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A New Chiral Axis due to N(open-chain imide)—Ar Bond: Unexpected Racemization Effect of an Acyl Group

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Abstract

The first example of optically active compound **3c** which possesses axial chirality based on the N(open-chain imide)-Ar bond rotation, is described. Furthermore, a quite interesting result is also described, namely, that **3a** bearing a bulky acyl group rather than a small one racemized more rapidly. To explain this phenomenon, ^{13}C NMR experiments and the reaction with benzylamine of **3a-d** were undertaken. These preliminary results suggest that the *t*-BuCO-N bond in **3a** which racemized easily, is more twisted, compared with the CO-N bonds in **3b-d** which were relatively stable to racemization.

Keywords: *ortho*-substituted *N,N*-diacylanilines; N-C axial chirality; optically active compounds; twisted imide; racemization

In contrast to biaryl compounds such as binaphthyl and biphenyl derivatives,[1] optically active compounds which possess axial chirality based on the N-C bond rotation, have received little attention. After a pioneering report by Curran,[2] only a few examples of optically active N-C axially chiral compounds, have been reported.[3] However, no optically active compound has been reported that possesses axial chirality based on the N(open-chain imide)-Ar bond rotation. In the course of our study on the chemistry of *ortho*-substituted *N,N*-diacylanilines,[4] we became very interested in the N-C axial chirality of these compounds. We report herein the first example of optically active compound **3c** which possesses axial chirality based on the N(open-chain imide)-Ar bond rotation. Furthermore, a quite interesting result is also described, namely, that diacylaniline **3a** bearing a bulky acyl group rather than a small one racemized more rapidly.

The imide group and the phenyl ring of diacylaniline **1** are not coplanar in the ground state, but instead twist to relieve unfavorable steric interactions between the *ortho*-hydrogens on the phenyl ring and the imide group.[5] Replacing one *ortho*-hydrogen with a bulky group (**1** to **2**) increases both the imide N-Ar torsion angle and the barrier to rotation through planarity. On the basis of the foregoing concept, we planned to search for an optically active N-C axially chiral compound. We chose compounds **3a-d** bearing one large (*t*-butyl) and one small (H) *ortho* substituent as the candidates, which might retain sufficient rotational barriers to be stable to

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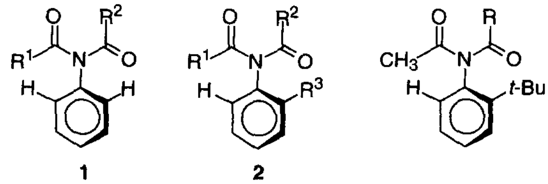
racemization at room temperature (Figure 1).

Figure 1



At first, the stability to racemization was investigated with optically active diacylanilines **3a-d**,[6] which were given through the optical resolution of racemic ones by HPLC using chiral phase column (DAICEL CHIRALCEL OD). The results are shown in Table 1. Surprisingly, optically active **3a** bearing a bulky *t*-BuCO group racemized rapidly at 25 ℃ within 30 min, affording the racemate (Entry 1). Slight racemizations of **3b, d** bearing a sterically medium-sized *i*-PrCO and phenyl group were observed at 25 ℃ (Entries 2,5). On the other hand, no loss of the optical purity of **3c** bearing a sterically small EtCO group, was observed at 25 ℃, even after 3 d (Entry 3). Slow racemization of **3c** occurred at 40 ℃ (Entry 4). Thus, the order of racemization was roughly as follows: **3a** (R = *t*-Bu) > **3b** (R = *i*-Pr), **3d** (R = Ph) > **3c** (R = Et). To the best of our knowledge, **3c** which is stable to racemization at room temperature, is the first example of an optically active compound which possesses axial chirality based on the N(open-chain imide)-Ar bond rotation (eluted first: $[\alpha]^{27}_{D}$ = +14 °(*c* 0.57, benzene), >99% ee, eluted second: $[\alpha]^{27}_{D}$ = -15 °(*c* 1.1, benzene), >99% ee).[7,8]

