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Atropisomerism of Aromatic Carbamates

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Dedicated to Professor Horst Kessler on the occasion of his 70th birthday

Abstract: *ortho*-Haloarylcarbamates like **1**–**4** show a high rotational barrier about the N–aryl bond of up to 91.6 kJ mol^{-1} as found for **1**, which was determined by 2D exchange NMR spectroscopy (EXSY). It was further demonstrated that the height of the barrier not only depends on the substituents at the axis of chirality, but is also influenced by electronic effects.

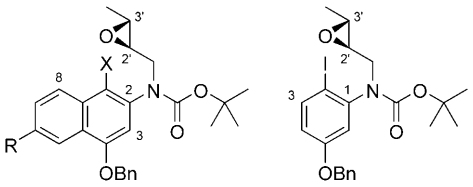
Keywords: atropisomerism · carbamates · EXSY spectroscopy · NMR spectroscopy · rotational barriers

Introduction

Atropisomerism is a well-known phenomenon of biaryls, sulfonamides, maleimides, succinimides, and simple carboxyamides.[1] The latter have been intensively studied not only in connection with their existence in peptides, but also as prochiral auxiliaries in so-called atropselective reactions.[2] Pioneering work in this field was done by Curran and DeMello, as well as Simpkins et al., who found that high enantioselectivities could be achieved with *ortho-tert*-butylanilides.[3] In addition, not only stable carbamate atropisomers have been reported,[4] but also asymmetric reactions of axially chiral carbamates.[5] Clayden et al. have shown that naphthalene-based amides have unusually high rotational barriers,[6] and the challenge of atropisomerism in drug discovery has recently been reviewed by this group.[7] With respect to the potential impact on medicinal chemistry, the stereoselective total synthesis of naturally occurring and biologically active atropo-(dia-)stereoisomers, such as that recently completed by Bringmann et al. for N,C-coupled naphthylisoquinolines, will become much more important in the discovery of lead structures.[8]

A clear requirement for high selectivities in atrop-selective reactions are high rotational barriers of >96 kJ mol^{-1} between the different atropisomers, which allow their separation and storage for many weeks at $<25\,^{\circ}C$ without racemization.[9] However, the different contributions to the rotational barriers have still not been sufficiently studied, although the bulkiness of the substituents at the axis of chirality is known to play a dominant role.[10] But there are also results indicating that electronic effects within the molecule are more important than has been anticipated so far.[11]

Herein, we report on the atropisomerism of *N*-(*ortho*-halonaphthyl)carbamates **1**–**3** and the related compound **4** using NMR spectroscopy, showing that the bulkiness of the halo atom as well as the steric demand of the aryl moiety, but also electronic effects of the aryl moiety have an important influence on the rotational barriers about the N–aryl bond in **1**–**4**. Details of synthetic procedures are given in the Supporting Information.



1: X = I, R = H
2: X = Br, R = H
3: X = Br, R = CN

Bn = benzyl

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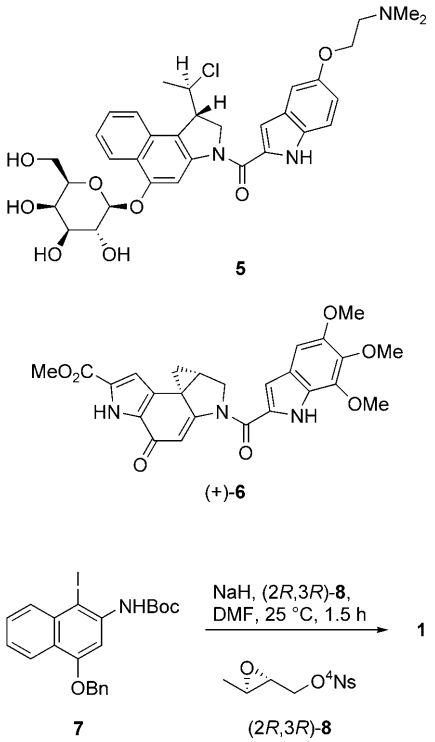
Results and Discussion

