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NMR studies of rotamers with multi-substituted amides

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Abstract. Rotamers existed in the multi-substituted amide play an important role in the chemical reactivity function. Diverse chemical reactivity of substrates which contain an amide group is significantly affected by their rotamers. In this paper, rotamers of amides were studied and confirmed by means of NMR spectra. It was found that the ratio of related rotamers of amides depend on the amides bulk. When the nitrogen atom is located in the ring rigid structure, the rotation of C-N bond is limited and it is difficult to produce rotational isomers. In addition, we also found that substituted groups in phenyl ring cannot affect the ratio of related rotamers.

Keyword: NMR, ^{1}H NMR, ^{13}C NMR, Rotamers, Amide.

1. Introduction

Rotamers, owing to the double-bond character of the amide C-N bond, play a key role in the regulation of actions of biologically active peptides and functional molecules that have amide skeletons [1-3]. Moreover, the chemical reactivity of substrates which contain an amide group is significantly influenced by these isomers [4-8]. In amide family, secondary and tertiary amide shown well-known rotamerism. The secondary amide bonds are assigned as *cis*-rotamers and these *cis*-amides are usually located near the functional site in a protein and thus play an important role in protein function [9-16]. The tertiary amide backbone architecture at proline in natural peptides and proteins renders them unable to stabilize putative folded structures by forming intramolecular hydrogen-bond networks.

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Furthermore, amide bonds in the tertiary backbone give rise to increase flexibility of molecule due to a low-energy barrier between *cis* and *trans* configurations [17-23]. If the rotation was hampered, the axial chirality from anilides was formed [24]. The effect of various N-alkyl side chain functionalities on this *cis−trans* equilibrium in peptoids has been studied (Fig. 1).

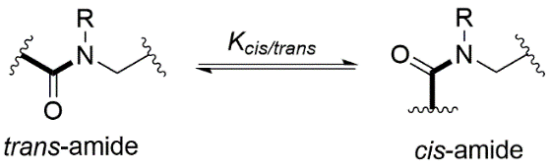

Fig. 1 *cis-trans* Equilibrium in amide.

Normally, the rotamers cannot be isolated because interconversion occurs easily at room temperature [25-29]. Therefore, spectrum studies of *cis−trans* isomerization has become the significant tool for years. For example, the structural influence on *cis−trans* amide bond isomerization is usually confirmed by means of NMR spectroscopy. In 2014, our group has synthesized a series of multi-substituted amides in the program of decarboxylative cross-coupling of *α, β*-unsaturated carboxylic acids with amides, and the amide rotamers also existed (Fig. 1) [30]. Considering their high value in synthetic chemistry, herein, we would like to discuss these rotamers by NMR spectra.

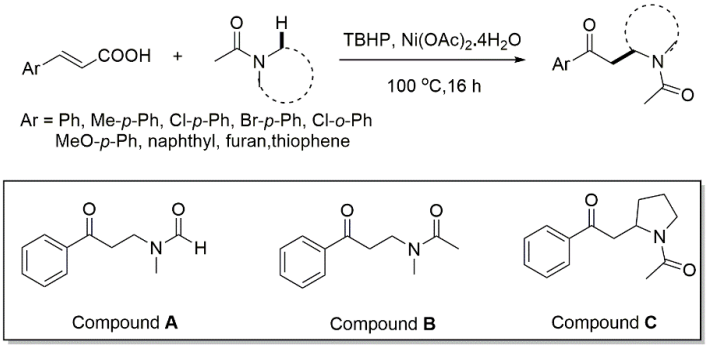

Fig. 2**.** Synthesis of multi-substituted amides.

2. Materials and methods

2.1 General experimental details

All solvents and chemicals were used directly from commercial sources without further purification. All of products were purified by ordinary silica gel column (200-300 mesh). Analytical Thin Layer Chromatography was carried out on precoated plates (silica gel 60), visualized with UV light. NMR spectra was performed on a Bruker DPX-400 spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). All spectra were recorded in $CDCl_3$ and the chemical

shifts (δ) are reported in ppm relative to tetramethylsilane referenced to the residual solvent peaks.

