Supporting Information

Atropisomeric Racemization Kinetics of MRTX1719 Using Chiral Solvating Agent-Assisted $^{19}$F NMR Spectroscopy

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General experimental and materials

All chemicals were purchased from commercial suppliers and used as received unless otherwise indicated. MRTX1719 was synthesized as described before.\textsuperscript{1} TBPTA was purchased as racemic and separated using preparative chiral SFC. All other CSAs were purchased as enantiopure materials and used without further purification. 2 M HCl in MeOH was prepared by diluting 3 M HCl in MeOH (Sigma #90964) with MeOH.

NMR Spectra of CSA screen

General sample preparation. A 1 mg sample of racemic free base MRTX1719 was dissolved in 0.7 mL od D\textsubscript{2}-TCE and 5, 10 or 20 eq of a CSA was added. Selected \textsuperscript{1}H NMR and/or \textsuperscript{19}F NMR data are shown below.
$^1$H NMR with CSA (+)-Pirkle’s alcohol

![NMR spectra with CSA](image-url)

5 eq

20 eq

 EW14002-1267-P1D1.1.fid
 EW14002-1267-P1D1 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D2.1.fid
 EW14002-1267-P1D2 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D1.1.fid
 EW14002-1267-P1D1 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D2.1.fid
 EW14002-1267-P1D2 C2Cl4D2 Bruker_A_400MHz

5 eq

20 eq

 EW14002-1267-P1D1.1.fid
 EW14002-1267-P1D1 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D2.1.fid
 EW14002-1267-P1D2 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D1.1.fid
 EW14002-1267-P1D1 C2Cl4D2 Bruker_A_400MHz

 EW14002-1267-P1D2.1.fid
 EW14002-1267-P1D2 C2Cl4D2 Bruker_A_400MHz
$^{19}$F,$^1$H{NMR with CSA (+)-Pirkle’s alcohol

![NMR Spectra]

5 eq

20 eq

EW14002-1267-P1D1.2.fid
EW14002-1267-P1D1
C2Cl4D2
Bruker_A_400MHz

EW14002-1267-P1D2.2.fid
EW14002-1267-P1D2
C2Cl4D2
Bruker_A_400MHz
$^1$H NMR with CSA (-)-TBPTA

![NMR Spectra](EW24742-218-P1B1.1.fid)

- 5 eq
- 20 eq

![NMR Spectra](EW24742-219-P1B1.1.fid)

- 5 eq
- 20 eq

![Chemical Structure](EW24742-218-P1B1.1.fid)

- 23-H
- 19-H
- 12-H

![Chemical Structure](EW24742-219-P1B1.1.fid)

- 23-H
- 19-H
- 12-H
$^{19}$F{¹H} NMR with CSA (-)-TBPTA

- 5 eq
- 20 eq
$^1$H NMR with CSA Reychler’s acid
$^{19}\text{F}\{^1\text{H}\}$ NMR with Reychler’s acid

$^1$H NMR with Reychler’s acid

5 eq

20 eq
$^1$H NMR with CSA (-)-MTPA
$^{19}$F-$^{1}$H NMR with (-)-MTPA

5 eq

20 eq
$^1$H NMR with CSA Δ-TRIPSPHAT

0 eq

1 eq

10 eq

23-H

EW14002-1245-P1A1.1.fid
EW14002-1245-P1A2
C2Cl4D2
Bruker_A_400MHz

EW14002-1245-P1A3.1.fid
EW14002-1245-P1A3
C2Cl4D2
Bruker_A_400MHz
$^{19}$F-$^1$H NMR with CSA Δ-TRIPSPHAT

0 eq

1 eq

10 eq
$^1$H NMR with CSA (+)-TiPSY
$^{19}$F{${}^1$H} NMR with CSA (+)-TiPSY

![Graph showing $^{19}$F{${}^1$H} NMR spectra with CSA (+)-TiPSY for 5 eq and 20 eq of the compound. The spectra show distinct peaks at different ppm values, indicating the presence of the compound in the samples.](image-url)
Data acquisition and signal processing for NMR-controlled racemization experiment