Within our work on the development of new selective anticancer agents, we prepared glycosidic prodrugs such as **5**,[12] which are based on the natural antibiotic duocarmycin SA ((+)-**6**).[13] In the asymmetric synthesis of these prodrugs,[14] the intermediate **1** was obtained through alkylation of aniline **7** with the enantiomerically pure nosylate **8**, containing an epoxy functionality, to give a mixture of two compounds in a ratio of about 1:1 (Scheme 1), which showed distinct NMR signals even at elevated temperatures up to 100 °C (Figure 1).



Scheme 1. Prodrug **5** and the natural antibiotic duocarmycin SA ((+)-**6** and the synthesis of **1** from naphthalene **7** using the enantiomerically pure epoxy nosylate (2*R*,3*R*)-**8**. Boc = *tert*-butyloxycarbonyl, Ns = nosyl.

The presence of multiple broad NMR signals of **1** at 25 °C could be explained by slow rotation around the carbamate N–C(O) bond resulting in carbamate *E* and *Z* isomers. For rotation around such bonds, energy barriers of 50–67 kJ mol^{-1} with little solvent dependence have been reported.[1b,15] At 100 °C, however, this rotation is sufficiently fast (about 10^4 s^{-1}) to completely average the NMR signals of the individual carbamate isomers.

The presence of different constitutional isomers of **1** could be excluded by synthetic experiments (Scheme 2; for details on the synthesis, see the Supporting Information), since single products without split NMR signals were obtained upon removal of the iodine atom of **1** to give **9** (along with a complex mixture of byproducts), or quantitative cyclization of **1** to oxazolidinone **10**. Moreover, the Zn-mediated transformation of **1** led to a single enantiomerically pure product **11**.[14]

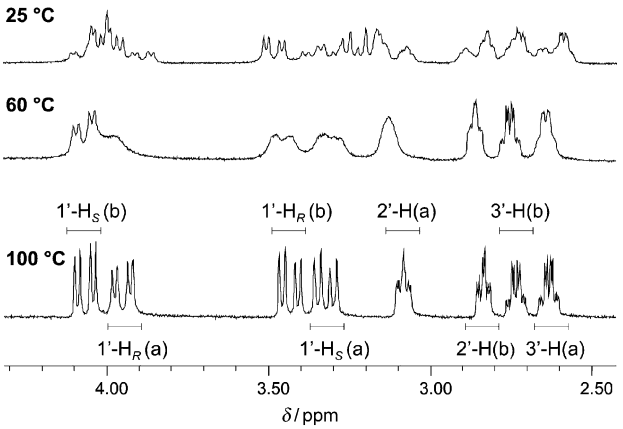
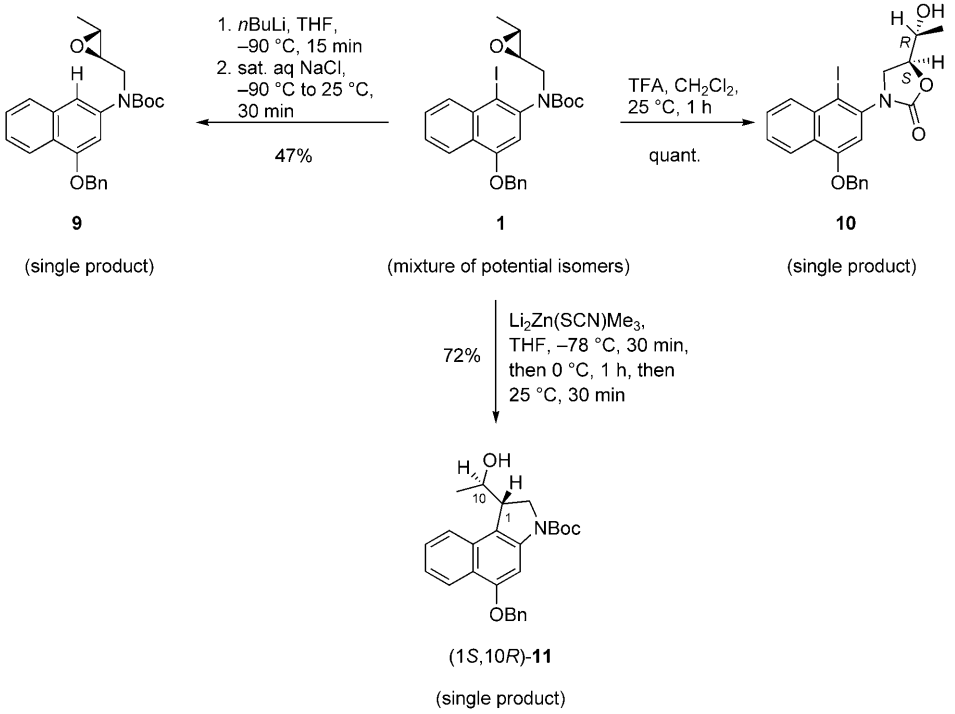


