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Structural and conformational analysis of 1-oxaspiro[2.5]octane and 1-oxa-2-azaspiro[2.5]octane derivatives by ^{1}H, ^{13}C, and ^{15}N NMR

Rubén Montalvo-González[a] and Armando Ariza-Castolo[b]*

A structural and conformational analysis of 1-oxaspiro[2.5]octane and 1-oxa-2-azaspiro[2.5]octane derivatives was performed using ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. The relative configuration and preferred conformations were determined by analyzing the homonuclear coupling constants and chemical shifts of the protons and carbon atoms in the aliphatic rings. These parameters directly reflected the steric and electronic effects of the substituent bonded to the aliphatic six-membered ring or to C3 or N2. The parameters also were sensitive to the anisotropic positions of these atoms in the three-atom ring. The preferred orientation of the exocyclic substituents directed the oxidative attack. Copyright © 2012 John Wiley & Sons, Ltd.

Additional NMR data as well as some example of ^{1}H and ^{13}C NMR spectra may be found in the online version of this article.

Keywords: ^{1}H, ^{13}C, ^{15}N, NMR; conformation; oxaziridines; oxiranes; spirocyclic

Introduction

Three-membered heterocyclic rings, which can be converted into a large number of functional groups,[1] have been invaluable intermediates in organic synthesis. They are easily synthesized from the oxidation of alkenes (oxiranes)[2] or imines (oxaziridines)[3] with preservation of their configuration, and their rings are easily broken through addition reactions. Nitrogen centers functionalized with three different substituents are usually achiral because of lone-pair inversion; however, inversion is prevented in oxaziridines at room temperature by a ≥ 100.32 kJ/mol energy barrier,[4] resulting in a stable configuration at the nitrogen.[5] This property has been advantageous in the synthesis of chiral oxaziridines. The synthesis of chiral oxiranes or oxaziridines, followed by ring opening via various reactions, provides access to many important chiral compounds.[6] In each part of the synthetic process, knowledge of the configuration and conformational preference of the spirocyclic oxiranes or oxaziridines is essential.

A ^{1}H NMR structural analysis has been reported for the spirocyclic oxaziridines with a methylbenzyl group bonded to the oxaziridine nitrogen.[7] The preferential conformation of the N-substituent determined the effects of this group on the 5,7 *syn-diaxial* protons.

Here, we report that the anisotropic positions (*axial* or *equatorial*) of the three-membered ring atoms guided an oxidant to preferentially attack the double exocyclic bond in an olefin or imine. The preferential conformation of a six-atom ring containing a monosubstituted alkyl group and the orientations of an oxirane or oxaziridine substituent also are described with consideration for the effects of this group on the chemical shifts of the six-membered ring atoms. To test this approach, we synthesized compounds with or without an alkyl group on the six-membered ring in which either an aromatic or an alkyl group bonded to one of the atoms of the heterocyclic ring (Fig. 1).

Results

Assignment of the ^{1}H and ^{13}C NMR spectra of the oxiranes and oxaziridines was conducted based on one- and two-dimensional NMR experiments. The connectivities were established by means of homonuclear (^{1}H,^{1}H-COSY) and heteronuclear (^{1}H,^{13}C-HETCOR) correlation spectroscopy. Additionally, *J*-modulated spectra were recorded using the attached proton test pulse sequence (APT) to distinguish between the C, CH, CH$_2$, and CH$_3$ groups in compounds **1b–e**, **2b–e**, **3b–e**, **4b–e**, **5d**, and **5e**.

The three-atom ring substituent (R2) effect on the atoms of the cyclohexenyl moiety of the oxaziridines or oxiranes was assigned based on the change in the chemical shifts of the *equatorial* and *axial* protons in the compounds derived from symmetric ketones (**1a**, **1d**, **1e**, **2a**, **2d, 2e**, **3a**, **3d**, **3e**, **4a**, **4d**, **4e**, **5a**, **5d**, and **5e**) or the *syn/anti* carbons. The magnitude of the CH- or N-substituent effects was related to their orientation (*pseudoaxial* or *pseudoequatorial*).

Analogs without substituent groups on the six-membered ring (**1a, 2a, 3a, 4a,** and **5a**) were obtained, and they were analyzed as racemic mixtures. Oxaziridine **4a** and oxirane **1a** displayed a ring inversion frequency that was slower than the 300 MHz NMR time scale, and a pair of conformers was detected (see the spectra in the supporting material).

