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N-Arylpiperidine with Axial N–Aryl Bond. Conformational Variation in Crystals.

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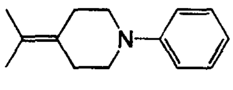
Abstract: Single crystal X-ray diffraction and ^{13}C NMR spectroscopic study of two new *N*-arylpiperidines **4** and **6** reveals that **4** adopts the conformation with the axial N–aryl bond in crystals in contrast to the general tendency of *N*-arylpiperidines to assume the conformation with an equatorial N–aryl bond. It is shown that the degree of pyramidalization of the nitrogen atom and the orientation of the N–aryl bond are strongly affected by intermolecular interactions in crystals. © 1997 Elsevier Science Ltd.

While it is well known that *N*-alkylpiperidines adopt the conformation with an equatorial N–alkyl bond, the conformation of *N*-arylpiperidines has not yet been studied thoroughly.[2] A search of the Cambridge Structural Database reveals that although most *N*-arylpiperidines assume the conformation with an equatorial N–aryl bond, there are some exceptions.[3] Three *N*-arylpiperidines, *i.e.*, **1**,[4] **2**,[5] and **3**[6] contain an axial N–aryl bond in crystals. The fact that the N–aryl bond resides in the axial position in these compounds has not been reported in the literature with the exception of **1**. The origin of the axial N-aryl conformation in **1** was explained by Krijnen *et al.* in terms of an intramolecular interaction, *i.e.*, the through-bond interaction between the lone pair electrons on the N atom and the π orbitals of the exomethylene unit separated by three σ-bonds.[4,7]

We demonstrate here that a new *N*-arylpiperidine **4** adopts the axial N-aryl conformation in crystals and that the conformation of *N*-arylpiperidines is strongly affected by intermolecular interactions in crystals. This conclusion is based on the results of single crystal X-ray diffraction and of a ^{13}C NMR spectroscopic study of **4** and related compounds **5** and **6**.[8]



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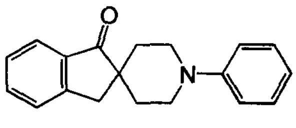

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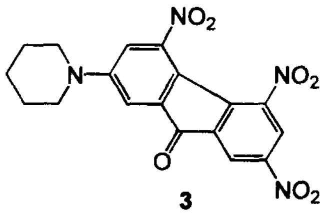

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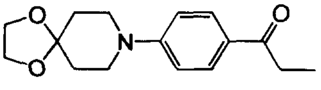

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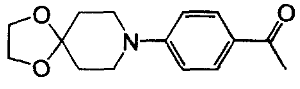

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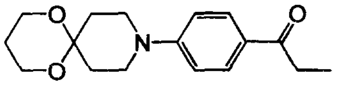

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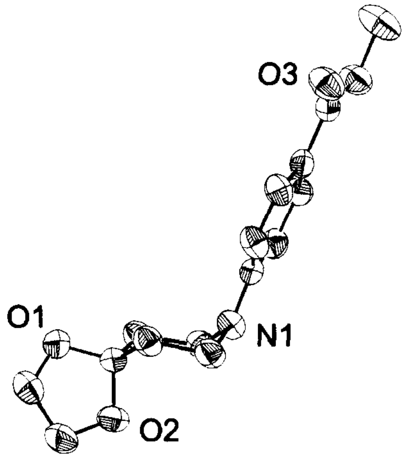

Fig. 1. Perspective view of **4**.

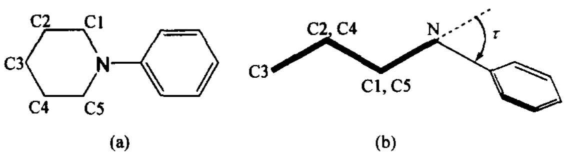

Fig. 3. (a) Atom numbering for the piperidine ring; (b) definition of angle τ.

