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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)C_6H_4 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.[1] 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,[2] 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).[3,4] On the other hand, in **IIC** and **IIIC** 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.

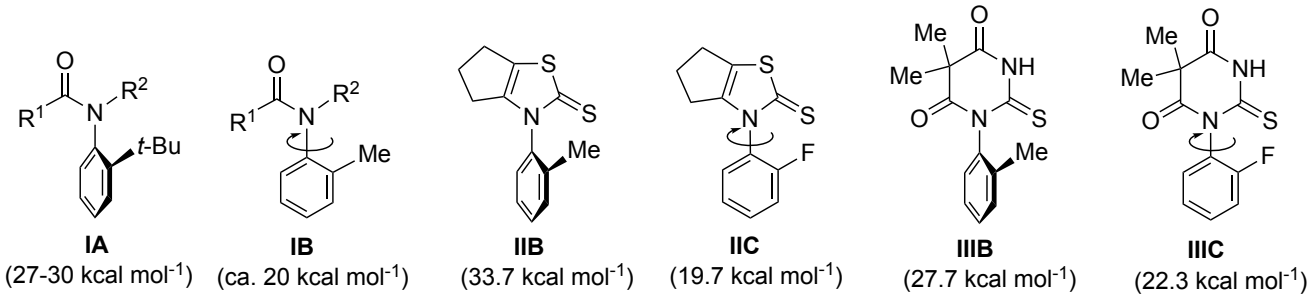
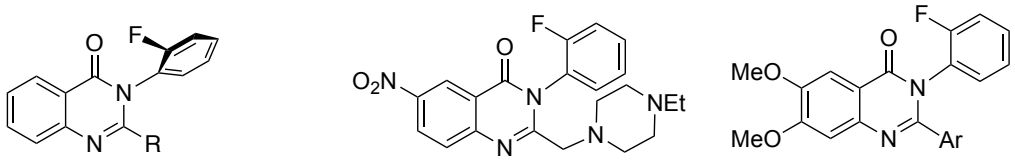


Figure 1. Several N-C axially chiral compounds and their rotational barriers

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).[5] 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).[6,7] 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.



	$\Delta G^{\ddagger}_{exp}$ at 298K	$t_{1/2}$ at 298K
1a (R = Me)	26.1 kcal mol^{-1}	8.7 days
1b (R = Et)	26.5 kcal mol^{-1}	17.0 days
1c (R = *i*-Pr)	26.2 kcal mol^{-1}	10.4 days

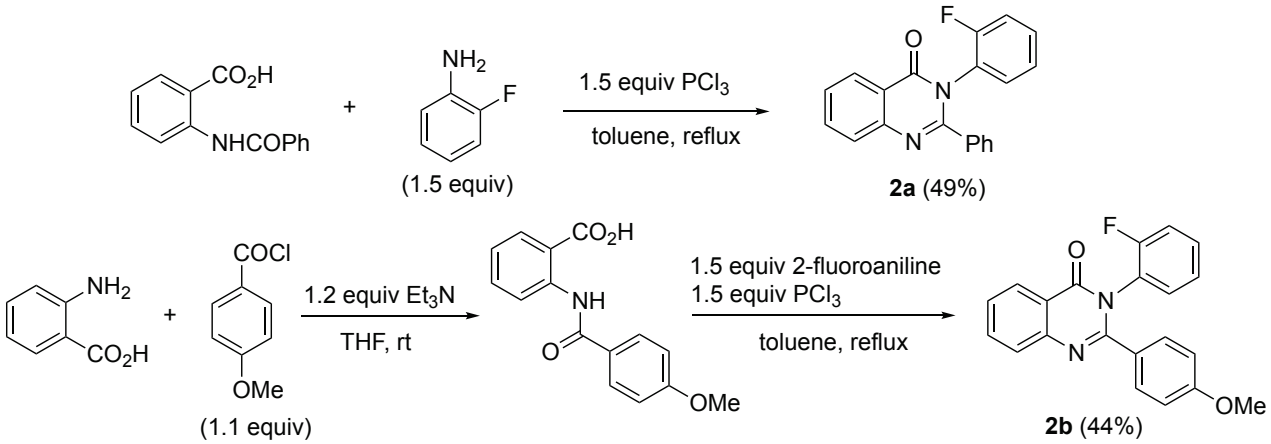
IV (anti-viral agent)
"rotationally stable?"

V (anti-tumor activity)
"rotationally stable?"

Figure 2. Quinazolin-4-one derivatives bearing *ortho*-fluorophenyl group

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.[8]



Scheme 1. Synthesis of 2-aryl-3-(2-fluorophenyl)quinazolin-4-ones **2a** and **2b**

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.

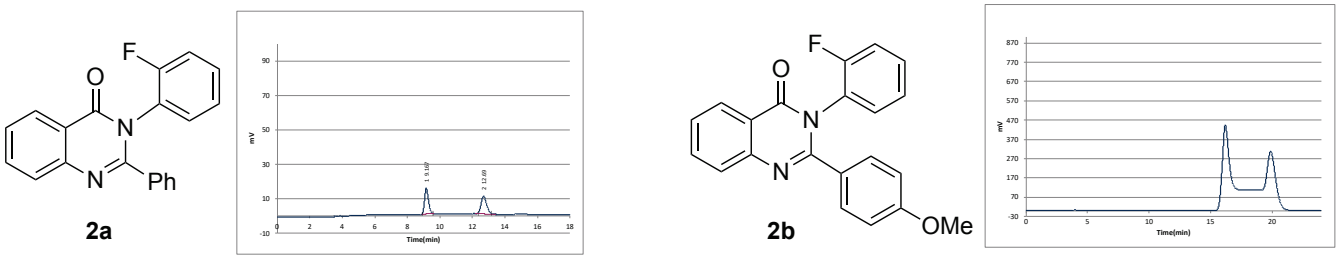


Figure 3. HPLC charts of **2a** and **2b** using a chiral AS-H column (eluent: 15% *i*-PrOH in hexane)

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.[3,9] 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).[10] 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.

