Supplementary Information

Asymmetric Organocatalytic Friedel-Crafts Hydroxyalkylation of Indoles Using Electrophilic Pyrazole-4,5-diones

Fabrizio Vetica, Pankaj Chauhan, Suruchi Mahajan, Gerhard Raabe, and Dieter Enders*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

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DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 5i

A solution of compound 5i in acetonitrile (10⁻³ mol/l) was measured at room temperature and a path length of 0.05 cm on an AVIV 62DS electronic circular dichroism (ECD) spectrometer. The corresponding calculations assuming the configuration R at the chiral center of 5i were performed employing the Gaussian09 suite of quantum-chemical routines running on the facilities of the IT center of the RWTH Aachen University (project rwth0219). Molecular mechanics calculations were employed in order to locate the energetically most stable conformational isomers. The two most stable conformers were subjected to further optimization at the correlated MP2 level employing the 6-31+G* basis set for H, C, N, and O, while the Stuttgart-Dresden (SDD) effective core potentials (ECPs) were used for Iodine. At this level of theory the energy difference between the two most stable isomers from the molecular mechanics calculation was found to be 4.01 kcal/mol and, therefore, only the energetically most favorable one had to be considered in the calculation of the ECD spectrum. This calculation including 40 excited states was performed at the time-dependent level of density functional theory (TD-DFT) with the CAM-B3LYP functional, the 6-311++G(3df,3pd) basis set for H, C, N, and O and the above-mentioned ECPs for iodine. The measured and the calculated spectra are compared to each other in Figure 1.

We assign the negative Cotton effect observed at 295 nm to the positive one at 276 nm. This band is governed by a state at 276 nm which is dominated by the HOMO → LUMO transition. The HOMO is widely located at the indole part of the molecule where it has local π symmetry. The
LUMO has its largest coefficients at the pyrazolone ring, and it is approximately of local $\pi^*$ symmetry. Therefore, the state at 276 nm can be considered as governed by a local $\pi \rightarrow \pi^*$ transition with intramolecular charge transfer.

The positive band observed at 265 nm is correlated with the negative one calculated at 257 nm. The calculated Cotton effect at 257 nm derives most of its intensity from a state at 255 nm. The strongest contribution to this state comes from a HOMO-2 to LUMO+1 configuration. The HOMO-2 orbital is almost entirely located at the indole system. It is of local $\pi$ symmetry. The LUMO+1 has also its largest coefficients at the indole part. Different from the HOMO-2 it is of local $\pi^*$ symmetry. Thus, the Cotton effect calculated at 257 nm is predominantly due to a local $\pi \rightarrow \pi^*$ transition of the indole system.

The strongest band in the experimental spectrum is the negative one at 240 nm. It appears with opposite sign at 236 nm in the calculated ECD curve. The main component of the underlying state calculated also at 236 nm is due to an excitation from the HOMO-1 to the LUMO+3. The HOMO-1 is of local $\pi$ symmetry and has its largest coefficients at the pyrazole ring and the attached phenyl substituent. The LUMO+3 is predominantly located at the same part of the molecule. It is of local $\pi^*$ symmetry, and the state that governs the band calculated at 236 nm is, therefore, a local $\pi \rightarrow \pi^*$ transition of the pyrazolone system.

Moreover, the much weaker positive band observed at 227 nm is assigned to the positive minimum at 225 nm in the calculated spectrum.

Finally, the strong negative Cotton effect at 208 nm in the experimental spectrum is correlated with the positive one at 209 nm. The calculated band gets its intensity from to two intense states with positive rotational strengths at 212 and 207 nm. The strongest contribution to the former one comes from a HOMO→LUMO+10 configuration which corresponds to a local $\pi \rightarrow \pi^*$ transition of the pyrazolone ring. Latter one involves a multitude of configurations with no coefficient larger than 0.28.

In spite of the significant blue shift of the calculated spectrum in the long wave lengths region the general shapes of the calculated and measured spectra in Figure 1 appear like image and mirror image. Since the calculation was performed assuming the configuration $R$ at the stereocenter we conclude that the absolute configuration of the measured compound is $S$. 
\textbf{NMR Spectra}

\textit{(S)-4-Hydroxy-4-(1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5a)}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{spectrum1.png}
\caption{NMR spectrum of (S)-4-Hydroxy-4-(1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5a) in CD$_3$OD solvent.}
\end{figure}
(S)-4-Hydroxy-4-(1H-indol-3-yl)-5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (5b)
(S)-2-(4-Chlorophenyl)-4-hydroxy-4-(1H-indol-3-yl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (5c)
(S)-5-Ethyl-4-hydroxy-4-(1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5d)
(S)-4-Hydroxy-4-(1H-indol-3-yl)-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5e)
(R)-5-(tert-Butyl)-4-hydroxy-4-(1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5f)
(R)-4-Hydroxy-4-(1H-indol-3-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one (5g)
(S)-4-(7-Bromo-1H-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5h)
(S)-4-Hydroxy-4-(5-iodo-1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5i)
(S)-4-(5-Fluoro-1H-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5j)
(S)-4-(1H-benzol[g]indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5k)
(S)-4-Hydroxy-4-(5-methoxy-1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5l)
(S)-4-Hydroxy-5-methyl-4-(5-methyl-1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5m)
4-Hydroxy-5-methyl-4-(1-methyl-1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5n)
HPLC DATA

