.02 Å increments starting from 5 Å separated reactants. The configurational space of the TIP4P water molecules was explored with a MC sampling where equilibration runs of 2.5 M configurations were followed by production runs of 4 M configurations.[12]

These TSs were re-optimized at the B3LYP/6-31+G(d) level with CPCM solvation corrections by constraining the TS distances to those obtained from FEP calculations. These B3LYP/6-31+G(d) free energies are given in Table 4. The

Table 4. Activation Free Energies for Reactions of **1b** and **4b**−**7b**

substrate	TS1-B3LYP	intermediate	TS2-B3LYP
1b	24.0	19.0	27.2
4b	23.1	17.6	23.2
5b	24.2	18.8	24.9
6b	24.7	19.4	24.6
7b	21.3	16.0	23.9

root-mean-square error between B3LYP/6-31+G(d) computed activation free energies for substrates **1b** and **4b**−**7b** and experimental activation free energies for substrates **1a** and **4a**−**7a** was 0.8 kcal/mol. Substrate **1b** is the most stable substrate, which is also consistent with the result of the isodesmic reactions. Since the increase in the activation free energy for substrates **1b** and **4b**−**7b** does not correlate with the size of the substituents, steric effects are not expected to be responsible for the slow hydrolysis of **1b**. The stability of ester **1b** results from the larger activation free energy for the base-promoted hydrolysis, since the TS lacks the hyperconjugative stabilization. This same principle applies to the acid-catalyzed hydrolysis.

In summary, the significant stability of cyclopropane esters can be attributed to a hyperconjugative stabilization particular to this group. The utility of the stabilization is currently being studied in the design of prodrug esters that can be beneficial for delivering active drugs in man.

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Supporting Information Available: Experimental procedures for compounds, descriptions of computational methods, and coordinates of computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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