Intramolecular Edge-to-Face Aromatic-Aromatic Ring Interactions in 3-(3-Aryl-2-isopropylpropanoyl)-4-phenylmethyl-1,3-oxazolidin-2-ones Prepared from Evans Chiral Auxiliary

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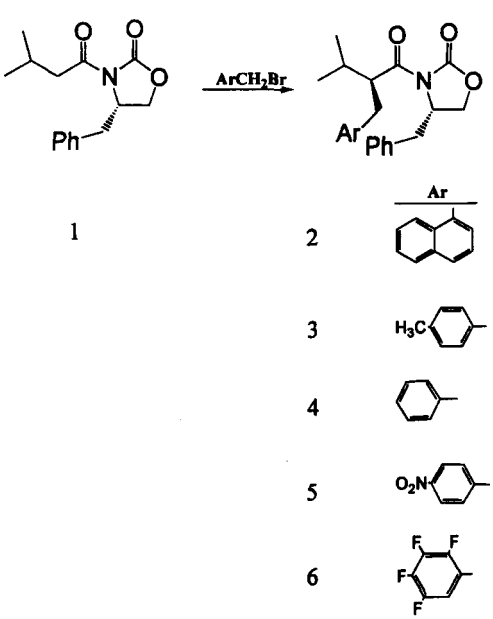
Currently there is considerable interest in noncovalent attractive binding forces that are in effect between aromatic rings.[1,2] Although the energies of these interactions are relatively small, they are known to play important roles in biological systems.[1] These interactions may also play important roles in molecular recognition[2] and stereochemcial control[3] in organic reactions. In the course of synthesizing optically active small molecule enzyme inhibitors using Evans oxazolidinone chiral auxiliary (Scheme 1), we have noted that an intermediate **4** obtained by benzylating 3-(3-methyl-1-oxobutyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one[4] (**1**) exhibits anomalous ^{1}H NMR signals, suggesting that two protons in one of the aromatic rings of the molecule are apparently shielded by the induced magnetic field arising from the circulating π-electrons of the other aromatic ring. We wish to report herein that the two aromatic rings in **4** and related compounds (**2**, **3**, **5**, and **6**) are involved in arene interactions to have an intramolecular edge-to-face arrangement.

The ^{1}H NMR spectrum of **4** obtained in deuteriochloroform solution shows a multiplet at δ 6.89 ppm with an integral corresponding to two protons. The other aromatic protons signals appear in the region of 7.27-7.14 ppm (Figure 1). The aromatic ring protons of the unbezylated precursor **1** show resonance signals at 7.37-7.21 ppm, indicating that the upfield shifted multiplet at δ 6.89 ppm for **4** are due to two equivalent protons in aromatic ring *a*, *i.e.*, the phenyl ring of the benzyl moiety at the 4-position of the oxazolidinone ring. It is then envisaged that the two protons lie close to the face of the other phenyl ring. The chemical shift of the two proton signals moved further upfield to 6.80 ppm as the temperature of the solution decreased to 213 K (Table 1). It can be concluded from the variable temperature NMR study that there exist two rapidly interconverting atropisomers in solution (Figure 2). In one conformer (A) the two aromatic rings are situated in close proximity each other so that two protons of one ring are shielded by the induced magnetic field of the π-electron ring cur-



Scheme 1.

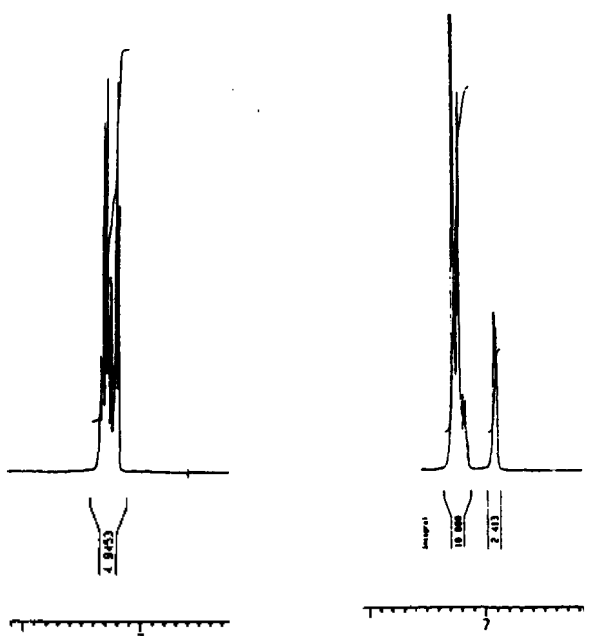


Figure 1. ^{1}H NMR spectra (300 MHz) of aromatic protons in **1** (left spectrum) and **4** (right spectrum) recorded in deuteriochloroform.