2.2 General procedures

To a mixture of cinnamic acid (0.148g, 1mmol), $Ni(OAc)_2 \cdot 4H_2O$ (25mg, 0.1mmol) and *N*,*N*-dimethylacetamide (2mL), *tert*-butyl hydroperoxide (0.39g, 3mmol, 70% in water) was added dropwise at room temperature. The resulting mixture was heated at 100℃ for 16 hours. After the reaction, the mixture was added in dichloromethane (40mL) and washed with water and saturated brine. The organic solution was dried by anhydrous magnesium sulfate. The product was separated on a silica gel column by using petroleum ether and ethyl acetate as eluent [30].

3. Results and Discussion

Firstly, we have chosen the simple and typical model, compound **A**, to more clearly discuss the structure of rotamers. Normally, we guessed that all of hydrogen protons of the compound **A** should only form single resonance signal. And the simulative spectrum using ChemDraw also shows single signal peak. However, in ^{1}H NMR spectrum of compound **A**, the N-methyl **a** and formyl **b** respectively gives two overlapping signals. The shifts of double signals of N-methyl **a** appear in 3.02 and 2.88ppm (Fig. 3), but no coupling was formed between the two signals. From integral area of the two signals, protons of *N*-methyl give two single peaks following integrated area ratio of 1:1. Similarly, formyl **b** also gave two signal peaks following integrated area ratio of 1:1 in 8.17 and 8.02ppm. Other hydrogen protons form single signal peak. However, distinct difference occurs in the ^{13}C NMR spectra of compound **A**, all of asymmetrical carbon atoms formed overlapping double signals (Fig. 4). This phenomenon suggests that the *cis* and *trans* configuration can affect the shifts of carbon atoms. Combined with relevant references, we tried to explain the unexpected results. From the Figure 3 and 4, the formation of double signal was due to that compound **A** generated rotamers. In addition, the p-π conjugation performed between amide carbonyl group and the nitrogen atom lone pair electrons. Thus, the C-N bond was similar to double bond and rotation was hindered to some extent. Meanwhile, there are some relatively stable *cis* and *trans* configurations in the product. That's to say, the product was a mixture of *cis* and *trans* configurations with different proportions. Therefore, methyl protons adjacent to the nitrogen atom and formyl protons appeared overlapping signals in the related NMR spectra. Similarly, all of carbon atoms in *cis* and *trans* configurations can change with the rotation of C-N.