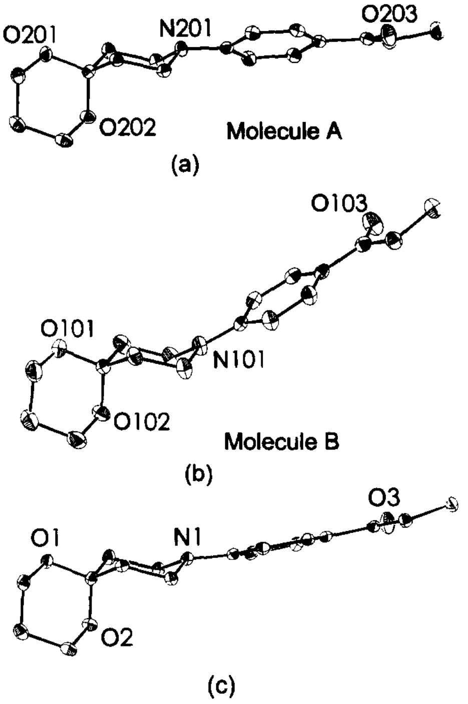

Fig. 2. Perspective views of **6** in crystals. (a) and (b) α form; (c) β form.

Table 1. Geometry of the Ring N Atom in the X-ray Structures of **4**, **5**, and **6**.

Cryst.	**4**	**5**[a]	**6**αA[b]	**6**αB[b]	**6**β[b]
$\Sigma\theta_i$[c]	352.9(4)	350.4(8)	344.4(1)	359.0(2)	351.2(3)
τ(°)[d]	-24.7(6)	29.2(9)	37.8(2)	9.0(2)	28.2(4)

[a] Reference 13. [b] See the text. [c] Sum of the bond angles around the N atom. [d] Definition of τ is given in Fig. 3.

Structure drawings of **4**[9] and **6**[10,11] determined by X-ray diffraction are shown in Figs. 1 and 2, respectively. There is no significant intermolecular contact. The geometry of the ring N atom, which is shown in Table 1, is expressed by using two parameters, (i) the sum of the bond angles around the N atom and (ii) the angle τ, which is defined as the angle between the plane made by C1, N, and C5 and the N–aryl bond (Fig. 3). Both parameters reflect the degree of pyramidalization of the N atom. The angle τ also reflects the orientation of the N–aryl bond.[12]

In compound **4**, the N atom is pyramidal, and the N–aryl bond occupies the axial position. This conformation is strikingly different from the conformation of a very similar compound **5**, in which the N–aryl bond occupies the equatorial position in crystals.[13]

For single crystals of compound **6**, two modifications (α and β forms) were found. In the α form, which was obtained by recrystallization from ethanol, there are two independent molecules in the asymmetric unit.[10] One molecule (Molecule A) adopts the conformation in which the N–aryl bond is equatorial and the other (Molecule B) assumes the conformation that possesses nearly a trigonal planar N atom. In the β form, which was obtained by recrystallization from methanol, there is an independent molecule in the asymmetric unit, and the molecule adopts that conformation in which the N–aryl bond is equatorial.[11]

In contrast, there seems to be no such a conformational variation in solution among these compounds. The ^{13}C NMR chemical shifts for the corresponding C atoms of the piperidine rings of **4** and **5** coincide, thereby indicating that the ratio of the equatorial to the axial conformer is nearly the same for the two compounds in solution (Table 2).

Table 2. ^{13}C Chemical Shifts for the Piperidine Ring Carbons of **4** and **5**.

	$\delta(CDCl_3)$	
Assignment	**4**	**5**
C1, C5	45.88	45.88
C2, C4	34.26	34.25
C3	107.02	107.04

The results clearly show that the degree of the pyramidalization of the N atom and the orientation of the N–aryl bond in crystals depend on *inter*molecular interactions as well as *intra*molecular interactions which determine the conformation of an isolated molecule. In other words, the energy differences between various conformers would be so small that a conformer which is not the most stable in an isolated molecule could appear in crystals.