Table 1. Stability to Racemization in Benzene with Optically Active **3a-d**

Entry	Compound	Temperature (°C)	Results
1	**3a**	25	0 h, 64% ee; within 30 min, 0% ee
2	**3b**	25	0 h, 91% ee; after 3 days, 89% ee
3	**3c**	25	0 h, >99% ee; after 3 days, >99% ee
4	**3c**	40	0 h, >99% ee; after 3 days, 94% ee
5	**3d**	25	0 h, 97% ee; after 3 days, 94% ee

Heating optically active **3b-d** in benzene at four different temperatures and measurement of the rate constants for their racemization at each temperature[9], gave the following.[10] **3b**: $\Delta H^{\ddagger}$ = 22.7±1.44 kcal/mol; $\Delta S^{\ddagger}$ = -13.3±4.46 cal/K•mol. **3c**: $\Delta H^{\ddagger}$ = 28.1±0.398 kcal/mol; $\Delta S^{\ddagger}$ = -1.01±1.20 cal/K•mol. **3d**: $\Delta H^{\ddagger}$ = 25.1±0.225 kcal/mol; $\Delta S^{\ddagger}$ = -4.05±0.709 cal/K•mol. The racemization of **3a** was too rapid at 25 ℃ for the exact rate constant to be determined. Among above results, the nearly zero value in the entropy of activation ($\Delta S^{\ddagger}$) for **3c** is interesting. The $\Delta S^{\ddagger}$ of **3c** suggests that its racemization occurs with retention of the imide geometry in the ground state. This result prompted us to investigate the relationship between the imide geometry and the stability to racemization of **3a-d**.

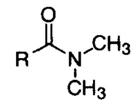
To obtain structural information on the imide moieties of **3a-d** in the ground state, we undertook a series of ^{13}C-NMR experiments as shown in Table 2.[11] The data of the acyl carbonyl signals[12] of **3a-d** were corrected by subtracting those of the corresponding *N,N*-dimethyl carboxyamides **4a-d** to cancel out the substituent effect on the carbonyl group, and the differences were indicated as $\Delta\delta^{13}$C. From these results, it is clear that the

$\Delta\delta^{13}C$ value of *t*-butylcarbonyl carbon of **3a** is larger than those of the other acyl carbonyl carbons of **3a-d** (Entry 1). The large difference can be explained as due to the reduction of amide resonance throughout the CO-N bond rotation. Accordingly, the *t*-BuCO-N bond in **3a** is more twisted than the other CO-N bonds in **3a-d**.

Table 2. ^{13}C NMR Chemical Shifts (δ, ppm)[a]

Entry	Compound	$\delta^{13}C$ RCO	$\delta^{13}C$ CH_3CO	$\Delta\delta^{13}C$ RCO	$\Delta\delta^{13}C$ CH_3CO
1	**3a**	184.6 (176.4)[b]	173.2 (169.2)[f]	8.2	4.0
2	**3b**	180.2 (175.9)[c]	173.2 (169.2)[f]	4.3	4.0
3	**3c**	176.4 (172.4)[d]	172.8 (169.2)[f]	4.0	3.6
4	**3d**	173.1 (170.8)[e]	173.3 (169.2)[f]	2.3	4.1

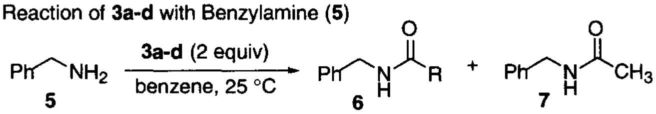
[a] Recorded at 100 MHz in C_6D_6. [b] The data of **4a**. [c] The data of **4b**. [d] The data of **4c**. [e] The data of **4d**. [f] The data of **4e**.