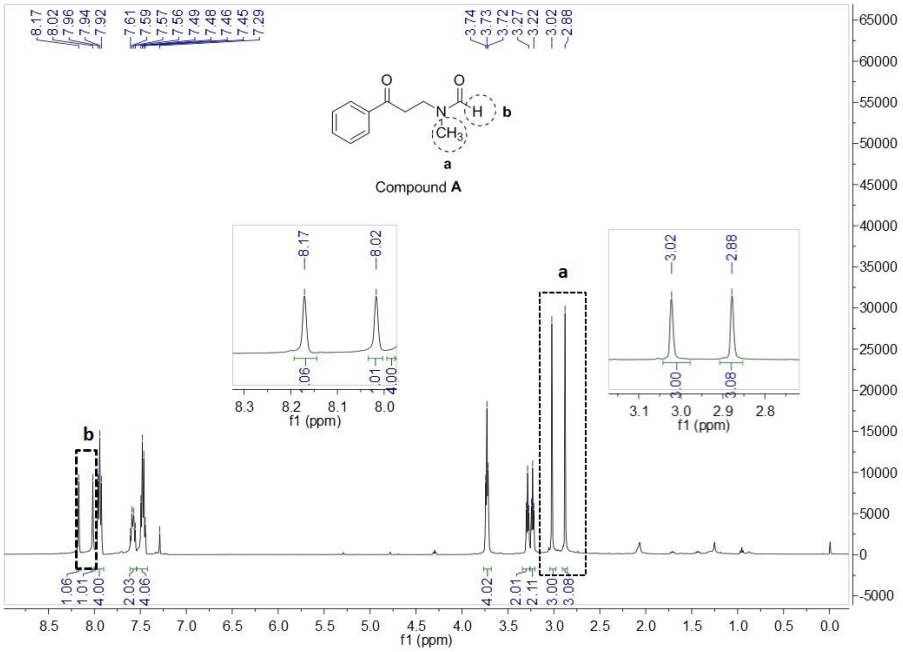

Fig. 3. ^{1}H NMR spectra of compound A at room temperature in $CDCl_3$.

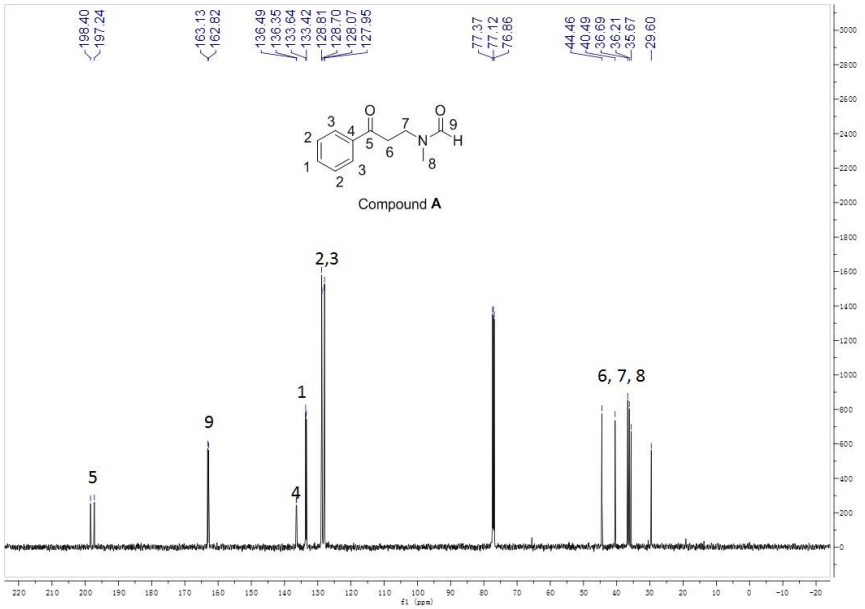

Fig. 4. ^{13}C NMR spectra of compound **A** at room temperature in $CDCl_3$.

To examine this universality of this rotamer, we chose other amide compounds from our decarboxylative cross-coupling reaction of *α, β*-unsaturated carboxylic acids with amides. Firstly, we changed the part of amide such as compound **B** and

C (Fig. 5 and Fig. 6). From the ^{1}H NMR spectra of compound **B**, methyl protons adjacent to the nitrogen atom and methyl protons adjacent to the carbonyl also respectively appeared overlapping double signal peaks following the ratio of related rotamers is 2:1. However, approximate single structure was acquired in this compound **C**, we believed that the cyclic rigid structure of amide hampers the rotation of C-N bond. Therefore, we speculated the rotamers of amides were affected by the structure of C-N bond in amides. And then, substituted groups in phenyl ring of the compound **B** were investigated (**B-L**), we found that the electron-rich and poor aromatic structure cannot affect the ratio of related rotamers of amides part, and the ratio keeps in 2:1, suggesting the equilibrium is stable at room temperature (Fig. 7).