This interpretation is consistent with the results of the quantum mechanical calculations for *N*-phenylpiperidine **7** and *N*-methylpiperidine **8** performed by using density functional theory (DFT[14]), as shown in Table 3. The results of DFT calculations indicate that the axial conformer is less stable than the equatorial conformer in **7**. This result is in harmony with the fact that most of *N*-arylpiperidines adopt the equatorial conformation in crystals. However, despite its steric bulk, the axial/equatorial energy difference for phenyl group (1.5 kcal mol^{-1}) is much smaller than that for a methyl group (3.4 kcal mol^{-1}).[15] The calculations show that the pyramidality of the N atom in **7** is much smaller than that in **8**. The small degree of pyramidalization in **7** is ascribed to delocalization of the lone pair electrons on the N atom through the aryl group. The magnitude of the 1,3-diaxial repulsive interaction thereby decreases, and the axial/equatorial energy difference is reduced substantially. The energetic advantage of the equatorial conformation in **4** and **6** is so small that an unfavorable conformation, such as axial or planar, could appear in crystals.

It is therefore concluded that the conformational variation of *N*-arylpiperidines in crystals results primarily from intermolecular interactions in crystals.

Table 3. Geometry of the N Atom and Conformational Energy of **7** and **8** Calculated from the DFT Calculations [a]

Compound	**7**		**8**	
Conformation [b]	ax [c]	eq [d]	ax [c]	eq [d]
$\Sigma\theta_i$ (°) [e]	351.7	346.7	348.8	334.9
τ (°) [f]	–26.9	34.9	–38.5	49.0
Energy (kcal mol^{-1}) [g]	1.5	0	3.4	0

[a] B3LYP/6-31G* level in Gaussian94.[14] [b] The lowest energy conformations were sought and obtained. [c] Conformation with axial N–C bond. [d] Conformation with equatorial N–C bond. [e] Sum of the bond angles around the N atom. [f] Definition of τ is given in the text. [g] Total energy of the equatorial conformation of each compound is set equal to 0.

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3. Cambridge Structural Database Ver.5.13 (April, 1997) was used. Sixty structures that contain an *N*-phenylpiperidine fragment were found. These structures do not contain an *N*-phenyl-2-piperidone or 1-benzoquiolizidine fragment. Five structures were found to possess the axial N-aryl conformation. In two of them, whose refcodes are VATZU and

VAVBAV (Ref. 4), the piperidine ring is incorporated into 8-azabicyclo[3.2.1]octane system and the phenyl group adopts the axial position to avoid steric repulsion from the exo protons of the ethylene bridge. Thus, there are three structures that adopt the axial N-aryl conformation.

