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4-Substituted carbamazepine derivatives: Conformational analysis and sodium channel-blocking properties

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ABSTRACT

The physicochemical properties of 4-substituted carbamazepine derivatives were investigated. It was elucidated that the 4-substitution is not effective in reducing the rotations (*E*/*Z*) about the N—C1′ axes around the outer carbamoyl moiety. However, the atropisomers were isolated with high stereochemical stability, meaning that the 4-substitution reduced the butterfly motion of the tricyclic ring system efficiently. The Cl/CH_3-substituted carbamazepine derivatives showed greater inhibitory effects on hNa_v1.2 channel currents compared with carbamazepine, although no difference in the activity between enantiomers was observed.

1. Introduction

Carbamazepine, a sodium channel inhibitor, has been used for the treatment of epilepsy and trigeminal neuralgia.[1] In the course of our research on axial chirality and its relationship to biological activities,[2] we became interested in the stereochemical properties of the tricyclic ring system of carbamazepine.

We anticipated that carbamazepine might adopt chirality, which is closely related to the *E*/*Z*-amide rotation about the N5—C1′ axis (Fig. 1).[3] However, analysis using chiral HPLC revealed that carbamazepine exists as an achiral compound at room temperature (rt) due to the rotation of the N5—C1′ axis. Since the carbamoyl group itself is insufficient to induce chirality in carbamazepine, we planned to introduce a substituent to the tricyclic ring system in anticipation of hindrance to the rotation of the axes. We describe here the synthesis of the 4-substituted carbamazepine derivatives and their physicochemical properties in detail. We also evaluated them as sodium channel inhibitors.

2. Results and discussion

First, various 4-substituted iminostilbenes (**1a**[4], **1b**[5], **1c**[6], **1d**[4]) were synthesized following the conventional synthetic route. Carbamoylation of **1a**—**d** using chlorosulfonylisocyanate in dichloromethane at rt provided the corresponding urea derivatives (**2a**—**d**) in 28–91% yield (Scheme 1). The 4-methoxy-substituted compound **2d** was further treated with BCl_3 to afford 4-hydroxy compound **2e** in 80% yield.

As shown in Fig. 2, the urea compounds **2a**—**e** theoretically have *E*/*Z*-amide isomers around the N5—(C1′=O) bond, in addition to atropisomers (A/B) based on the coordinated rotation of four sp^2—sp^2 axes (axis 1—axis 4). Therefore, four stereoisomers (conformers) may exist in the molecules. In this paper, we denote the absolute stereochemistry of compound 2 as M/P (chiral helical nomenclature).[7]

The conformations of **2a**—**e** were examined using VT-NMR. As a clear example, the spectrum of 4-chloro derivative **2b** is shown in Fig. 3. At +23 °C, only one set of broad signals was observed. However, as the temperature decreased, the peaks gradually changed into two broad sets of diastereomers.

Further decreases in temperature caused each peak to divide further so that four sets of diastereomers were observed at −90 °C. For example, the broad singlet peak observed around 4.3 ppm at +23 °C, which is consistent with NH_2 protons, was first divided into two broad peaks at −10 °C, and then, through broadening and downfield shifting, each peak was further divided into two peaks at −90 °C. It was interesting that two sets of resonances in a 3: 1 ratio were observed at each.

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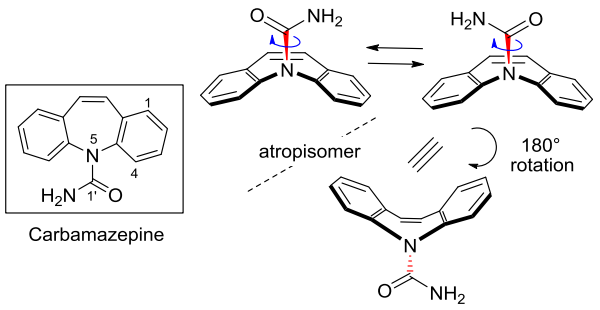
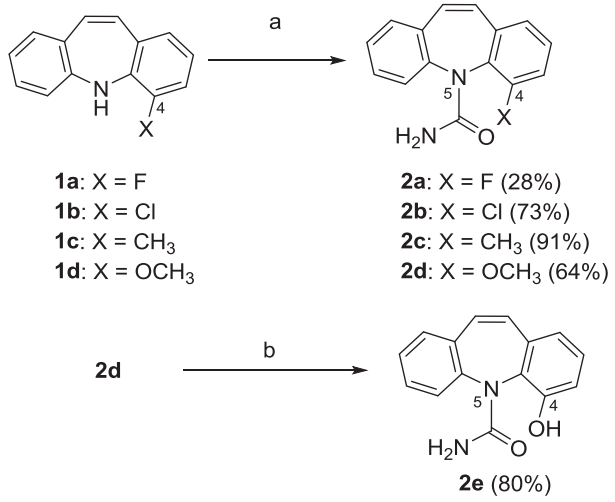


Fig. 1. Atropisomers of carbamazepine.



Scheme 1. Synthesis of 4-substituted 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (a) chlorosulfonylisocyanate, CH_2Cl_2, rt, (b) BCl_3, CH_2Cl_2, −78 °C–0 °C.

