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Investigation of the barrier to the rotation of carbamate and amide C–N bonds in antidepressant (6a*R**,11b*S**)-7-[carbobenzyloxy-L-alanyl]-2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,2,12a(*S*)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole by dynamic NMR and molecular mechanics☆

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Abstract—Two concurrent exchanges arising due to the restricted rotation around the carbamate C–N bond and amide C–N bond were observed in (6a*R**,11b*S**)-7-[carbobenzyloxy-L-alanyl]-2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,2,12a(*S*)-decahydropyrazino-[2′,1′:6,1]pyrido[3,4-*b*]indole by NMR spectroscopic experiments. A total of four low energy conformers were evaluated in the molecule, out of those, two were observed because of the restricted rotation of the amide C–N bond in $CDCl_3$ and two were observed due to restricted carbamate C–N bond rotation in DMSO-d_6 and $(CD_3)_2CO$. The barrier to the rotation ($\Delta G^{\ddagger}$) around carbamate C–N bond and amide C–N bond was determined using dynamic NMR calculations. Molecular mechanics calculations also provided evidence for the presence of four low energy conformers for the compound due to restricted amide rotation and carbamate C–N bond rotation, with the value of barriers ($\Delta G^{\ddagger}$) between them of the order of 15.0 kcal/mol, which is in agreement with the dynamic NMR results. Since the molecule has shown potent antidepressant activity, it is proposed that these dynamic properties could influence the activity profile of these classes of molecules.

1. Introduction

In recent years, the kinetics and thermodynamics of the stereodynamic processes occurring due to restricted intramolecular rotation have been extensively explored using dynamic NMR studies.[1] The phenomenon of hindered rotation about carbamate[2] and amide[3] C–N bonds has received much attention as rotational changes play significant role in conformational stereochemistry of a compound, which could influence the activity profile. From the previously reported experimental data, it has been observed that carbamate C–N bond and amide C–N bond have nearly equal barriers to the rotation ($\Delta G^{\ddagger}$).[4] Previously Lectka and Cox demonstrated[4] the effect of various solvents on $\Delta G^{\ddagger}$ of the carbamate and amide C–N bonds, where the rotational barrier of the carbamate C–N bond was found to have least sensitivity toward the solvent polarity. Contrary to that of carbamates, $\Delta G^{\ddagger}$ of the amide C–N bond was considerably increased upon changing the polarity of solvents.[4] Moreover, the lowering of the rotational barrier of carbamate C–N bond has also been reported,[5] which was attributed to the resonance effect exerted by an *N*-substituted aryl ring. This evidence indicated that the barrier to rotation of the carbamate and amide C–N bonds might depend upon some of the other analogous factors, which still remained unexplored. Although much of the work carried out so far specifically deals with the study of solvent effects on $\Delta G^{\ddagger}$ of a molecule containing either the carbamate functionality or amide functionality, there has been no report in the literature regarding the effect on $\Delta G^{\ddagger}$ of either of the functional groups when both of them existed in the same system.

In our ongoing process of synthesizing derivative of CNS active nucleus decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]-indole, we synthesized a potential antidepressant molecule (6a*R**,11b*S**)-7-[carbobenzyloxy-L-alanyl]-2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,12,12a(*S*)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**4**). During the process of characterization of this molecule the ^{1}H NMR spectrum

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revealed few broad resonances at room temperature, indicating the effect of barrier to the rotation of the carbamate and or amide C–N bond, which led us to the current study. In the present communication, we herein describe the investigation of the barrier to the rotation of carbamate and amide C–N bonds when both are present in a single system. Further calculations of the activation parameters involved in this dynamic exchange process were also determined in two different solvents by two-dimensional exchange spectroscopy and molecular mechanics.

2. Results and discussion

2.1. Synthesis

We synthesized a new analogue of CNS active drug centbutindole,[6] (6a*R**,11b*S**)-7-[carbobenzyloxy-L-alanyl]-2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,12,12a(*S*)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**4**), which has both carbamate and amide functional groups. The selection of this molecule was based upon the unique semi-rigid conformation of the pyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole nucleus (**1**) that does not acquire any dynamic behavior and also possesses CNS depressant,[7] antihistaminic,[8] hypotensive,[6] phosphodiesterase inhibitory,[9] and neoplasm inhibitory activities.[10]