NMR spectra were acquired at 300K in tetrachloroethane-d2 on a Bruker 400 MHz spectrometer equipped with a BBO Plus probe and reprocessed with MNova. \(^1\)H NMR spectra were acquired with the zg30 sequence and \(^1\)H decoupled \(^{19}\)F NMR spectra with the zgfhigqn sequence. For determination of racemization kinetics, the \(^1\)H decoupled \(^{19}\)F NMR spectra were acquired at 376 MHz with 64K real data points and a d1 of 5 secs (except for the 353K experiments at 4 and 8 hr that were acquired with a d1 of 1 sec). Satisfactory data was obtained at number of transient (number of scans, NS) as low as 8, but we elected to use NS 128 for enhanced accuracy of the kinetics study. The resulting fids were zero filled to 512K, fourier transformed with a Stanning function of 8, base line corrected with a Whittaker Smoother, and peak picked using quantitative GSD. Integrals were obtained from GSD peak areas except for the 313K experiments for which line fitting was used as a result of non-ideal peak shapes.

NMR study conditions refinement

Several observations were made during testing conditions for experimental determination of \(\Delta E_{rot}\) that helped in obtaining most reliable results: 1) Quality consistency of the initial enantiopure sample was important for achieving reliable resolution of peaks in \(^{19}\)F NMR and improved peak shape. Therefore, re-crystallized from alcohol sample was used. 2) In agreement with some prior reports\(^2,3\) presence of (+)-TiPSY has accelerating effects on the rate of racemization. As a result, we conducted sample heating in a pure solvent (without CSA present) and only added (+)-TiPSY to a sample that was cooled to room temperature and then determined ratio of enantiomers using \(^{19}\)F NMR.

Correlation between \(^{19}\)F NMR and HPLC data

Table S1. Racemization of free base MRTX1719 tracked by chiral HPLC vs \(^{19}\)F NMR with (+)-TiPSY

| Sample heating conditions* | HPLC* | NMR# |
|---------------------------|-------|------|
|               | area % | % ee | area (integrated) | % ee |
| isomer (+) | isomer (-) | isomer (+) | isomer (-) |
| 24h at 80 °C | 41.5 | 58.5 | 0.75 | 14.3 |
| 48h at 80 °C | 48.8 | 51.2 | 2.4 | 1.01 | 9.2 |
| 48h at 60 °C | 26.2 | 73.8 | 47.6 | 0.38 | 1 | 44.9 |
48h at 40 °C | 3.7 | 96.3 | 92.6 | 0.05 | 1 | 90.5

* heating conducted in D$_2$-TCE

a)

b)

R$^2$ = 0.9898
Figure S1. a) Processed $^{19}$F NMR and data and relative areas in HPLC for each corresponding sample. b) Correlation between $^{19}$F NMR and HPLC data.

Calculations of experimental racemization rate constants and torsion rotational energy barrier

**General equations and considerations**

Below is a general review of kinetics of atropisomerization (or, indeed, any racemization reaction), assuming first-order kinetics. The rate constant for conversion from one enantiomer, $A$, into another, $B$, is assumed to be the same as the rate for conversion in the opposite direction and can be described by a rate constant, $k_e$. In terms of the rate equations, the change in population of each species can be written as follows:

$$\frac{d[A]}{dt} = -k_e([A] - [B]) \quad \text{Eq. (1)}$$

$$\frac{d[B]}{dt} = k_e([A] - [B]) \quad \text{Eq. (2)}$$

Taking the difference of the above two equations gives the following equation:

$$\frac{d([A] - [B])}{dt} = -2k_e([A] - [B]) \quad \text{Eq. (3)}$$

which, in turn, can be rewritten in terms of enantiomeric excess, $ee$, as follows:

$$\frac{d(ee)}{dt} = -2k_e(ee) \quad \text{Eq. (4)}$$

since the total concentration of the two enantiomers, $[A] + [B]$, is constant and $ee$ is defined according to the following relation:

$$ee = \frac{([A] - [B])}{([A] + [B])} \quad \text{Eq. (5)}$$

Rearranging Eq. (4) and integrating yields the following linear relation

$$\ln (ee) = -2k_et + \ln (ee_0) \quad \text{Eq. (6)}$$

where $(ee_0)$ is the initial enantiomeric excess and is equal to 1.0 when starting from a pure enantiomer, $A$.