Table 1. Chemical shift shown by the two *ortho* protons in ring *a* of **4** at variable temperatures

Temp (K)	333	318	303	288	273	258	243	228	213
δ (ppm)	6.95	6.92	6.90	6.89	6.88	6.87	6.85	6.84	6.80

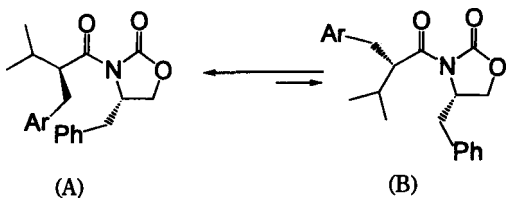


Figure 2. Two rapidly interconverting atropisomers of **4**.

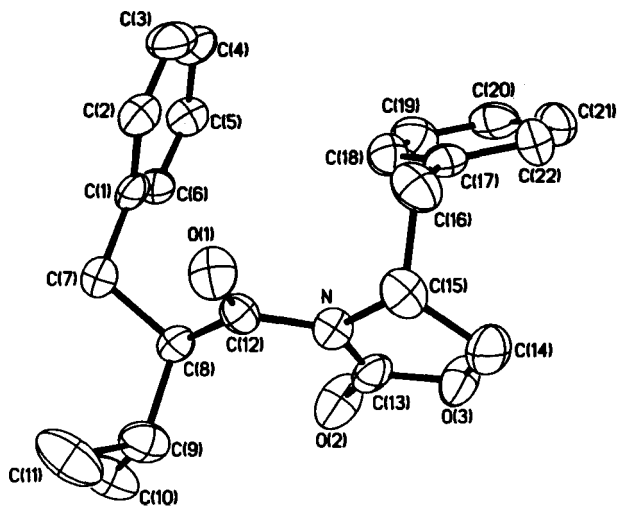


Figure 3. ORTEP drawing of **4**. Hydrogen atoms are omitted for clarity.

rent of the other ring. In the other conformer (B) which is entropically more favored, the two aromatic rings are apart from each other and no ring current shielding is observable. The temperature effect on the chemical shift further suggests that conformer A becomes increasingly important at lower temperature.

The X-ray crystallographic analysis of **4** confirms the conclusion from the NMR study and establishes that the major conformer is the one in which the two aromatic rings are arranged in an edge-to-face relationship with the *ortho* proton of ring *a* being pointed toward the face of the other aromatic ring (Figure 3). The distance between the proton and the center of the counter aromatic ring is shown to be 2.74 Å, which falls within the distance reported for edge-to-face aromatic ring interactions.[5,6] The distance between the centers of the two rings is 4.90 Å which also agrees well with the values of theoretical calculations[5] and experimental measurements[6] for such interactions. The two aromatic rings are not in perfect perpendicular relationship but in a slightly tilted T-geometry with a dihedral angle of 68.8°, again in accord with theoretical calculations[5] and other experimentally determined[6] values. Such offset geometry of aromatic side chains of amino acid residues is known to be preferred in proteins.[1]

The signals shown at 6.89 ppm in the ^{1}H NMR spectrum of **4** can now be assigned to the two *ortho* protons in ring *a*. These protons are shielded by the π-electron circulations of the other aromatic ring as the protons lie close to the face of the other phenyl ring. Apparently, the edge-to-face aro-

Table 2. Reaction time and yield, as well as spectroscopic and elemental analysis data of products **1-5**

