STUDIES ON ROTATIONAL STABILITY OF 2-ARYL-3-(2-FLUOROPHENYL)QUINAZOLIN-4-ONE DERIVATIVES

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Abstract – The rotational barriers around an N-(2-F)C₆H₄ bond in 2-aryl-3-(2-fluorophenyl)quinazolin-4-ones considerably lowered (ca. 4 kcal mol⁻¹ lower) in comparison with those of 2-alkyl-3-(2-fluorophenyl)quinazolin-4-ones. The transition state structure estimated by the DFT calculation indicates that the considerable decrease in the rotational barriers in 2-aryl derivatives is caused by the alleviation of the steric repulsion between an ortho-substituent of 2-fluorophenyl group and 2-aryl group.

Chiral compounds owing to the rotational restriction around an N-C bond have been attracting much attention in the fields of synthetic organic chemistry, structural organic chemistry and medicinal chemistry. Most of such N-C axially chiral compounds have ortho-substituted aniline skeletons, and the rotational stability depends on both the steric bulkiness of the ortho-substituent and the skeleton on a nitrogen side. For example, in anilide derivatives I, a bulky tert-butyl group as an ortho-substituent is required for a rotationally stable structure, while in 3-arylthiazoline-2-thiones II and 1-aryl-2-thiobarbituric acids III, ortho-methyl derivatives IIB and IIIB are also stable atropisomeric compounds (Figure 1). On the other hand, in IIC and IIIIC bearing ortho-fluorophenyl group, the rotation around an N-Ar bond easily occurs at ambient temperature (Figure 1). The steric size of fluorine atom would be too small to restrict the N-Ar bond rotation. Indeed, the rotationally stable N-C axially chiral compounds bearing an ortho-fluorophenyl group have been uncommon to date.
Quite recently, we found that 2-alkyl-3-(2-fluorophenyl)quinazolin-4-one derivatives 1a-c possess the rotational barriers more than 26 kcal mol$^{-1}$ and the enantiomers in 1a-c are isolable at ambient temperature (half-lives for the racemization in 1a-c at 298 K = 8.7-17 days, Figure 2). Furthermore, the rotational stability was also revealed to be not much influenced by the steric factor of C2-alkyl substituents. Although quinazolin-4-one derivatives bearing ortho-fluorophenyl group such as IV and V had already been reported by other groups, no the rotational stability of IV and V was explored (Figure 2). Since IV and V are pharmaceutically attractive compounds possessing anti-viral action and anti-tumor activity, respectively, the elucidation of their rotational stability should be important in terms of not only structural organic chemistry but also medicinal chemistry. Especially we have been curious on the rotational stability of quinazolinone V bearing C2-aryl group because the steric and electronic characters of an aryl group considerably differs from those of an alkyl group. In this paper, we report the rotational stability of 2-aryl-3-(2-fluorophenyl)quinazolin-4-one derivatives and the DFT study on the N-Ar bond rotation.

1. Preparation of quinazolinones and attempt of enantiomer separation

As simplified model compounds of V, we prepared 2-phenyl- and 2-(4-methoxyphenyl)-3-(2-fluorophenyl)quinazolin-4-one derivatives 2a and 2b in moderate yields in accordance with Scheme 1.
Subsequently, the enantiomer separation of 2a,b through the HPLC using a chiral AS-H column was attempted. Their HPLC charts are shown in Figure 3. In 2-phenyl derivative 2a, although two peaks corresponding to the enantiomers were detected, 2a recovered from the less polar and more polar peaks (fractions) were both racemates. The chart of para-methoxy derivative 2b showed elution profiles with a plateau between the peaks, suggesting the interconversion between the enantiomers. Thus, it was revealed that an N-Ar bond in 2-aryl derivatives 2a,b easily rotates at ambient temperature, and this result is sharply in contrast to 2-alkyl derivatives 1a-c with a stable atropisomeric structure.

Figure 3. HPLC charts of 2a and 2b using a chiral AS-H column (eluent: 15% i-PrOH in hexane)

2. Crystal structures

It has already been reported in other compounds that an aryl side chain is lowered the rotational barrier around a single bond in comparison with an alkyl side chain, but the origin was not theoretically well-supported. For the elucidation of the rotational instability in 2-aryl derivatives 2a,b, the X-ray crystal structural analyses of 2-methyl derivative 1a and 2-phenyl derivative 2a were performed (Figure 4). The values of the bond angles around N3 atom and the dihedral angles on the amide part in 2a were close to those in 1a. That is, in 2a, the pyramidalization of the nitrogen atom and the distortion around the amide bond, which would cause the decrease in the rotational barrier, were not detected.
bond angles around N3
\( \angle C4-N3-C1 = 117.0^\circ \)
\( \angle C4-N3-C2 = 122.5^\circ \)
\( \angle C2-N3-C1 = 120.6^\circ \)

dihedral angles
\( \angle O-C4-N3-C1' = 1.2^\circ \)
\( \angle O-C4-N3-C2 = 177.8^\circ \)
\( \angle C4a-C4-N3-C1 = 169.8^\circ \)
\( \angle C4a-C4-N3-C2 = -0.9^\circ \)