A plot of the natural logarithm of the enantiomeric excess versus time according to Eq. (6) has a slope with the following magnitude:
In other words, the rate constant for racemization is twice the rate constant for the reaction of an individual enantiomer. This is due to the fact that conversion of one molecule of \( A \) into one molecule of \( B \) reduces the contribution to the enantiomeric excess by two molecules. Equilibrium in a racemization experiment is reached when both enantiomers are present in solution in equal concentrations, corresponding to \( ee = 0 \).

Finally, the half-life for the racemization process, \( t_{1/2} \), can be calculated by rearranging Eq. (6) and making use of Eq. (7):

\[
t_{1/2} = \frac{\ln (2)}{k_{rac}} = \frac{\ln (2)}{2k_e}
\]

These equations are used for analysis of NMR or HPLC data.

Once the rate constants (\( k_e \) and \( k_{rac} \)) have been determined at several different temperatures, it is possible to extract the activation energy for enantiomerization using the Eyring equation:

\[
k_e = \left( \frac{k_B T}{h} \right) e^{-\Delta G_{e}^{\ddagger}(T)/RT}
\]

where \( k_B \) is the Boltzmann constant (1.381 x 10\(^{-23} \) J K\(^{-1} \)), \( h \) is Planck’s constant (6.626 x 10\(^{-34} \) J s), and \( \Delta G_{e}^{\ddagger} \) is the free energy of activation for enantiomerization (or torsion rotational energy barrier).

The Gibbs free energy of activation for enantiomerization can be divided into an enthalpic (\( \Delta H_{e}^{\ddagger} \)) and an entropic (\( \Delta S_{e}^{\ddagger} \)) terms:

\[
\Delta G_{e}^{\ddagger}(T) = \Delta H_{e}^{\ddagger} - T \Delta S_{e}^{\ddagger}
\]

Substituting Eq. (10) into Eq. (9) and linearizing gives a form of the Eyring equation that is useful for analysis:

\[
\ln \left( \frac{k_e}{T} \right) = -\left( \frac{\Delta H_{e}^{\ddagger}}{R} \right) \left( \frac{1}{T} \right) + \left[ \left( \frac{\Delta S_{e}^{\ddagger}}{R} \right) + \ln \left( \frac{k_B h}{R} \right) \right]
\]

Using Eq. (11) it is possible to plot the natural logarithm of \( (k_e/T) \) versus the inverse temperature and extract \( \Delta H_{e}^{\ddagger} \) from the slope and \( \Delta S_{e}^{\ddagger} \) from the intercept. From these values, \( \Delta G_{e}^{\ddagger} \) (or \( \Delta E_{rot} \)) can be calculated at a given temperature using Eq (10).
The results of the calculations are summarized in Table 2.

$^{19}$F NMR-controlled kinetics

\[ y = -0.0007x - 0.0472 \]
\[ R^2 = 0.8173 \]

\[ y = -0.0124x - 0.2411 \]
\[ R^2 = 0.965 \]
Figure S2. $^{19}$F NMR-controlled racemization kinetics measured at a) 313K b) 333K or c) 353K.
**Table S2.** Summary of $^{19}$F NMR kinetics data

| T, K | 1/Temp | $k_{rac}$ hrs$^{-1}$ | $t_{1/2}$, hrs | $k_{e}$ hrs$^{-1}$ | $k_{e}$ s$^{-1}$ | $\ln(k_{e}/T)$ seconds$^{-1}$ |
|------|--------|----------------------|----------------|------------------|----------------|--------------------------|
| 313  | 0.003195 | 0.0007               | 990.2103       | 0.00035          | 9.72E-08       | -21.89246972             |
| 333  | 0.003003 | 0.0124               | 55.89897       | 0.0062           | 1.72E-06       | -19.0800376              |
| 353  | 0.002833 | 0.6481               | 1.069507       | 0.32405          | 9E-05          | -15.18201464             |

**Chiral HPLC-controlled kinetics**

HPLC method:
Chiral NP-HPLC with UV Detection
Agilent Series 1100 HPLC instrument with an Agilent 1260 Infinity degasser and Chromeleon Version 7.2.10 software.