Figure 1. ^{1}H NMR spectra (300 MHz, $C_2D_2Cl_4$) of (2′*R*,3′*R*)-**1** at variable temperatures showing the 1′-, 2′- and 3′-protons of the epoxide side chain. The spectra indicate the existence of two distinct isomers (denoted (a) and (b)) of **1**.

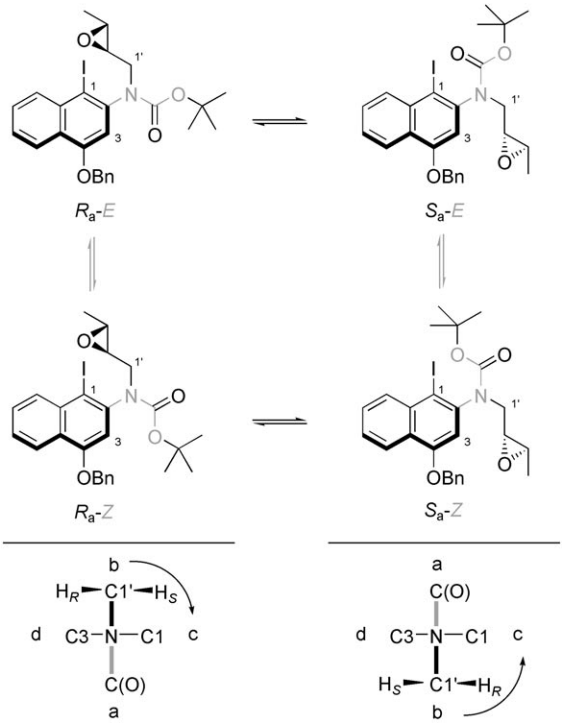
We therefore assume that at 100 °C **1** exists as a mixture of two diastereomers due to hindered rotation about the N–aryl bond, which can be attributed to the large iodine substituent in the *ortho* position. In accordance with earlier reports on related compounds, the naphthyl ring thus adopts an orientation perpendicular to the carbamate plane, and the N–aryl bond becomes an axis of chirality.[16] As a result of the hindered rotation about the N–aryl bond and the N–C(O) bond, **1** exists as four different isomers (depicted in Scheme 3) at room temperature.

The N–aryl rotation in **1** is so slow that no coalescence of NMR signals was observed up to 130 °C, at which temperature **1** started to decompose. However, 2D exchange spectroscopy (EXSY) revealed that the two rotamers do interconvert at much lower temperatures (Figure 2): The spectrum contains positive cross peaks (exchange peaks) connecting corresponding resonances of the two rotamers as well as negative cross peaks (NOE peaks) due to spatial proximity of protons within the individual rotamers.