Compd. No.	Aryl	Chirality	Yield (%)	Mp (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular formula	Anal. (%) calcd./(found) C	H	N	IR (cm^{-1}); (C=O)	^{1}H NMR ($CDCl_3$, ppm)
2	1-Naph	(αS,4S)	71	83-84	−117.94 (0.51)	$C_{26}H_{27}NO_3$ (401.51)	77.78 (78.17)	6.78 (6.86)	3.49 (3.43)	1778 1695	8.11 (d, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.56 (t, 1H), 7.50-7.43 (m, 2H), 7.39 (t, 1H), 7.15-7.07 (m, 3H), **6.71**[b] (d, *J*=7.11 Hz, 2H), 4.57 (m, 1H), 4.48 (m, 1H), 3.99 (dd, 1H), 3.45 (dd, 1H), 3.45-3.48 (m, 2H), 2.63 (dd, 1H), 2.14 (m, 1H), 2.03 (dd, 1H), 1.20-1.146 (m, 6H)
3	4-Me-Ph	(αS,4S)	67	103-103.5	+27.39 (0.58)	$C_{23}H_{27}NO_3$ (365.47)	75.59 (75.39)	7.44 (7.22)	3.83 (3.82)	1782 1701	7.27-7.14 (m, 5H), 7.05 (d, 2H), 6.87 (m, 2H), 4.57 (m, 1H), 4.20 (m, 1H), 4.02 (dd, 1H), 3.94 (dd, 1H), 2.91 (m, 2H), 2.77 (dd, 1H), 2.27 (s, 3H), 2.14 (dd, 1H), 1.98 (m, 1H), 1.03 (dd, 6H)
4[a]	Ph	(αR,4R)	64	128-128.5	−17.6 (0.50)	$C_{22}H_{25}NO_3$ (351.45)				1758 1688	7.27-7.15 (m, 8H), 6.89 (m, 2H), 4.56 (m, 1H), 4.25 (m, 1H), 4.01 (dd, 1H), 3.93 (dd, 1H), 3.02-2.93 (m, 2H), 2.75 (dd, 1H), 2.09 (dd, 1H), 1.99 (m, 1H), 1.08-1.04 (dd, 6H)
5	4-NO_2-Ph	(αS,4S)	78	116-116.5	+22.67 (0.60)	$C_{22}H_{24}N_2O_5$ (396.44)	66.65 (66.45)	6.10 (5.91)	7.06 (7.04)	1777 1692	8.11 (d, 2H), 7.43 (d, 2H), 7.24-7.21 (m, 3H), 6.90 (m, 2H), 4.60 (m, 1H), 4.23 (m, 1H), 3.99 (m, 2H), 3.07 (dd, 1H), 3.00 (dd, 1H), 2.85 (dd, 1H), 2.23 (dd, 1H), 2.02 (m, 1H), 1.08-1.05 (dd, 6H)
6	2,3,4,5-4F-Ph	(αS,4S)	79	120-120.5	+19.32 (0.58)	$C_{22}H_{21}F_4NO_3 \cdot 1/2\ H_2O$	61.11 (61.27)	5.13 (5.08)	3.24 (2.90)	1782 1701	7.32-7.26 (m, 3H), 7.03 (m, 2H), 6.94-6.87 (m, 1H), 4.59 (m, 1H), 4.15-4.05 (m, 3H), 3.06 (dd, 1H), 3.02-2.96 (m, 2H), 2.44 (dd, 1H), 2.02 (m, 1H), 1.01 (m, 6H)

[a] D. A. Evans; T. C. Britton; J. A. Ellman *Tetrahedron Lett.* **1987**, *28*, 6141-6144. [b] Chemical shift reported in bold letter represents ^{1}H NMR signals of the *ortho* protons of ring *a*.

matic-aromatic attractive ring interaction,[5] the energy of which is estimated to be in the range of 1.0-2.5 kcal mol^{-1}, shifts the equilibrium (Figure 2) in favor of the constrained conformer A. However, in a recent study made using atropisomers of N-[1-(1'-naphtyl)ethylidene]-1-phenyl-2-propylamine as a model, Boyd *et al.* concluded that entropy is also an important factor in deciding the conformational equilibrium.[6g]