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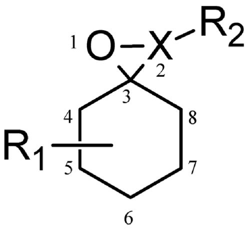
* Correspondence to: Armando Ariza-Castolo, Centro de Investigación y de Estudios Avanzados del IPN, Apartado Postal, 14–740, 07000 México D.F., México. E-mail: aariza@cinvestav.mx

a Unidad Académica de Ciencias Químico Biológicas y Farmacéuticas, Universidad Autónoma de Nayarit, Tepic Nayarit, México

b Centro de Investigación y de Estudios Avanzados del IPN, Apartado postal, 14-740, 07000 México, D.F., México



$X = CH$
$R_2 = Phenyl$

1a $R_1 = H$
1b $R_1 = 4\text{-}CH_3$
1c $R_1 = 5\text{-}CH_3$
1d $R_1 = 6\text{-}CH_3$
1e $R_1 = 6\text{-}$*tert*-butyl

$X = N$
$R_2 = 2\text{-}Pyridyl$

3a $R_1 = H$
3b $R_1 = 4\text{-}CH_3$
3c $R_1 = 5\text{-}CH_3$
3d $R_1 = 6\text{-}CH_3$
3e $R_1 = 6\text{-}$*tert*-butyl

$X = N$
$R_2 = Phenyl$

2a $R_1 = H$
2b $R_1 = 4\text{-}CH_3$
2c $R_1 = 5\text{-}CH_3$
2d $R_1 = 6\text{-}CH_3$
2e $R_1 = 6\text{-}$*tert*-butyl

$X = N$
$R_2 = n\text{-}Propyl$

4a $R_1 = H$
4b $R_1 = 4\text{-}CH_3$
4c $R_1 = 5\text{-}CH_3$
4d $R_1 = 6\text{-}CH_3$
4e $R_1 = 6\text{-}$*tert*-butyl

$X = N$
$R_2 =$ *tert*-butyl

5a $R_1 = H$
5d $R_1 = 6\text{-}CH_3$
5e $R_1 = 6\text{-}$*tert*-butyl

Figure 1. Structure and numbering of oxiranes **1a-1e** and oxaziridines **2a-2e**, **3a-3e**, **4a-4e**, **5a**, **5d**, and **5e**.

The resonance integrals from the ^{1}H NMR spectra were used to determine the ratio of isomers produced by oxidant attack of either of the exocyclic double bond orientations (*axial* or *equatorial*) was 9:1 for aromatic ketimines (oxaziridines **2b–2e** and **3b–3e**) and 7 : 1 for aliphatic ketimines (oxaziridines **4a–4e, 5a, 5d**, and **5e**), which showed an *equatorial* attack preference. The ratio for the aromatic exocyclic alkenes (oxiranes **1a, 1c–1e**)[8] was 2.3 : 1, indicating that the *axial* attack was favored for the oxidant. The olefin **1b** yielded an oxidation ratio of 6 : 4 (*equatorial*/*axial*). The derivatives with an alkyl group on C6 of the six-atom aliphatic ring (**1d**, **1e**, **2d**, **2e**, **3d**, **3e**, **4d**, **4e**, **5d**, and **5e**) were present in two enantiomeric pairs (*cis-R* and *cis-S or trans-R* and *trans-S*). Derivatives of 3- or 2-methylcyclohexanone (**1b**, **1c**, **2b**, **2c**, **3b**, **3c**, **4b**, and **4c**) were present in four pairs of isomers (namely, *cis-anti, trans-anti, cis-syn*, and *trans-syn*; Fig. 2). The *anti* : *syn* isomeric ratios were 10 : 1 for the 2-methylcyclohexanone derivatives (**1b, 2b, 3b**, and **4b**) and 10 : 9 (*anti* : *syn*) for the 3-methylcyclohexanone derivatives (**1c**, **2c**, **3c**, and **4c**). The ^{1}H NMR spectra showed overlapping resonances for all isomers, which made complete assignment difficult (see the supporting material). The assignment of the atoms in the cyclohexenyl moiety was determined based on the R1 alkyl substituent effects and the *cis/trans* and/or *syn/anti* three-atom heterocyclic substituent (R2) effects. An unequivocal assignment of the ^{13}C NMR spectra was made after partial chromatographic separation of isomers **1c, 2b, 3c**, and **4c** (for instance, see the ^{13}C NMR spectrum of compound **2b** in the supporting material). The N-aromatic oxaziridines (**2a–2e** and **3a–3e**) were transformed into the corresponding ε-lactams as a thermodynamic isomer.[9]

Discussion

^{1}H NMR

The strategy used for the ^{1}H NMR spectral assignment included analysis of the oxiranes and oxaziridines without substituents on the cyclohexane, followed by spectral analysis of the derivatives that included an alkyl group at C6. The experimental data were interactively fit to simulated spectra (Fig. 3) using the program NUTS or NUMARIT, which yielded the same results.[10] The data of compounds **1d, 1e, 2d, 2e, 3a, 3d, 3e, 4a, 4d, 4e, 5d**, and **5e** are provided in Tables 1 and 2. The requirement for simulated spectra arose from the complexity of the results, which included similar chemical shifts and complicated coupling patterns. The signals of most of the protons revealed up to five different couplings to other protons. The assignment was performed with consideration for the chemical shifts, the multiplicity, and the connectivity.