Figure 2 shows that the NOE peaks within the C-1′ methylene group are particularly strong and very close to the corresponding exchange peaks, indicating that N–aryl bond rotation nearly swaps the chemical shifts of the two protons as a result of their position relative to the naphthyl ring. As evidenced by NOE correlations with 3-H (Figure S1 in the Supporting Information), the downfield 1′-H protons face C-3, which is in agreement with a shielding effect of the large iodine atom on the other 1′-H protons. Further NOE correlations between 3-H and 2′-H/3′-H suggest that the bond between C-1′ and C-2′ is preferentially oriented *syn* with respect to the N–aryl bond (as already indicated in the structures in Scheme 3), thereby tilting the epoxide side chain away from the bulky Boc group. If this is true, the absolute configuration of the two rotamers can be determined from the stronger NOE correlation between 3′-H and 3-H, which



Scheme 2. Experimental exclusion of constitutional isomers of **1**. TFA = Trifluoroacetic acid.



Scheme 3. R_a and S_a rotamers of the N–aryl bond of **1** and their *E* and *Z* isomers resulting from rotation around the carbamate N–C(O) bond as well as the projections for the determination of the axial configuration (showing also the prochiral 1′-H_R and 1′-H_S protons).

identifies the isomer denoted (b) in Figures 1 and 2 as the one with S_a configuration.

EXSY spectra can be employed to measure rate constants of isomerization processes in the range from about 0.05 to 20 s^{-1}. We were thus able to obtain the rate constants of the N–aryl bond rotation in **1** between 60 and 110 °C (Table 1). As expected, the values increase exponentially with the temperature and fit well to the linear Eyring equation (Figure 3, see also the Supporting Information). The free energy barrier ($\Delta G^{\neq}$) of N–aryl bond rotation is dominated by an enthalpy ($\Delta H^{\neq}$) contribution and amounts to 91.6 kJ mol^{-1} at 25 °C, which corresponds to a rotamer lifetime of about 30 min.

To investigate the influence of the size of the *ortho* substituent on the N–aryl rotational barrier, we repeated the analysis on the corresponding *ortho*-bromonaphthyl carbamate **2**.

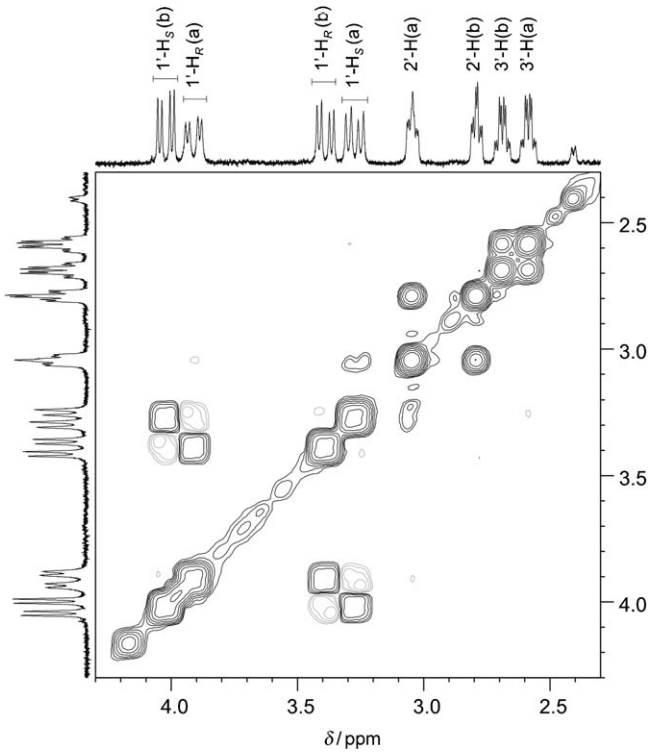


Figure 2. 2D-EXSY spectrum (80 °C, mixing time 0.5 s) of **1** showing the 1′-, 2′- and 3′-protons of the epoxide side chain. Positive (exchange) and negative (NOE) peaks are shown in black and grey, respectively. Distinct isomers are denoted (a) and (b).