(S)-4-hydroxy-4-(1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5a)

AK Prof. Enders - Analytiklabor 4.04

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Acq. Analysis method: CHIRALPAK IC.1.M
Column: Chiralpak IC, (150 x 4,6) mm, 5µ, SN: IC00CD-QF015

Pressure at start: 43 bar Start flow: 0.700 ml/min Column oven: 29.99 °C

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Column: Chiralpak IC, (150 x 4,6) mm, 5µ, SN: IC00CD-QF015

Pressure at start: 43 bar Start flow: 0.700 ml/min Column oven: 29.99 °C

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(S)-4-Hydroxy-4-(1H-indol-3-yl)-5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (5b)

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-226
Data file: C:\SNOOPY\FV\FV226.D
Description: The sample is solved in DCM/MP
Injection date: 9/1/2017 3:35 PM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036

Pressure at start: 9 bar
Start flow: 0.500 ml/min
Columns oven: 30.01 °C

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7.67 BV | 48.56 | 5899.83 | 2993.15 | 0.27
13.01 VB | 56.44 | 7643.16 | 3633.88 | 0.45
Sum | 100.00 | 135413.93

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-232
Data file: C:\SNOOPY\FV\FV232.D
Description: The sample is solved in DCM/MP
Injection date: 9/4/2017 4:21 PM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036

Pressure at start: 19 bar
Start flow: 0.500 ml/min
Columns oven: 29.99 °C

Name | FV-232 | RT [min] | Area% | Area | Height Width [min]
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7.62 BB | 79.27 | 6805.80 | 483.59 | 0.21
13.01 BB | 20.73 | 1727.28 | 63.59 | 0.42
Sum | 100.00 | 8333.08

Chiral 1260 Infinity
Page 1

Agilent 1260 Infinity
Page 1
(S)-2-(4-Chlorophenyl)-4-hydroxy-4-(1H-indol-3-yl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (5c)
(S)-5-Ethyl-4-hydroxy-4-(1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5d)
(S)-4-Hydroxy-4-(1H-indol-3-yl)-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5e)

Sample name: FV-223
Data file: C:\SNOOPY\DIFF\FV223.D
Description: Mobile phase: n-Heptane/iPrOH 7:3. The sample is solved in DCM/MP
Injection date: 8/29/2017 11:07:41 AM
Acq. Analysis method: CHIRALPAK-IA.M
Column: Chiralpak IA, (250 x 4,6) mm, 5µ, SN: IA00CE-RC036

Pressure at start: 42 bar
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(R)-5-(tert-Butyl)-4-hydroxy-4-(1H-indol-3-yl)-2-phenyl-2,4-
dihydro-3H-pyrazol-3-one (5f)

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-224
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Description: Mobile phase: n-Heptane/iPrOH 7:3;
The sample is solved in DCM/MP
Injection date: 8/26/2017 11:58 AM
Acq. Analysis method: CHIRALPAK IA-M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036
Pressure at start: 42 bar
Start flow: 0.700 ml/min
Column oven: 29.99 °C

Name | FV-224 | RT [min] | Type | Area% | Area | Height Width [min]
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9.91 | BB | 9.91 | 46.77 | 27334.58 | 1670.10 | 0.22
11.62 | VB | 11.60 | 53.33 | 31030.61 | 1584.38 | 0.29
Sum | | | 100.00 | 58365.19 | | 0.29

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11.80 | BB | 11.80 | 54.99 | 2751.61 | 161.35 | 0.25
Sum | | | 100.00 | 5004.47 | | 0.25

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-230
Data file: C:\SNOOPY\FF\FF\FV230.D
Description: Mobile phase: n-Heptane/iPrOH 7:3;
The sample is solved in DCM/MP
Injection date: 8/29/2017 11:23:47 AM
Acq. Analysis method: CHIRALPAK IA-M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036
Pressure at start: 42 bar
Start flow: 0.700 ml/min
Column oven: 29.99 °C

Name | FV-230 | RT [min] | Type | Area% | Area | Height | Width [min]
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11.80 | BB | 11.80 | 54.99 | 2751.61 | 161.35 | 0.25
Sum | | | 100.00 | 5004.47 | | 0.25
(R)-4-Hydroxy-4-(1H-indol-3-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one (5g)
(S)-4-(7-Bromo-1H-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5h)

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-235
Data file: C:\SNOOPY\DIFF\FV235.RIC.D
Description: Mobile phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/Me
Injection date: 9/2/2017 1:04:15 AM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036