The observed preference of the oxidant for the *equatorial* face in the exocyclic ketimine double bond C = N was caused by the presence of steric restriction over the *axial* face by the C5 and C7 *axial* protons and the preferential orientations of the aromatic or alkyl N-substituents in the imines (the aromatic ring was perpendicularly oriented over the plane of the six-atom aliphatic ring).[8] Among aromatic exocyclic alkenes, the oxidant showed preference for the *axial* face because of the preferential conformation of the aromatic C substituent (the aromatic ring was in the same plane as the six-atom aliphatic ring)[8] and to the less energetic transition state.[11] The *equatorial* orientation of attack was preferred only in the

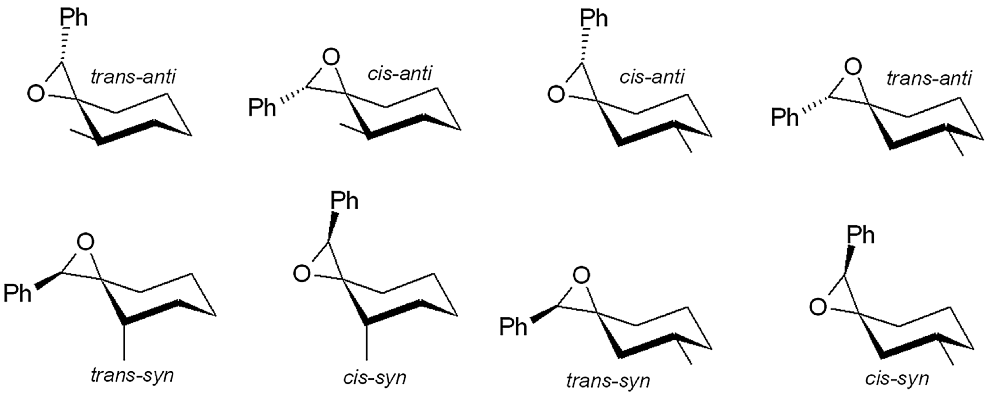


Figure 2. Stereoisomers of compounds 1b and 1c. Only one enantiomer is shown, and both are presented as a racemic mixture.

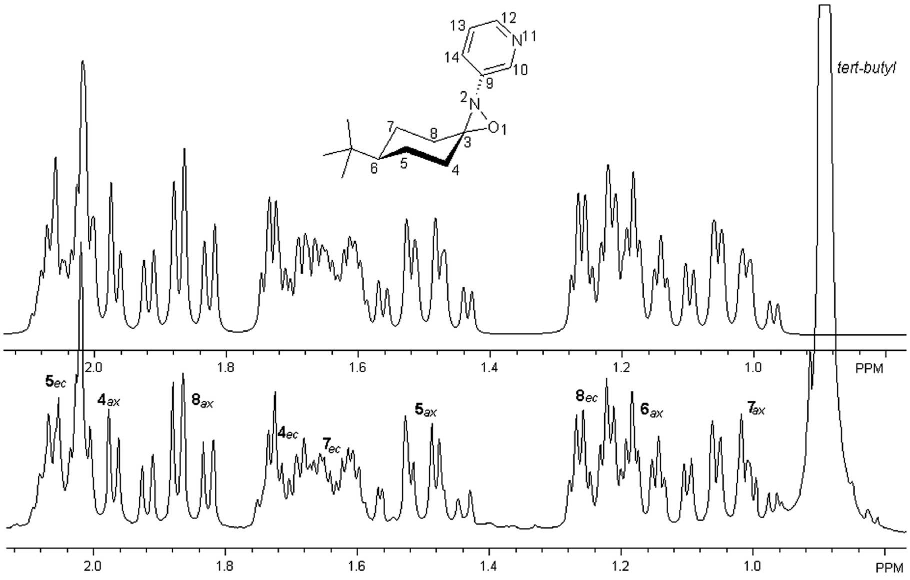


Figure 3. 1H NMR aliphatic region of oxaziridine **3e**. From top to bottom: simulated and experimental spectra with the corresponding assignments.