The energy involved in the interactions between two aromatic rings may be divided into polar (electrostatic and induction) and van der Waals (dispersion) terms. The polar term depends on the relative charge distribution, while the van der Waals term depends on the contact surface area. In the case of aromatic-aromatic edge-to-face interactions, the polar term plays dominant role because the contact surface area is relatively small, and the presence of substituents in the aromatic rings is expected to modulate the polar term. Thus introduction of an electron withdrawing group on the face ring should decrease the electron density of the π-electron cloud and lower interaction energy. This lowered interaction energy should be observable in the ^1H NMR spectrum. The ^1H NMR signals (Table 2) arising from the *ortho* protons in ring *a* of **6** is moved significantly downfield (δ 7.03 ppm) relative to the corresponding signals of **2** (δ 6.71 ppm). This observation reflects the importance of the polar term in the edge-to-face interaction of aromatic rings. Lastly, compounds described in this report represent readily available and versatile model compounds for the study of the edge-to-face aromatic association.

Table 3. Crystal data and structure refinement for **4**

Empirical formula	$C_{22}H_{24}NO_3$
Formula weight	350.42
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$p2_12_12_1$
Unit cell dimensions	a=6.4010(9) Å α=90°
	b=17.414(5) Å β=90°
	c=17.595(2) Å γ=90°
Volume, Z	1961.3(7) $Å^3$, 4
Density (calculated)	1.187 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	748
Crystal size	0.50×0.10×0.10 mm
θ range for data collection	1.65 to 21.97°
Limiting indices	$0\le h\le 6$, $0\le k\le 18$, $0\le 1\le 18$
Reflections collected	1421
Independent reflections	1421 (R_{int}=0.0000)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1421/0/235
Goodness-of-fit on F^2	1.095
Final R indices [I>2σ(I)]	R1=0.0669, wR2=0.1292
R indices (all data)	R1=0.1108, wR2=0.1512
Absolute structure parameter	7(5)
Largest diff. Peak and hole	0.180 and −0.231 $eÅ^{-3}$

Experimental

Melting points were taken with a Thomas Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker FT-NMR spectrometer (300 MHz) in deuteriochloroform, and chemical shifts are reported in ppm relative to tetramethylsilane used as internal reference. Infrared absorption spectra were obtained using a Bruker EQUINOX 55 FT-IR spectrophotometer. Optical rotations were measured on a Rudolph Research Autopol III digital polarimeter. Elemental analysis were performed with an Elementar elemental analyzer Vario EL.

General procedure for α-arylmethylation of 3-(3-methyl-1-oxobutyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (1) to prepare 2-6. To a freshly prepared stirred solution of lithium diisopropylamide (2.1 mmole) in 6 mL of tetrahydrofuran was added under nitrogen atmosphere and at −78 °C a solution of 3-(3-methyl-1-oxobutyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (**1**)[1] (500 mg, 1.91 mmole) in 5 mL tetrahydrofuran, and the stirring was continued at −78 °C for 1 h. To the resulting solution was added a solution of aryl bromide (10 mmole) in 5 mL tetrahydrofuran. The reaction mixture was stirred at −10 °C for additional 3-7 h until when **1** was completely consumed by TLC test. The reaction was quenched with 10% aqueous