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6. REFCODE = DISLIA. Chetkina, L.A.; Povert'eva, Z.P.; Bel'skii, V.K.; Bespalov, B.P. *Kristallografiya* **1985,** *30*, 910–914.
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8. Compounds **4** and **6** were synthesized by a similar procedure that was employed for the synthesis of **5**.[10] 8-(4-Propionylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (**4**): A mixture of *p*-fluoropropiophenone (9.89 g, 0.065 mol), 1,4-dioxa-8-azaspiro[4.5]decane (**9**) (8.59 g, 0.06 mol), and potassium carbonate (11.7 g, 0.085 mol) in dimethyl sulfoxide (25 mL) was stirred vigorously with heating at 323 K for 30 h. Then the reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water. Evaporation of the extract gave a pale-yellow solid, which was recrystallized from ethyl acetate (7.45 g, yield 41.7 %). Single crystals for the X-ray measurements were obtained via a slow evaporation of ethanol solution at room temperature. Mp. 379–380 K. 9-(4-Propionylphenyl)-1,5-dioxa-9-azaspiro-[5.7]undecane (**6**): 1,5-Dioxa-9-azaspiro-[5.6]undecane was used instead of **9**. Slow evaporation of the ethanol solution gave single crystals of the α form (mp. 391 K). Similar evaporation of the methanol solution afforded single crystals of the β form (mp. 390 K).
9. Crystal data for **4**: $C_{16}H_{21}NO_3$, $M_r = 275.38$, $T = 296$ K, monoclinic, space group $P2_1$, $a = 5.545(2)$, $b = 10.338(2)$, $c = 12.648(1)$ Å, $V = 720.3(4)$ Å^3. $Z = 2$, $\rho_{calcd} = 1.269$ g cm^{-3}, λ(Mo, Kα) = 0.71073 Å, $\mu = 0.08$ mm^{-1}. Rigaku AFC6A four-circle diffractometer, $\theta/2\theta$ scans, 1970 measured reflections within $3° < 2\theta < 55°$ of which 1753 are independent, 1385 with $I > 2.0\sigma(I)$. Structure solution with direct methods and refined on $|F_o|$ to $R = 0.046$, $R_w = 0.050$ for 264 variables. GOF = 1.832. Residual density 0.21/–0.30 eÅ^{-3}. All the crystallographic calculations were carried out using Xtal3.2 (Hall, S.R.; Flack, H.D.; Stewart, J.M. Eds., **1992**, Universities of Western Australia, Geneva, and Maryland.)
10. Crystal data for α form of **6**: $C_{17}H_{23}NO_3$, $M_r = 289.41$, $T = 150$ K, triclinic, space group $P\bar{1}$, $a = 11.0370(9)$, $b = 14.963(1)$, $c = 9.301(1)$ Å, $\alpha = 98.247(9)$, $\beta = 99.892(8)$, $\gamma = 81.981(7)$, $V = 1487.2(3)$ Å^3. $Z = 4$, $\rho_{calcd} = 1.292$ g cm^{-3}, λ(Cu, Kα) = 1.54184 Å, $\mu = 0.71$ mm^{-1}. Rigaku AFC6A four-circle diffractometer using an Oxford Cryosystem Cryostream Cooler (Cosier, J.; Glazer, A.M.; *J. Apply. Cryst.* **1986**, *19*, 105–107), $\theta/2\theta$ scans, 4697 measured reflections within $6° < 2\theta < 120°$ of which 4337 are independent, 3744 with $I > 2.0\sigma(I)$. Structure solution with direct methods (Shelxs86, Sheldrick, G. M. **1986**, University of Göttingen, Germany) and refined on $|F_o|$ to $R = 0.044$, $R_w = 0.058$ for 563 variables using Xtal3.2. GOF = 1.917. Residual density 0.32 /–0.48 eÅ^{-3}.
11. Crystal data for β form of **6**: $C_{17}H_{23}NO_3$, $M_r = 289.41$, $T = 96$ K, monoclinic, space group $P2_1$, $a = 6.245(4)$, $b = 8.108(3)$, $c = 14.641(3)$ Å, $\beta = 97.56(3)$, $V = 734.9(6)$ Å^3. $Z = 2$, $\rho_{calcd} = 1.308$ g cm^{-3}, λ(Mo, Kα) = 0.71073 Å, $\mu = 0.09$ mm^{-1}. Rigaku AFC6A four-circle diffractometer using an Oxford Cryostream cooler, $\theta/2\theta$ scans, 2018 measured reflections within $6° < 2\theta < 55°$ of which 1814 are independent, 1569 with $I > 2.0\sigma(I)$. Structure solution with direct methods (SIR92, Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.C.; Polidori, G.; Camalli, M. *J. Apply. Cryst.* **1994**, *27*, 435) and refined on $|F_o|$ to $R = 0.037$, $R_w = 0.047$ for 281 variables (Xtal3.2). GOF = 1.167. Residual density 0.25/–0.25 eÅ^{-3}.
12. A positive τ value indicates that the N–aryl bond occupies the equatorial position, and a negative τ value indicates it occupies the axial position. The larger the absolute value of τ, the more highly pyramidalized is the nitrogen atom. When the N atom assumes the ideal sp^3 hybridization, τ is ±60 °. When the N atom is in the ideal sp^2 hybridized state, then τ is 0°.
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15. This result contrasts markedly with the situation in the corresponding cyclohexane, for which the axial/equatorial energy difference is 3.0 kcal mol^{-1} for the phenyl group and 1.7 kcal mol^{-1} for the methyl group. (Hirsh J. A.: Table of Conformational Energies. In *Topics in Stereochemistry*; *Vol.* 1, Allinger, N. L.; Eliel, E. L. Eds.; Wiley, New York, **1967**, pp. 199–222.)

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