Table 1. ^{1}H NMR chemical shifts of six member ring region of the oxiranes **1d** and **1e** and the oxaziridines **2 d**, **2e**, **3 d**, **3e**, **4 d**, **4e**, **5 d**, and **5e**

		4		5		6		7		8	
Compound		*eq*	*ax*	*eq*	*ax*	*eq*	*ax*	*eq*	*ax*	*eq*	*ax*
1 d	*trans*	1.46	1.99	1.88	1.22	—	1.5	1.52	0.74	1.23	1.6
	cis	1.47	1.94	1.74	1.3	—	1.48	1.63	1.29	1.24	1.42
1e*	*trans*	1.41	1.96	1.93	1.24	—	1.04	1.56	0.75	1.25	1.55
	cis	1.45	1.93	1.81	1.34	—	1.06	1.72	1.35	1.23	1.32
2 d	*trans*	1.69	1.98	1.92	1.44	—	1.54	1.51	1.01	1.27	1.76
2e	*trans*	1.7	1.97	2.01	1.5	—	1.14	1.57	1.06	1.29	1.79
3a		1.84	1.84	1.79	1.79	1.53	1.53	1.54	1.54	1.41	1.41
3 d	*trans*	1.7	2.02	1.96	1.45	—	1.59	1.57	1	1.22	1.84
3e	*trans*	1.71	2.01	2.05	1.5	—	1.18	1.63	1.04	1.24	1.87
4a		1.58	1.58	1.54	1.54	1.72	1.72	1.64	1.64	1.85	1.85
4 d	*trans*	1.39	1.85	1.83	1.26	—	1.58	1.83	1.16	1.93	1.89
4e	*trans*	1.4	1.86	1.92	1.4	—	1.14	1.94	1.22	1.94	1.9
5a		1.42	1.75							1.98	1.91
5 d	*trans*	1.44	1.7	1.88	1.28		1.61	1.82	1.28	2.17	2.01
5e	*trans*	1.41	1.74	1.94	1.29		1.2	1.9	1.29	2.24	1.99

* The chemical shifts were established from 2D spectra (COSY and HETCOR).

Table 2. The $^3J_{H,H}$ and dihedral angle of six member ring part of oxirane **1 d** and oxaziridine **5e**

	1 d (*cis*)	Dihedral angle (°)	**1 d** (*trans*)	Dihedral angle (°)	**5e** (*trans*)	Dihedral angle (°)
4ax,5ax	13.0	160	13.0	160	12.8	158.0
4ax,5 eq	4.4	53	4.4	53	4.1	55.0
4 eq,5ax	3.7	56	3.7	56	3.8	56.0
4 eq,5eq	3.4	58	2.7	62	3.2	59.0
5ax,6ax	12.0	170	11.9	169	12.6	180.0
5 eq,6ax	3.5	56	3.5	56	2.9	60.0
6ax,7ax	13	180	13.0	180	12	170.0
6ax,7 eq	3.5	58	3.5	58	2.8	61.0
7ax,8ax	13.8	166	13.0	160	13.8	164.0
7ax,8 eq	3.8	56	3.8	56	3.3	59.0
7 eq,8ax	3.5	57	4.5	53	4.7	51.0
7 eq,8eq	3.4	58	3.4	58	3.1	59.0

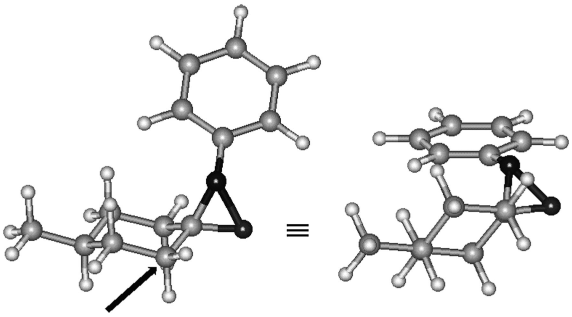


Figure 4. Anisotropic positions of the *equatorial/axial* protons on C4 or C8 with respect to the three-atom heterocyclic ring.

oxirane **1b**. During *axial* oxidant attack of the alkene obtained from 2-methylcyclohexanone (oxirane **1b**), large steric interactions were present in the spirocyclic transition state[12] because of the position of the methyl bonded to the aliphatic six-membered ring.

The *equatorial* protons bonded to the C4 and C8 carbons of the C2-phenyl oxiranes (**1d** and **1e**) and of the N-Ar oxaziridines (**2d**, **2e**, **3d**, and **3e**) exhibited abnormal chemical shifts. These protons appeared at frequencies lower than the frequency corresponding to the *axial* proton ($\Delta\delta = 0.45 \pm 0.15$).[13] This was caused by the anisotropic positions of the *equatorial* C4 and C8 protons relative to the three-membered heterocyclic ring (Fig. 4).[13] Oxiranes display a $\Delta\delta_H$ for the C4 protons that is 0.2 ppm larger than the corresponding values of the N-Ar oxaziridines; however, C8 protons in the N-Ar oxaziridines display a $\Delta\delta_H$ that is 0.55 ± 0.05 ppm larger than the corresponding oxirane shift. The $\Delta\delta_H$ of the C4 protons of N-propyl (**4d** and **4e**) and N-t-butyl (**5d** and **5e**) oxaziridines are similar to those of the corresponding protons of the N-Ar oxaziridines (**2d**, **2e**, **3d**, and **3e**); however, among the C8 protons of the N-aliphatic oxaziridines, *equatorial* protons occurred at positions 0.06 ± 0.01 ppm higher than the *axial* protons. This was caused by the presence of strong steric interactions between the N-alkyl group and the *equatorial* proton.[14]