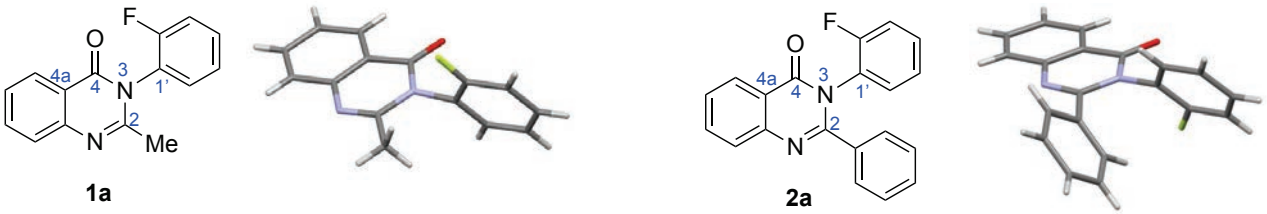


Figure 4. X-Ray crystal structures of **1a** and **2a**

3. DFT study[11]

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[12]/6-31G(d,p)/CCl_4(PCM)[13] 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).

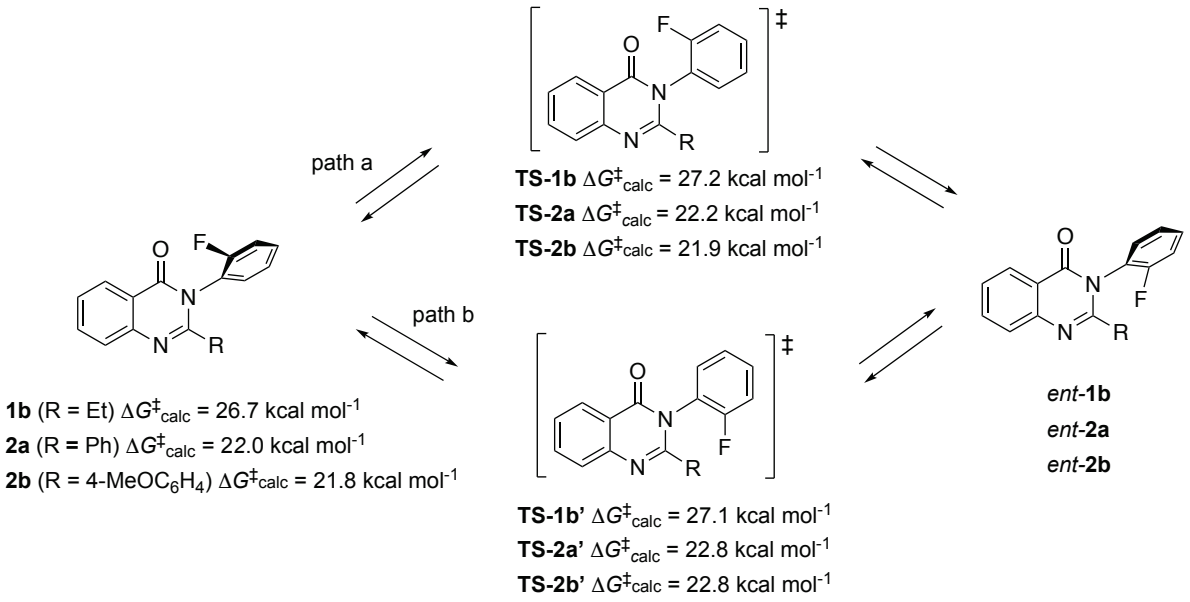


Figure 5. Barriers during an N-Ar bond rotation evaluated by DFT calculation under the B3LYP/6-31G(d,p)/CCl_4(PCM) level of theory

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 ($\Delta\Delta G^{\ddagger} < 0.9$ 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.

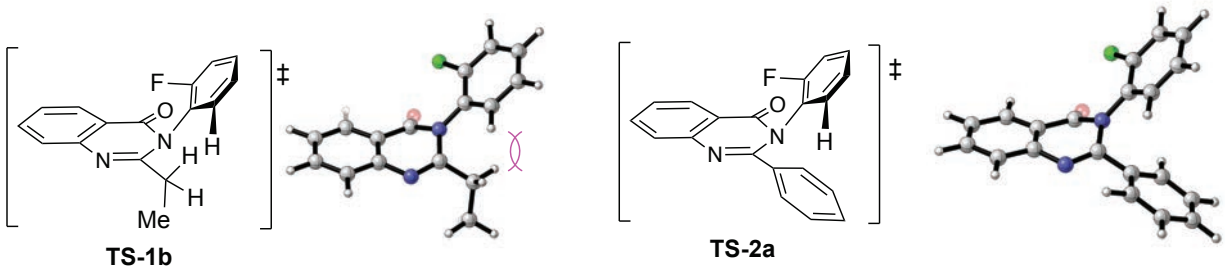


Figure 6. Transition state structures during an N-Ar bond rotation in **1b** and **2a** evaluated by DFT calculation under the B3LYP/6-31G(d,p)/CCl_4(PCM) level of theory

We found that the rotational barriers around an N-(2-F)C_6H_4 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.

ACKNOWLEDGEMENTS

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SUPPORTING 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

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