\( \angle C4-N3-C1' = 116.5^\circ \)
\( \angle C4-N3-C2 = 122.0^\circ \)
\( \angle C2-N3-C1' = 121.4^\circ \)
\( \angle O-C4-N3-C1 = 1.2^\circ \)
\( \angle O-C4-N3-C2 = 178.7^\circ \)
\( \angle C4a-C4-N3-C1' = 169.8^\circ \)
\( \angle C4a-C4-N3-C2 = -0.9^\circ \)

Figure 4. X-Ray crystal structures of 1a and 2a

3. DFT study

For the evaluation of the transition state structures as well as the barriers of N-Ar bond rotation in 2a,b, the DFT studies with 2-ethyl derivative 1b and 2-aryl derivatives 2a,b were performed. The rotational barrier (26.7 kcal mol\(^{-1}\)) of 1b, which was calculated under the B3LYP/6-31G(d,p)/CCl\(_4\)(PCM) level of theory, was very close to the value (26.5 kcal mol\(^{-1}\), Figure 2) evaluated by racemization experiment in CCl\(_4\) (Figure 5).

Meanwhile, the calculated rotational barrier (22.0 kcal mol\(^{-1}\)) in 2a was 4.7 kcal mol\(^{-1}\) lower than that in 1b. The barrier value of 2a shows that the enantiomer separation at ambient temperature is very difficult (half-life of the racemization in 2a at 298 K = \(t_{1/2} = 10.7\) min). The calculated rotational barrier (21.8 kcal mol\(^{-1}\)) and the half-life (\(t_{1/2}\) at 298 K = 7.1 min) in 2-(4-methoxyphenyl)quinazolinone 2b further
lowered in comparison with those of 2-phenyl derivative 2a. These results support the chiral HPLC experiment shown in Figure 3.

Furthermore, on the rotational pathway around the N-Ar bond, the DFT calculation indicates that path a (TS-1b, TS-2a, TS-2b) in which ortho-fluoro group passes through carbonyl group side and path b (TS-1b', TS-2a', TS-2b') in which ortho-fluoro group passes through 2-alkyl group side, possesses similar activation energies (ΔΔG‡ < 0.9 kcal mol⁻¹, Figure 5).

The significant decrease in the rotational barrier in 2-phenyl derivative 2a is rationally explained on the basis of the comparison of the transition state structures TS-1b and TS-2a (Figure 6). In both TS-1b and TS-2a, ortho-fluorophenyl group is located in the out-of-plane position of quinazolinone ring to alleviate the steric repulsion with C2-substituent and carbonyl oxygen. In addition, the planar C2-phenyl group in TS-2a can be orientated so as to alleviate the steric repulsion with ortho-hydrogen of fluorophenyl group, while in TS-1b, the alleviation of the steric repulsion would be difficult due to C2-ethyl (alkyl) group having a three-dimensional spread. As a result, the rotational barriers of 2-alkyl derivatives 1a-c are much higher than those of 2a,b bearing planar 2-aryl groups.

![Figure 6. Transition state structures during an N-Ar bond rotation in 1b and 2a evaluated by DFT calculation under the B3LYP/6-31G(d,p)/CCl₄(PCM) level of theory](image)

We found that the rotational barriers around an N-(2-F)C₆H₄ bond in 2-aryl-3-(2-fluorophenyl)quinazolin-4-ones considerably lowered (ca. 4 kcal mol⁻¹ lower) in comparison with those of 2-alkyl-3-(2-fluorophenyl)quinazolin-4-ones. It was also revealed that the rotational instability of 2-aryl derivatives is caused by the alleviation of the steric repulsion between an ortho-substituent of 2-fluorophenyl group and 2-aryl group through the evaluation of the transition state structures based on DFT calculation.

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SUPPLEMENTARY INFORMATION

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at URL:
https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26632/103/1

REFERENCES AND NOTES


9. CCDC 1897964 (1a) and CCDC 1898906 (2a) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif. In addition, the detailed X-ray crystal data of 1a was already published in the following paper. T. Imai, E. Niijima, S. Terada, A. Wzorek, V. A. Soloshonok, A. Hori, and O. Kitagawa, CrystEngComm., 2019, 21, 3385.


11. All calculations were performed by using Gaussian 09, Revision D.01. See Supporting Information for detail.