The *equatorial* protons bonded to C5 and C7 of the *trans* isomers of the oxiranes (**1d** and **1e**) and N-Ar oxaziridines (**2d**, **2e**, **3d**, and **3e**) displayed indistinguishable spectral signatures; however, the *axial* proton bonded to C7 of these compounds was shifted toward lower frequencies by 0.40 ± 0.05 ppm relative to the proton bonded to C5. This showed that the C7 *axial* proton was shielded by the aromatic C3 (**1d** and **1e**) or N2 (**2d**, **2e**, **3d**, and **3e**) substituents (Fig. 5). The same proton in the *cis* isomers of **1d** and **1e** but the C7 *axial* protons were shifted toward higher frequencies by 0.55 ± 0.05 ppm relative to the corresponding protons in the *trans* **1d** and **1e** isomers. In the oxiranes, protons bonded to C3 in the *pseudoaxial* orientation were shifted toward higher frequencies by 0.04 ± 0.01 ppm relative to those in the *pseudoequatorial* position.

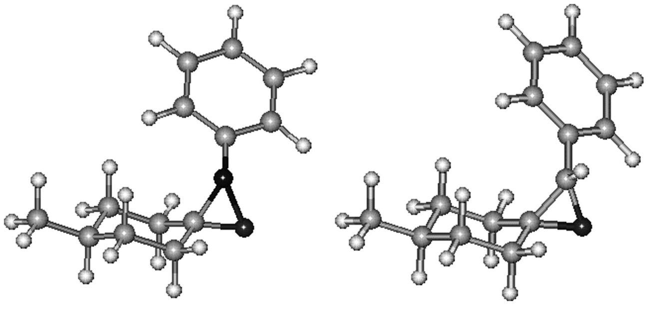


Figure 5. Preferential orientations of the aryl groups (left) in the oxaziridines, and (right) in the oxiranes.

The coupling constant pattern (Table 2) presented by the proton base of the methyl group ($^3J_{H6ax,H5ax} = 12.5 \pm 0.5$; $^3J_{H6ax,H5ec} = 3.2 \pm 0.3$; $^3J_{H6ax,H7ec} = 3.2 \pm 0.3$; and $^3J_{H6ax,H7ax} = 12.5 \pm 0.5$ Hz) showed that the chair conformation was preferred based on the dihedral angles.[15] The four bond coupling constants *W* ($^4J_{H4ec,H8ec}$) were larger among the oxaziridines than among the oxiranes, yielding four bond coupling constant differences between the oxaziridines and oxiranes of $\Delta^4J_{H4ec,H8ec} = 0.7 \pm 0.1$ Hz for the N-aromatic oxaziridines and $\Delta^4J_{H4ec,H8ec} = 1.4 \pm 0.2$ Hz for the N-aliphatic oxaziridines.

The *syn* isomers of the 2-methylcyclohexanone derivatives yielded three-bond coupling constants between the C4 and Me protons ($^3J_{H4,Me} = 7.2$ Hz), revealing that the methyl group was axially oriented.[16]

^{13}C NMR

The complete ^{13}C NMR spectral assignments of all isomers of oxiranes (**1a–1e**) and oxaziridines (**2a–2e**, **3a–3e**, **4a–4e**, **5a**, **5d**, and **5e**) are shown in Table 3. These assignments were made considering the substituent effects, their positions and orientations, and the connectivity and abundance of isomers of all compounds, except for those obtained from the imines derived from cyclohexanone (**1a**, **2a**, **3a**, **4a**, and **5a**). Unequivocal assignment of all isomer derivatives produced by oxidation of the imines obtained from 2-methyl- (**1b**, **2b**, **3b**, and **4b**) or 3-methylcyclohexanone (**1c**, **2c**, **3c**, and **4c**) was made using the spectra obtained after partial chromatographic separation.

^{13}C NMR analysis of the substituent effects on the six-membered ring atoms was performed with consideration for the chemical shifts of the unsubstituted cyclohexyl compounds (**1a**, **2a**, **3a**, **4a**, and **5a**).

The spiro carbon (C3) signal of the N-aromatic oxaziridines (**2a–2e** and **3a–3e**) was shifted toward higher frequencies by 4.15 ± 0.2 ppm relative to the positions of the corresponding carbons of the N-aliphatic oxaziridines (**4a–4e**, **5a**, **5d**, and **5e**). The nitrogen in the heterocyclic three-membered oxaziridines (**2a–5e**) shifted the spiro carbon signal by 21.5 ± 2.0 ppm relative to the positions of the corresponding carbons (C2) on the oxiranes (**1a–1e**). Larger shifts were observed among the aromatic oxaziridines.