Table 1. Rate constants k [s^{-1}][a] of the N–aryl bond rotation in compounds **1**, **2**, **3**, and **4** at variable temperature; free energy of activation at 25 °C; and corresponding rotamer lifetime at 25 °C.

	T [°C]								$\Delta G^{\ddagger}_{25}$	τ_{25}[b]
	25	40	50	60	70	80	100	110	[kJ mol^{-1}]	[s]
1	–	–	–	0.05	0.13	0.45	2.75	7	91.6	1830
2	0.04	0.23	0.65	1.65	4.3	11	–	–	80.9	25
3	0.18	0.93	2.5	6.3	15	–	–	–	77.2	5.5
4	0.10	0.55	1.24	3.3	8.2	19	–	–	78.6	9.8

[a] Assuming $k_1 = k_{-1}$. Experimental errors are ≈5%. [b] Derived from fitting the data to the Eyring model.

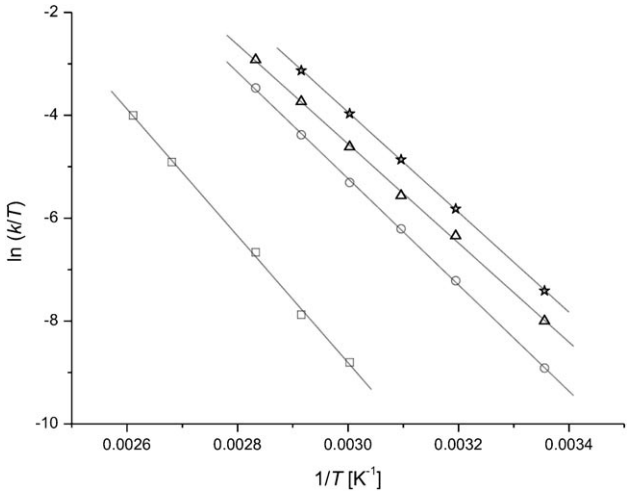


Figure 3. Eyring plot of the experimental rate constants of N–aryl bond rotation in the compounds studied (□: **1**, ○: **2**, ☆: **3**, and △: **4**). The solid lines represent best linear fits.

Here, the rate constants obtained in the range of 25 to 80 °C were much larger than in **1** by a factor of approximately 30, corresponding to a barrier that is about 10 kJ mol^{-1} lower in energy (Table 1). Similarly, we studied compound **3**, where the *ortho*-bromonaphthyl ring of **2** has a CN substituent in 7-position, as well as aniline **4**, where the *ortho*-iodonaphthyl ring of **1** is replaced by the corresponding *o*-iodophenyl moiety. In both cases, the N–aryl bond rotation was found to be greatly accelerated by a factor of about 4 and 40 compared with that in **2** and **1**, respectively. In **3**, the rotational barrier of 77.2 kJ mol^{-1} approaches that of the carbamate N–C(O) bond so that in EXSY spectra both processes can be observed simultaneously (Figure 4).

In all compounds investigated the ratio of the R_a and S_a rotamers deviates less than 5% from unity, whereas the carbamate rotamers are populated with a ratio of about 2:1 and, as expected, are separated by a free energy barrier of (68 ± 2) kJ mol^{-1}. For compound **1** the carbamate *E* and *Z* rotamers were assigned from a NOESY spectrum recorded at 0 °C where exchange between the carbamate rotamers is slower than 0.3 s^{-1} (Figure S5 in the Supporting Information). The major *Z* isomers (the *Z*/*E* ratio for **1** was 3:1 rather than 2:1) show dominant NOE correlations between the *tert*-butyl group and the 3-H, while in the minor *E* isomers the NOE correlations between the *tert*-butyl group and the epoxide side chain are dominant (Figures S6 and S7 in the Supporting Information).