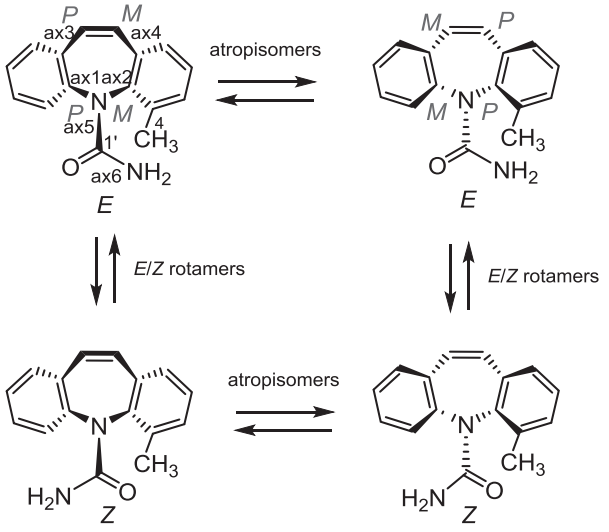


Fig. 2. Stereoisomers of 4-substituted carbamazepine.

We therefore assumed that the splitting is caused by the rotations of two N—C1′ axes (axis 5 and axis 6) of the urea moiety (Fig. 4).

At −90 °C, the rotation of both axes (axis 5 and axis 6) was restricted, and each proton in NH_2 should be diastereotopic. We assumed that the two peaks (6.4 ppm, 6.2 ppm) in a 3: 1 ratio should be Ha of the *E*-conformation and Ha of the *Z*-conformation, respectively. Such a downfield shift in Ha should be caused by a deshielding effect of the carbonyl group of urea. In contrast, we assumed that the two other peaks (4.4 ppm, 4.2 ppm) in a 3: 1 ratio should be Hb of the *E*-conformation and Hb of the *Z*-conformation, respectively. As the temperature increased, diastereotopic NH_2 protons gradually disappeared due to the rotation of axis 6, and thus only *E*/*Z*-conformations caused by the restriction of the rotation of axis 5 were observed as two set of resonances at −10 °C. For the assignment of the *E*/*Z*-conformations, the downfield shift of H6 at the tricyclic system caused by the carbonyl of urea in the *E*-conformation was considered, and the major conformation was determined to be the *E*-conformation. Similarly, VT-NMR of 4-fluoro derivative **2a**, 4-methyl derivative **2c**, and 4-hydroxy derivative **2e** exhibited the presence of the four conformational isomers (*E*/*Z*-amide conformers and the N—H urea conformers) at −90 °C (see the Supporting Information). It should be noted that the *E*-amide-enriched (*E*/*Z* = 1.5 ~ 5: 1) diastereomixture was observed in **2a**, **2b**, **2e**. Strangely, *E*/*Z*-amide conformers were not observed in 4-methoxy derivative **2d** irrespective of the temperature (−90 °C to +100 °C). We presumed that rotation of O—CH_3 single bond might be less effective to reduce the rotation of axis 5.

The activation free energy barrier to the rotation of axis 5 and axis 6 ($\Delta G^{\ddagger}$) was estimated by VT-NMR based on the coalescence method[8] (Table 1, see the Supporting Information).

It was revealed that the activation free energy barrier to the rotation of axis 5 is higher than that of axis 6. At any rate, these low energy barriers of less than 100 kJ/mol elucidate that 4-substituted carbamazepine derivatives should exist as conformational mixtures derived from axes 5 and 6 at rt.

We further attempted to separate the atropisomers of **2a**—**2e**, and each atropisomer was successfully isolated using preparative chiral HPLC. Due to the bulkier substitution at the 4-position, the butterfly motion of the tricyclic ring was reduced so that the stereochemical stability shown by the $\Delta G^{\ddagger}$ values[9] of **2b**—**e** was high (**2b**: 126 kJ/mol, **2c**: 130 kJ/mol, **2d**: 107 kJ/mol, **2e**: 112 kJ/mol). In contrast, the $\Delta G^{\ddagger}$ value of **2a** was 97 kJ/mol since the fluoride substitution is less bulky (Table 2).

Next, we synthesized the *N*,*N*-dialkyl 4-chloro-5*H*-dibenz[*b*,*f*]azepine-5-carboxamides **3a**—**c**, as shown in Scheme 2. We anticipated that the bulkier substitution of the urea moiety would provide more stable atropisomers.

The atropisomers of *N*,*N*-dialkylated compounds **3a**—**c** were isolated using preparative chiral HPLC. The stereochemical stability shown by the $\Delta G^{\ddagger}$ values was lower than expected (**3a**: 96 kJ/mol, **3b**: 100 kJ/mol, **3c**: 113 kJ/mol). Considering that the stereochemical stability with a $\Delta G^{\ddagger}$ value of 126 kJ/mol was observed for the corresponding carbamoyl compound **2b**, their lower stability seemed strange. We presumed that the rise in the ground state energy due to the bulkier urea substituents is responsible for lowering the barriers to the rotation of axes 1–4.[10]

Finally, we evaluated the inhibitory effects on $hNa_v1.2$ channel currents of **2b** and **2c** using an automated patch-clamp system (Fig. 5a, b). **2b** and **2c** in the racemic forms showed more potent inhibition of the sodium channel compared with carbamazepine. However, there was no significant difference between each atropisomer of **2b** and **2c**. This result means that the atropisomeric property in the carbamazepine derivatives **2b** and **2c** plays a less important role in the inhibition of $hNa_v1.2$ channel currents. However, it should be noted that the substitution at the 4-position of carbamazepine provided increased inhibitory activity on $hNa_v1.2$ channel currents.

3. Conclusions

4-Substituted carbamazepine derivatives were synthesized and their conformational properties were investigated. It was revealed