Although atoms 1 and 2 of the oxaziridines (O1 and N2) and oxiranes (O1 and C2) were present at the center of the plane formed by the six-membered ring, a small increase in the inductive effect transference of the chemical shift over C3 and C4 ($\Delta\delta_{C3} = 0.6 \pm 0.3$ ppm and $\Delta\delta_{C4} = 0.4 \pm 0.14$ppm) was observed for the case in which the oxygen (in the three-atom ring) was present in the *pseudoequatorial* position.

The *syn/anti* orientation of the aromatic substituent of those compounds obtained from the symmetrically substituted ketones generated a $\Delta\delta_{C4\text{-}C8}$ of 7.5 ± 0.2 between C4 and C8 and a $\Delta\delta_{C5\text{-}C7} = 1.5 \pm 0.3$ between C5 and C7 in the *trans* isomer. Larger effects were observed for the aromatic oxaziridines because of the preferred conformation of the

Table 3. ^{13}C Chemical shifts of the spirocyclic region of compounds **1a–5e**

Compound		3	4	5	6	7	8
1a[a]		64.5	35.4	25.43	24.69	25.3	28.54
	trans-anti[b]	60.52	37.24	33.57	24	24.98	27.91
1b	*cis-anti*[c]	63.36	36.61	32.78	24.7	26.33	29.9
	cis-syn[d]	64.59	30.31	30.59	20.13	24.32	30.22
	trans-syn[e]	64.72	29.49	29.87	19.53	25.53	29.58
	cis-anti[f]	64.76	44.14	33.11	34.07	24.09	27.98
1c	*trans-anti*[b]	64.46	43.3	30.73	34.28	23.32	27.85
	cis-syn[h]	64.82	36.8	29.89	31.63	25.2	35.28
	trans-syn[i]	64.35	36.44	30.71	34.49	23.65	34.66
1 d	*trans*[j]	64.85	35.2	34.52	31.78	33.35	27.89
	cis[k]	64.38	34.53	32.63	31.97	32.41	27.73
	trans[l]	64.95	35.71	27.1	47.25	25.88	28.38
1e	*cis*[c]	64.4	35.29	25.17	47.87	25.03	28.52
2a		87.76	35.76	25.07	24.06	24.69	29.15
	trans-anti	89.7	37.62	32.45	23.09	24.08	27.8
2b	*cis-anti*	89.26	37.27	32.66	23.67	24.56	28.7
	cis-syn	90.89	31.1	31.69	19.5	24.32	30.82
	trans-syn	90.59	29.82	30.92	19.07	25.25	29.27
	cis-anti	87.86	43.8	32.07	33.31	22.32	27.61
	trans-anti	87.5	43.65	31.81	33.78	23.39	29.89
2c	*cis-syn*	87.87	36.29	30.06	33.39	23.86	35.2
	trans-syn	87.5	37.97	30.99	33.97	23.8	34.97
2 d	*trans*	87.84	34.99	33.15	31.04	31.52	27.42
	cis	87.3	34.72	32.68	31.41	32.26	29.15
2e	*trans*	88.06	35.55	25.87	46.48	24.01	27.83
	cis	87.39	35.31	25.52	47.11	24.93	n.d.
3a		88.48	35.55	24.91	24.02	24.66	29.23
3b	*trans-anti*	90.47	37.28	32.36	22.95	23.76	27.79
	cis-anti	88.13	36.9	32.42	23.42	24.33	28.67
	cis-syn	91.41	30.88	31.42	19.24	24.12	30.49
	trans-syn	91.2	29.96	30.75	18.76	25.05	29.1
3c	*cis-anti*	88.37	43.3	31.85	32.89	22.03	27.47
3c	*trans-anti*	88.13	43.11	31.54	33.31	23.03	29.57
	cis-syn	88.41	36.11	29.89	32.98	23.59	34.75
	trans-syn	88.13	37.77	30.71	33.5	23.46	34.46
3 d	*trans*	88.69	34.77	33.1	30.94	31.42	27.52
	cis	87.92	34.59	32.64	31.27	32.23	29.23
3e	*trans*	88.98	34.93	25.49	45.98	23.62	27.55
	cis	88.05	34.5	nd	46.76	24.1	nd
4a		84.25	36.34	25.3	24.38	24.78	27.74
4b	*trans-anti*	86.31	38.33	31.83	22.68	25.06	26.02
	cis-anti	85.96	37.68	32.23	23.15	25.1	26.18
	trans-syn	86.9	31.75	31.2	19.74	24.02	30.89
	cis-syn	86.9	31.02	nd	19.25	25.23	29.14
4c	*cis-anti*	84.6	44.93	32.08	33.81	24.07	27.27
	trans-anti	83.04	44.36	nd	nd	nd	27.31
	cis-syn	84.64	36.28	31.98	33.97	32.16	36.01
	trans-syn	83.04	35.57	nd	nd	nd	36.14
4 d	*trans*	84.63	35.99	33.25	31.55	33.21	26.94
	cis	84.26	35.55	32.97	31.88	32.18	27.24
4e	*trans*	84.63	36.54	25.99	47.09	25.77	27.42
	cis	84.22	35.99	25.56	47.45	24.67	27.75
5a		85.03	38.16	25.3	24.43	25.3	29.67
5 d	*trans*	85.87	37.75	33.55	31.24	33.07	28.21
	cis	84.41	37.39	33.49	31.60-	32.36	29.15
5e	*trans*	86.22	38.66	26.17	47.01	25.86	28.9
	cis	84.45	37.83	26.1	47.11	24.81	29.63