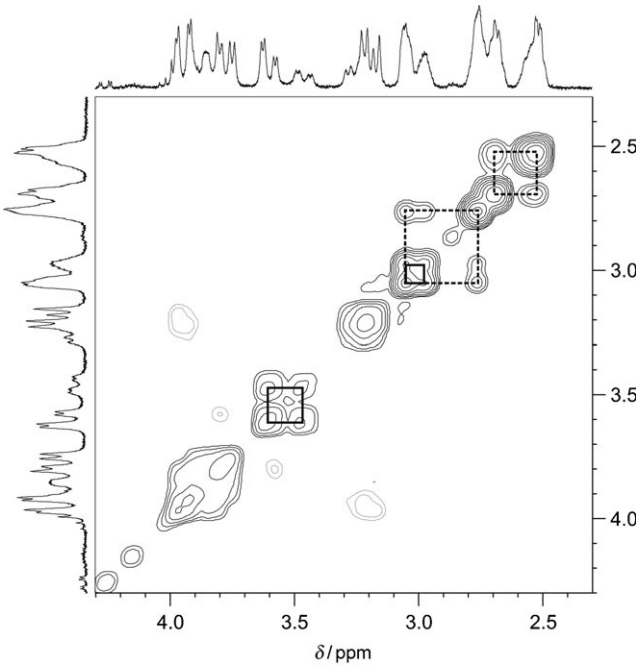
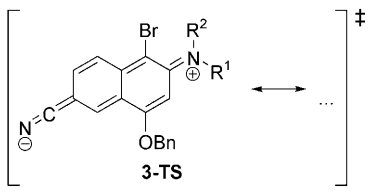


Figure 4. 2D-EXSY spectrum (25 °C, mixing time 0.5 s) of **3** showing the 1′-H, 2′-H, and 3′-H protons of the epoxide side chain. Positive (exchange) and negative (NOE) peaks are shown in black and grey, respectively. Exchange peaks due to N–aryl and N–C(O) bond rotations are highlighted with dashed and solid black squares, respectively.

When going from iodonaphthalene **1** to bromonaphthalene **2**, the decrease of the steric demand of the halogen substituent is expected to play the most important role in lowering of the rotational barrier (about 10–11 kJ mol^{-1}) about the N–aryl bond. However, when comparing the barriers found for **2** and the CN-substituted naphthalene **3**, both compounds have a bromo substituent in the *ortho* position, but **2** shows a rotational barrier that is almost 4 kJ mol^{-1} higher. As the lone pair of the nitrogen becomes available for resonance with the aryl–π systems in the transition states of the rotation about the N–aryl bond, we expect additional stabilization through resonance with the electron-withdrawing CN group in **3** (Scheme 4) to be the most likely explanation for the different barriers of **2** and **3**.

It can also be assumed that a significant change in the angle (halogen-C1-C2) for the naphthalenes **1**, **2**, and **3** and



Scheme 4. Additional generic resonance structure **3-TS** in the transition states of the rotation about the N–aryl bond in **3**. R^1 = C(O)*t*Bu and R^2 = epoxide side chain or R^1 = epoxide side chain and R^2 = C(O)*t*Bu.

the corresponding angle (I-C2-C1) in aniline **4** during the adaption of the transition-state geometries plays a dominant role. We expect that in the transition states the halogen atom is bent away from the substituted nitrogen atom, therefore, causing a 1,3-interaction with 8-H in naphthalenes **1–3** that does not exist in the aniline derivative **4**. Thus, this steric interaction might account for the difference of the rotational barriers of **1** and **4** of 13 kJ mol^{-1}. However, again electronic effects cannot be excluded.

Conclusion

2D-EXSY revealed that *ortho*-haloarylcarbamates with an alkyl side chain containing an epoxy moiety exist as two atrop-diastereomers with a rotational barrier of up to 91.6 kJ mol^{-1}. As expected, the height of the rotational barriers depends on the bulkiness of the halo substituent and the steric demand of the aromatic carbocycles. In addition, the electronic properties of the aryl moieties were also shown to have a significant influence on the rotational barriers as found for **3** containing an electron-withdrawing group at the naphthalene moiety. Here, a significantly decreased rotational barrier was found compared with **2**.

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