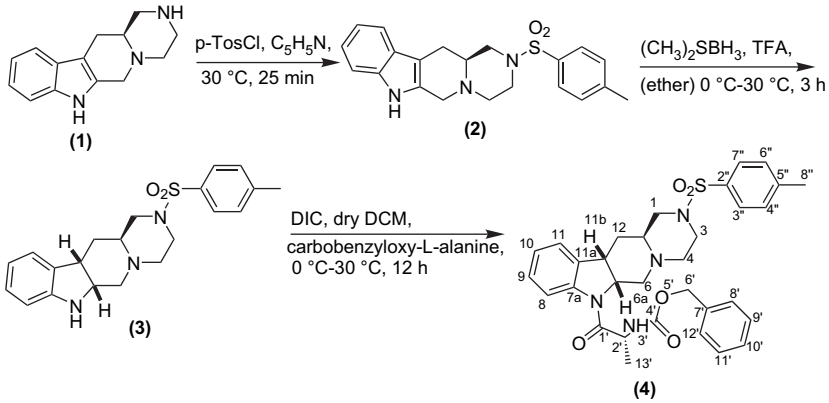
The synthetic methodology commenced with the synthesis of 2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,7,12,12a(*S*)-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*] indole (**2**) from the tosylation of the previously reported 1,2,3,4,6,7,12,12a(*S*)-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole molecule[6] (**1**) using tosyl chloride in pyridine. This was followed by the reduction of indole double bond using boranedimethylsulfide complex[11] in the presence of TFA at 0 °C. The reaction was completed in 3 h providing 2-[(4-methylphenyl)-sulfonyl]-1,2,3,4,6,6a,7,11b,12,12a(*S*)-decahydropyrazino-[2′,1′:6,1]pyrido[3,4-*b*]indole (**3**) with a high degree of purity and yield. Finally, compound **4** was prepared by the amidation of **3**, treating it with carbobenzyloxy-L-alanine in the presence of coupling agent DIC in dichloromethane. The overall yield of compound **4** achieved after three steps of reaction was 47% (Scheme 1).

Once the synthesis of the final compound (**4**) was achieved, the complete structure elucidation was carried out using various one- and two-dimensional NMR experiments. The unequivocal assignments of **4** were performed by the combined use of ^{1}H, ^{13}C, DEPT, COSY, edited HSQC, HMBC, and NOESY NMR spectra recorded in three solvents, in $CDCl_3$ at 248 K and in $(CD_3)_2CO$ and DMSO-d_6 solution at 298 K.

2.2. Exchange phenomenon in $CDCl_3$ solution

The ^{1}H NMR spectrum of **4** recorded at 298 K in $CDCl_3$ solution showed pronounced line broadening of all the resonances, revealing the expected dynamic exchange process in the system. Hindered rotation around the amide C–N bond was indicated by the signal of the H-8 proton, which appeared distinctly as a broad resonance at 7.8 ppm in ^{1}H NMR spectrum recorded in $CDCl_3$ solution at 298 K, and further emerged as an *ortho*-coupled doublet resonating at 8.0 ppm on decreasing the temperature to 248 K (Fig. 1a). The HSQC spectrum recorded at 248 K allowed observation of cross peaks owing to two rotamers and the exact ratio of population of rotamers was found to be 4:1 by taking the integral values of the partially resolved signals.

Moreover, the 2D exchange spectrum recorded at 248 K showed fully resolved exchange cross peaks for H-8 proton (Fig. 1b) further reinstating the hindered rotation of amide C–N bond of the carbobenzyloxy-L-alanyl side chain in the molecule. The rotation around the carbamate C–N bond was found beyond the NMR time-scale in $CDCl_3$ solution as no exchange cross peak for the NH proton was observed at any temperature. Armed with these observations it was stated that in $CDCl_3$ solution at 298 K, the presence of two populations was clearly visible but can only be determined within NMR time-scale by restricting the rotation around amide C–N bond at a low temperature of 248 K. The magnitude of the downfield shift of the major H-8 proton and upfield shift of minor H-8 proton also indicated the conformation of the molecule as reported earlier by Nagarajan et al. in case of *N*-acylindolines.[12] Although the exact conformation of both the rotamers was not deduced at this point of time, it was presumed that at lower temperature (248 K), the CO group is preferentially oriented toward the phenyl ring (rotamer A) while at room temperature it was in its reverse orientation (rotamer B). These presumptions were further supported by the results obtained by theoretical studies using Maestro 7.0.113 suite of programs with MMFF's force field.



Scheme 1. Strategy for the synthesis of **4**.