[a]$\delta_{C2} = 65.49$; [b] $\delta_{C2} = 68.13$: [c] $\delta_{C2} = 67.79$; [d] $\delta_{C2} = 68.00$; [e] $\delta_{C2} = 68.22$; [f] $\delta_{C2} = 65.73$;
[b]$\delta_{C2} = 65.31$; [h] $\delta_{C2} = 65.76$; [i] $\delta_{C2} = 65.35$; [j] $\delta_{C2} = 65.94$; [k] $\delta_{C2} = 65.07$; [l] $\delta_{C2} = 66.21$;
[c]$\delta_{C2} = 65.30$

aromatic substituent, which generated steric interactions between the *ortho* and *axial* C7 protons. The stronger steric effects induced by the propyl group in compounds **4a–4e** shifted C8 toward lower frequencies relative to other compounds. The *cis* isomers of the oxiranes and the oxaziridines C5 and C7 yielded almost identical chemical shifts. The low-frequency chemical shifts of C6 ($\delta_C = 19.7 \pm 0.4$) and C4 ($\delta_C = 30.5 \pm 1$) in the 2-methylcyclohexanone derivatives (**1b, 2b, 3b**, and **4b**) of the *Z* isomer resulted from the γ_{axial}–γ_{gauche} ($\Delta\delta = 4.5 \pm 0.8$) effects of the methyl substituent. Previous reports have attributed this observation to the nitrogen lone pair effects on the chemical shift, particularly with respect to Cα.[17]

^{15}N NMR

The ^{15}N NMR data for the majority of the isomers are given in Table 4. Only the derivatives of the methyl group at C3 (**2c**, **3c**, and **4c**) yielded two isomers corresponding to the *syn-anti* isomers of the *trans* compounds. The spectra of compounds **3a** and **3b** were not detected by the INEPT pulse sequence because it was not possible to estimate $J_{N,H}$ *a priori*. The coupling constant was 5.5–6.9, which agreed well with the values reported in the literature for $^2J_{N,H}$, in which an alkyl group was present *anti* to the *lone pair*.[18]

The chemical shifts determined here were similar to those previously reported.[19] The N-C_6H_5 and N-$CH_2CH_2CH_3$ derivatives did not display significant differences in the chemical shifts of ^{15}N ($\Delta\delta_N < 1.4$ derivative **2** with **4**) and the coupling constant $^{2/3}J_{N\text{-}H}$ ($\Delta J < 1.4$). The main differences were observed for the derivatives containing a C2-CH_3 moiety. Additionally, the *syn-anti* isomer of compound **2c** yielded a $\Delta\delta_N$ of 2.4, similar to that observed for **4c** ($\Delta\delta_N = 2.3$), whereas the difference was only 0.1 ppm for compound **3c**. These observations agreed well with previously reported observations for spiro[4.5]decanes.[20]

Conclusions

The perpendicular orientations of the N-aryl and N-propyl groups protected the *Re* face of the oxidant against attack in the ketimines, but the preferential coplanar orientations of the aromatic substituents and the exocyclic alkenes favored the *Re* face. The three bonds of the heterocyclic ring (oxiranes or oxaziridines) generated an unprotected diamagnetic current over the *equatorial* protons bonded to C4 and C8. The preferential conformation of the aryl substituent was one in which diamagnetic current lines protected the *axial* proton bonded to C7.