Pressure at start: 20 bar
Start flow: 0.500 ml/min
Column oven: 30 °C

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AK Prof. Enders - Analytiklabor 4.04

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Injection date: 9/4/2017 5:54:19 PM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036

Pressure at start: 19 bar
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(S)-4-Hydroxy-4-(5-iodo-1H-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5i)

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**Start flow:** 0.500 ml/min
**Column oven:** 26.69 °C

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**Acq. Analysis method:** CHIRALPAK-IC.M

**Column:** Chiralpak IC, (150 x 4.6) mm, 5µ, SN: IC00CD-QF015
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**Column oven:** 30.01 °C

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(S)-4-[(5-Fluoro-1H-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5j)

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**Column:** Chiralpak IC, (150 x 4,6) mm, 5µ, SN: IC00CD-QF015

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(S)-4-(1H-benzo[g]indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5k)
Chiralpak IC, (150 x 4.6) mm, 5µ, SN: IC00CD-QF015

Column:

Pressure at start: 20 bar
Start flow: 0.500 ml/min
Column oven: 29.90 °C

Sample name: FV-243
Data file: C:\SNOOPY\DIFF\FV243.D
Injection date: 9/8/2017 5:50:28 PM
Acq. Analysis method: CHIRALPAK-IC.M

Injection date: 9/8/2017 8:53:50 PM
Data file: FV-246
Sample name: FV-246
Acq. Analysis method: CHIRALPAK-IC.M

Column:

Pressure at start: 21 bar
Start flow: 0.500 ml/min
Column oven: 29.90 °C

Sample name: FV-246
Data file: C:\SNOOPY\DIFF\FV246.D
Description: Mobil phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
Acq. Analysis method: CHIRALPAK-IC.M

Injection date: 9/8/2017 8:53:50 PM
Data file: FV-246
Sample name: FV-246
Acq. Analysis method: CHIRALPAK-IC.M

Column:

Pressure at start: 21 bar
Start flow: 0.500 ml/min
Column oven: 29.90 °C

Sample name: FV-246
Data file: C:\SNOOPY\DIFF\FV246.D
Description: Mobil phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
Acq. Analysis method: CHIRALPAK-IC.M

Injection date: 9/8/2017 8:53:50 PM
Data file: FV-246
Sample name: FV-246
Acq. Analysis method: CHIRALPAK-IC.M

Column:
(S)-4-Hydroxy-5-methyl-4-(5-methyl-1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5m)

AK Prof. Enders - Analytiklabor 4.04

Sample name: FV-244
Data file: C:\SNOOPY\DIFF\FV244.D
Description: Mobile phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
Injection date: 9/8/2017 6:51:25 PM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IC, (150 x 4.6) mm, 5µ, SN: IC00CD-QF015

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Pressure at start: 30 bar
Start flow: 0.500 ml/min
Column oven: 29.98 °C

Sample name: FV-247
Data file: C:\SNOOPY\DIFF\FV247.D
Description: Mobile phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
Injection date: 9/8/2017 9:54:58 PM
Acq. Analysis method: CHIRALPAK-IC.M
Column: Chiralpak IC, (150 x 4.6) mm, 5µ, SN: IC00CD-QF015

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</table>

Pressure at start: 21 bar
Start flow: 0.500 ml/min
Column oven: 29.99 °C
4-Hydroxy-5-methyl-4-(1-methyl-1H-indol-3-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5n)

**Sample name:** FV-234
**Data file:** C:\SNOOPY\DIFF\FV234RIC.D
**Description:** Mobile phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
**Injection date:** 9/1/2017 11:53:08 PM
**Acq. Analysis method:** CHIRALPAK-IC.M
**Column:** Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036
**Pressure at start:** 19 bar
**Flow setup:** 0.500 mL/min
**Column oven:** 30 °C

---

**Sample name:** FV-238
**Data file:** C:\SNOOPY\FV238.D
**Description:** Mobile phase: n-heptane/iPrOH 8:2
The sample is solved in DCM/MP
**Injection date:** 9/4/2017 5:23:13 PM
**Acq. Analysis method:** CHIRALPAK-IC.M
**Column:** Chiralpak IA, (250 x 4.6) mm, 5µ, SN: IA00CE-RC036
**Pressure at start:** 19 bar
**Flow setup:** 0.500 mL/min
**Column oven:** 29.99 °C

---

Name | FV-234
---|---
RT [min] | Type | Area% | Area | Height | Width [min]
8.19 | BB | 50.90 | 20667.77 | 1393.72 | 0.23
16.80 | BB | 49.98 | 20853.21 | 691.13 | 0.47
Sum | 100.00 | 41720.98 | | |

Name | FV-238
---|---
RT [min] | Type | Area% | Area | Height | Width [min]
8.19 | BB | 50.69 | 859.23 | 53.75 | 0.23
16.84 | BB | 49.31 | 787.10 | 25.99 | 0.46
Sum | 100.00 | 1596.33 | | |