Table 4. Bond length (Å) and angles (°) for **4**

O(1)-C(12)	1.213(8)	O(2)-C(13)	1.193(9)
O(3)-C(13)	1.345(9)	O(3)-C(14)	1.442(9)
N-C(13)	1.387(10)	N-C(12)	1.395(9)
N-C(15)	1.475(9)	C(1)-C(2)	1.387(10)
C(1)-C(6)	1.392(10)	C(1)-C(7)	1.497(9)
C(2)-C(3)	1.383(11)	C(3)-C(4)	1.365(11)
C(4)-C(5)	1.380(10)	C(5)-C(6)	1.392(10)
C(7)-C(8)	1.532(9)	C(8)-C(12)	1.517(10)
C(8)-C(9)	1.545(9)	C(9)-C(11)	1.524(11)
C(9)-C(10)	1.528(11)	C(14)-C(15)	1.527(10)
C(15)-C(16)	1.524(10)	C(16)-C(17)	1.489(10)
C(17)-C(18)	1.382(11)	C(17)-C(22)	1.396(10)
C(18)-C(19)	1.363(11)	C(19)-C(20)	1.369(11)
C(20)-C(21)	1.395(12)	C(21)-C(22)	1.360(11)
C(13)-O(3)-C(14)	110.8(7)	C(13)-N(C(12)	128.4(7)
C(13)-N-C(15)	111.3(6)	C(12)-N(C(15)	120.3(7)
C(2)-C(1)-C(6)	117.2(7)	C(2)-C(1)-C(7)	123.0(8)
C(6)-C(1)-C(7)	119.8(7)	C(3)-C(2)-C(1)	121.2(8)
C(4)-C(3)-C(2)	120.2(9)	C(3)-C(4)-C(5)	121.1(9)
C(4)-C(5)-C(6)	117.9(9)	C(5)-C(6)-C(1)	122.4(8)
C(1)-C(7)-C(8)	112.3(6)	C(12)-C(8)-C(7)	109.5(6)
C(12)-C(8)-C(9)	108.2(6)	C(7)-C(8)-C(9)	114.4(6)
C(11)-C(9)-C(10)	109.5(8)	C(11)-C(9)-C(8)	114.6(7)
C(10)-C(9)-C(8)	109.8(7)	O(1)-C(12)-N	117.7(7)
O(1)-C(12)-C(8)	122.4(6)	N-C(12)-C(8)	119.9(7)
O(2)-C(13)-O(3)	121.9(8)	O(2)-C(13)-N	129.4(8)
O(3)-C(13)-N	108.7(7)	O(3)-C(14)-C(15)	105.3(6)
N-C(15)-C(16)	112.0(7)	N-C(15)-C(14)	100.5(6)
C(16)-C(15)-C(14)	114.3(7)	C(17)-C(16)-C(15)	115.6(7)
C(18)-C(17)-C(22)	117.4(8)	C(18)-C(17)-C(16)	122.5(8)
C(22)-C(17)-C(16)	120.0(9)	C(19)-C(18)-C(17)	122.1(8)
C(18)-C(19)-C(20)	120.5(9)	C(19)-C(20)-C(21)	118.3(9)
C(22)-C(21)-C(20)	121.3(8)	C(21)-C(22)-C(17)	120.4(9)

ammonium chloride solution and then diluted with ethyl acetate (30 mL). The organic layer was separated and washed with 10% citric acid (10 mL×3), saturated aqueous sodium bicarbonate solution (10 mL×2), and brine (10 mL), successively, and then dried over anhydrous $MgSO_4$. After removal of the solvent, the resulting oily residue was purified by column chromatography (silica gel, hexane/ethyl acetate= 20-10/1), and recrystallized from ethyl acetate and hexane to give crystalline product. Reaction time and yield as well as physical, spectroscopic and elemental analysis data of products are summarized in Table 2.

Determination of the X-ray crystal structure of 4. Diffraction data were collected on an Enraf-Nomius CAD4 diffractometer with graphite-monochromated MoKα radiation ($\lambda(K\alpha_1)$=0.70926 Å) and structure was solved by direct method and refined anisotropically for non-H atoms. Crystal data and structure refinement are summarized in Table 3, and bond lengths and angles are listed in Table 4. Crystallographic diagram (Figure 3) was obtained using the program of ORTEP-PC version.

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Benzoyl Rearrangement in Synthesis of Asymmetrically Substituted Calix[4]arenes

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Calixarenes are cavity containing metacyclophanes which are currently utilized as a versatile host molecules.[1,2,3] One of the most important aspects about host-guest chemistry is molecular recognition.[4,5] Like chiral cyclodextrines, calixarenes are expected to have similar chiral recognition ability because molecular structure of calixarenes could allow the preparation of synthetic molecule with a chiral cavity.[6] If molecular asymmetry could be originated directly from the calixarene framework, the efficient chiral recognition would be expected.

Chiral calixarenes first have been prepared by attaching chiral residues to the tetramer.[7] Also the various asymmetric calix[4]arenes were synthesized by the direct introduction of the three or four different substituents at the upper rim[8,9] of calix[4]arenes as well as by the selective alkylation at the lower rim[10,11] of calix[4]arenes. In 1995, González *et al.*[12] reported that an intermolecular migration of sulfonyl groups in 1,3-bistriflate and 1,3-bismesylate derivatives of *p-tert*-butylcalix[4]arene took place in the presence of a palladium catalysts and chloride anion. Mar-