Experimental Section

Synthesis

The synthesis of exocyclic olefin and imine precursors of the oxiranes (**1a–1e**) and oxaziridines (**2a–4e**) has been reported previously.[8] The synthesis of imines produced the oxaziridines **5a**, **5 d**, and **5e** using $TiCl_4$, as reported by Carlson *et al.*[21]

The oxiranes **1a–1e** and oxaziridines **2a–2e**, **3a–3e**, **4a–4e**, **5a**, **5d**, and **5e** were prepared by mixing 2 molar equivalent of the *m*-chloroperbenzoic acid and 1 equivalent of the corresponding imine or alkene in methylene chloride. The reactions were carried out at 0°C with constant stirring for 1 h. To the resulting solution was added water in a volume of ten times the methylene chloride volume, and the solution was extracted three times with 200 ml CH_2Cl_2. The portions were joined and dried over anhydrous $MgSO_4$. The oxaziridines were purified using a flash chromatography alumina (**2a–2e**) or silica gel (**3a–3e**, **4a–4e**, **5a**, **5d**, and **5e**) column and 90% hexane/10% ethyl acetate as the eluting agent. The oxiranes were not purified because no side products were obtained. The geometric isomers of **1d** and **1e** were separated by chromatography (silica gel flash column with hexane/ethyl acetate 95 : 5 as the eluent).

^1H NMR assignments

The chemical shifts and spin–spin coupling constants of the protons of the cyclohexane rings were determined based on computer simulations[10] carried out for subsystems of ten nuclei. The number of spins corresponding to the methyl protons was reduced by symmetry considerations because the three methyl protons were chemically and magnetically equivalent. The root mean square error between the experimental and simulated spectra was 0.21 Hz. Excellent agreement was observed with the experimental spectrum when the long-range coupling constants ($^4J_{H,H}$ and $^5J_{H,H}$) were taken into account.

Spectra

NMR spectra of compounds **1a–5e** were recorded at 18 ± 1°C using a Bruker 300 Avance spectrometer equipped with a 5-mm multinuclear probe. All spectra were obtained using a $CDCl_3$ solution (0.9 mmol of the compound per 0.4 ml solvent). The chemical shifts were referenced[22] with respect to an internal $(CH_3)_4Si$ ($\delta^1H = 0$, $\delta^{13}C = 0$) or neat CH_3NO_2 ($\delta^{15}N = 0$ for $\Xi^{15}N = 10.136767$ MHz). ^1H NMR spectra were recorded at 300 MHz (spectral width: 6188.1 Hz, acquisition time: 2.648 s, 16 384 data points, equivalent 30° pulse duration, 16 scans, recycle delay: 1 s). $^{13}C\{^1H\}$ NMR spectra were recorded at 75.47 MHz

Table 4. ^{15}N Chemical shifts of compounds **2a–4e**

Compound	$\delta\ ^{15}N$	$^3J_{H,H}$	Compound	$\delta\ ^{15}N$	$^3J_{H,H}$	Compound	$\delta\ ^{15}N$	$^3J_{H,H}$
2a	−212.7	6.2	**3a**	nd	nd	**4a**	−211.8	6.9
2b	−216.9	nd	**3b**	nd	nd	**4b**	−215.5	nd
2c	−212.5	6.2	**3c**	−218.0	nd	**4c**	−213.6	5.6
	−214.9	6.5		−218.1	nd		−215.9	5.5
2 d	−211.9	6.6	**3 d**	−217.4	nd	**4 d**	−210.9	nd
2e	−211.9	nd	**3e**	−217.4	5.9	**4e**	−210.8	nd

Nd, not determined.

(spectral width: 17 361.1 Hz, 32 768 data points, equivalent 30° pulse duration, 256 scans, recycle delay: 0.01 s). Similar conditions were used for the APT and INEPT spectra. ^{15}N NMR spectra of compounds **2a–5e** were recorded at 30.38 MHz by using INEPT methods[23] (spectral width: 15151.6 Hz; 16 384 data points, from 1024 to 13 706 scans, depending on the solubility; recycle delay: 4 s, the delays were optimized in agreement with $^{3}J_{N,H}$). ^{1}H–^{1}H COSY spectra were obtained using the cosy45 pulse sequence[24] with a 1024 × 512 data point matrix and a 751.20 × 751.20 Hz frequency matrix. The recycle delay was 2 s, and a total of 16 scans were performed. Fourier transformations were carried out for F1 and F2 using a sine function in the absolute value mode. ^{13}C–^{1}H COSY spectra were obtained with the HETCOR pulse sequence for the aliphatic region[22] using a 2048 × 256 data point matrix and a 6265 × 751 Hz frequency matrix. The pulse time intervals 1 and 2 were set to $2 \times 1/4J_{C,H} = 1.85$ ms. The recycle delay was 2 s, and a total of 16 scans were performed. Fourier transformations were carried out using a square sine function for F1 and F2 in the absolute value mode. MS studies of compounds **2a–5e** were conducted using a Hewlett–Packard 5890 spectrometer coupled to a gas chromatograph in the EI mode (at 70 eV). No mass spectra could be obtained for compounds **1a–1e** because of their instability at their respective boiling temperatures.

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