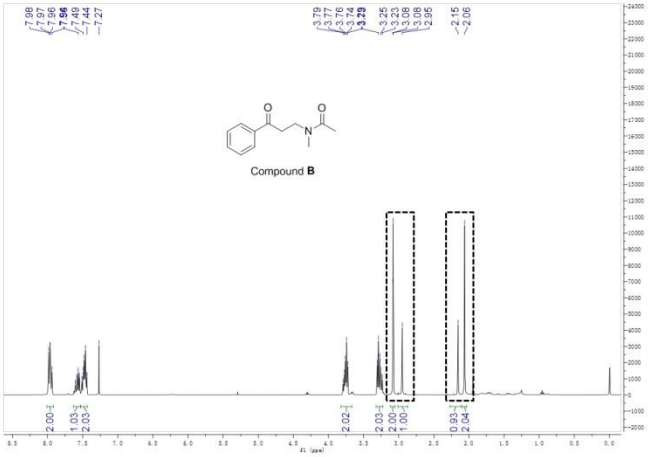

Fig. 5. ^{1}H NMR spectra of compound **B** at room temperature in $CDCl_3$.

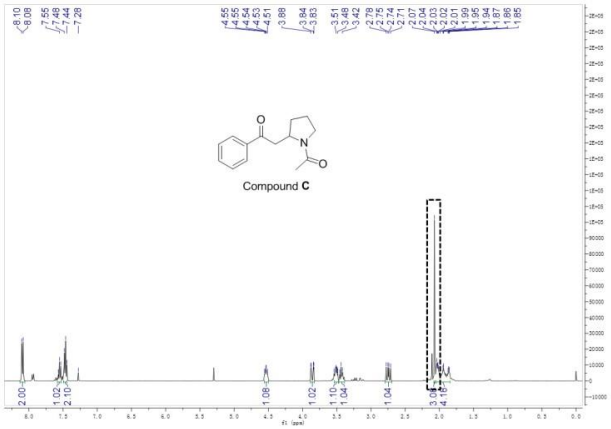

Fig. 6. ^{1}H NMR spectra of compound C at room temperature in $CDCl_3$.

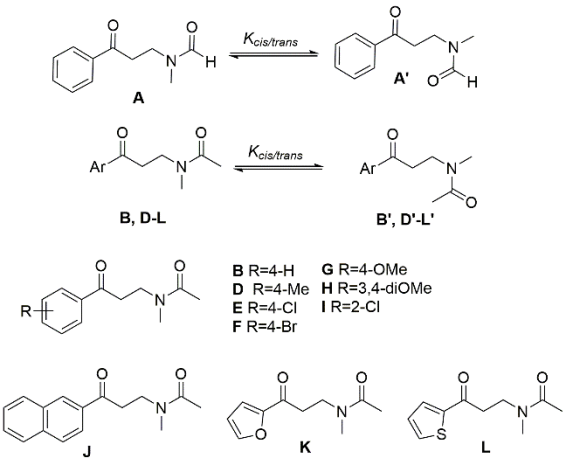

Fig. 7. The equilibrium of amides isomerization at room temperature.

4. Conclusion

In conclusion, we have found some rule about rotamers of amides from the program of decarboxylative cross-coupling of *α, β*-unsaturated carboxylic acids with amides. The rotamers ratio of product of *N,N*-dimethylformamide is 1:1， because that the obstacle was weak during the rotation of C-N bond. Following the substituent adjacent to the nitrogen atom became larger, the obstacle was stronger in the rotation of C-N bond, leading to the ratio of related rotamers increase to 2:1. When the nitrogen atom was located in the cyclic rigid structure, the rotation of C-N bond was restricted so that the rotamers was difficult to be generated. The substituted groups in phenyl ring including electron-rich and poor aromatic structure cannot affect the ratio of related rotamers of amides. The significant value of rotamers of amides stimulates chemists to deeply understand science of rotamers. Further research of relevant work will be expanded in our laboratory.

Conflict of interest

Authors declare no conflict of interest.

Supporting Information

Copies of spectra for all the compounds are provided. This material is available.

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