4a: R = *t*-Bu
4b: R = *i*-Pr
4c: R = Et
4d: R = Ph
4e: R = CH_3

With the intention of gaining further information on their structure, we chose to investigate the reactivity of diacylanilines **3a-d** with benzylamine (**5**). It has been known that twisted amide groups are more reactive to a nucleophile than the planar ones.[13] The twisted *t*-BuCO-N bond in **3a** is expected to be readily attacked by **5**, whereas the other CO-N bonds in **3a-d** are not. The results are shown in Table 3. As can be seen, only the *t*-BuCO-N bond in **3a** was readily reacted with **5** to give **6** chemoselectively (Entry 1). On the contrary, the reactivity of the CO-N bonds in **3b,c** was quite low (Entries 2 and 3). The reaction of **3d** required a prolonged period (10 h, Entry 4). These results support that the *t*-BuCO-N bond in **3a** is relatively more twisted than the other CO-N bonds in **3b-d**. It is noteworthy that the *t*-BuCO-N bond in **3a** which racemized easily, is more twisted, compared with the CO-N bonds in **3b-d** which were relatively stable to racemization. Although further investigation to clarify the relationship between the imide geometry of **3a-d** and their stability to racemization is needed, whether **3a-d** racemize rapidly or not might depend on the twist degree of each CO-N bond in **3a-d**. Ongoing efforts are focused on clarifying the detailed structure of **3a-d** and the mechanism for their racemization.

Table 3. Reaction of **3a-d** with Benzylamine (**5**)



Entry	Compound	Time (h)	Yield (%) of **6**	Yield (%) of **7**
1	**3a**	3.5	72	0
2	**3b**	7.5[a]	8	0
3	**3c**	7.5[a]	8	3
4	**3d**	10	80	0

[a] The quite slow reaction was observed.

In conclusion, we have demonstrated the first example of optically active compound **3c**, which possesses axial chirality based on the N(open-chain imide)-Ar bond rotation. Furthermore, a quite interesting result was also found, namely, that diacylaniline **3a** bearing a bulky acyl group rather than a small one racemized more rapidly.

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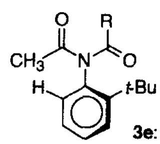
(6) The optical resolution of another diacylaniline **3e** bearing a bulky acyl group could not be achieved by using HPLC on a chiral stationary phase. This disappointed result could be due to decomposition of **3e** by a chiral column.



3e: R = cyclohex

(7) The absolute configuration of **3a-d** could not be determined.

(8) Preparation of **3c**: To a stirred solution of *N*-acetyl-*ortho*-*t*-butylaniline (413 mg, 2.16 mmol) in THF (6.5 mL) was gradually added 1.53 *M* BuLi in hexane (2.10 mL, 3.24 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 h, cooled to 0 °C, and then to this mixture was added $(EtCO)_2O$ (1.10 mL, 8.63 mmol). The whole mixture was stirred at 25 °C for 26 h, cooled to 0 °C, and quenched by the addition of H_2O at the same temperature. After usual work-up, purification by rapid silica gel column (5% EtOAc in hexane was used as eluent and the silica gel was pretreated with 3% Et_3N in hexane) afforded racemic **3c** (315 mg, 59%) as a pale yellow oil.

(9) The racemization rate constant of **3b-d** in benzene at four different temperatures is shown below.

Entry	Compound	Temp (°C)	Rate Constant (s^{-1})	Entry	Compound	Temp (°C)	Rate Constant (s^{-1})
1	**3b**	40	1.22±0.0883 X 10^{-6}	7	**3c**	63	20.9±0.063 X 10^{-7}
2	**3b**	47	2.44±0.0621 X 10^{-6}	8	**3c**	70	48.5±0.105 X 10^{-7}
3	**3b**	54	5.54±0.356 X 10^{-6}	9	**3d**	33	1.02±0.0243 X 10^{-6}
4	**3b**	61	12.8±0.976X 10^{-6}	10	**3d**	40	2.73±0.0243 X 10^{-6}
5	**3c**	49	3.08±0.096 X 10^{-7}	11	**3d**	51	10.9±0.229 X 10^{-6}
6	**3c**	56	8.36±0.224 X 10^{-7}	12	**3d**	58	25.0±0.444 X 10^{-6}

(10) According to Eyring's equation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of **3b-d** were calculated. For Eyring's equation, see: Cagle, Jr.F.W.; Eyring, H. *J. Am. Chem. Soc.* **1951**, *73*, 5628-5630.

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