**Table S3.** Parameters for the adapted, substance-specific HPLC method used for the kinetic measurements kinetic measurements on MRTX1719 HCl in 2 M methanol.$^{b)}$

| Parameter                  | Description                                                                 |
|----------------------------|-----------------------------------------------------------------------------|
| column (chiral)            | Chiralpak IC-3 C18, 50 mm x 4.6 mm, 3-μm particles                           |
| sample dilution system     | 30:70 (v/v) 0.05% DEA in heptane/0.05% DEA in EtOH                           |
| mobile phase (isocratic)   | 30:70 (v/v) 0.05% DEA in heptane/0.05% DEA in EtOH                           |
| run time of experiment     | 15 min                                                                      |
| flow                       | 1.0 mL min$^{-1}$                                                           |
| concentration              | approximately 0.23-0.24 mg mL$^{-1}$ (for reference solution)               |
| injection volume           | 10 μL                                                                       |
| detection                  | 220 nm                                                                      |
| column temperature         | 25°C                                                                        |
| retention time of initial API | 7.1-7.8 min $^{a)}$                                      |
| retention time of new enantiomer | 4.5-4.7 min $^{a)}$                                      |

$^{a)}$ The observed retention time varies slightly from sample to sample.

$^{b)}$ Similar HPLC method was used for kinetic measurements on free base MRTX1719 in DMSO.
Data for MRTX1719 HCl Salt in 2 M HCl in MeOH

Sample preparation and heating: ~5mg of MRTX1719 HCl salt was dissolved in 1mL 2 M HCl in MeOH (corresponding to an initial concentration of ~10 mM) and equilibrated in an Eppendorf Thermomixer comfort shaker at the given temperature and a shaking rate of 700 rpm for given amount of time. Most samples were injected without any pre-treatment other than dilution, but the solutions at 30°C were cloudy, so they were divided into two portions. One portion was diluted prior to injection, leading to clarification, and the other was filter-centrifuged through a 0.2-micron PVDF membrane prior to dilution and analysis.

Table S4. MRTX1719 HCl Salt in 2 M HCl in MeOH racemization summary

| time heated, days | % ee mean (n=2) |
|-------------------|-----------------|
|                   | 303K            | 303K†           | 313K  | 323K  | 333K  |
| 1                 | 93.8            | 96.1            | 93.1  | 91.9  | 72.1  |
| 2                 | 95.6            | 97.3            | 92.6  | 91.8  | 55.3  |
| 7                 | 93.9            | 97.0            | 85.7  | 70.1  | 46.8  |
| 14                | 91.1            | 94.4            | 79.2  | 51.9  | 1.1   |
| 21                | 88.4            | 91.4            | 71.4  | 38.3  | 0.1   |
| 28                | 87.8            | 88.9            | 65.5  | 30.2  | N/A   |

# unfiltered data
† filtered data
a) 

\[ y = -0.0031x - 0.0484 \]

\[ R^2 = 0.9291 \]

b) 

\[ y = -0.0032x - 0.0216 \]

\[ R^2 = 0.9218 \]
Figure S3. Racemization kinetics of MRTX1719 HCl salt in 2 M MeOH at a) 303K – the samples were not filtered before HPLC runs b) 303K – the samples were filtered before HPLC runs c) 313K d) 323K e) 333K

Table S5. Summary of MRTX1719 HCl salt in 2 M MeOH kinetics data

| T, K | 1/Temp | k_{rac} days^{-1} | t1/2, hrs | k_{eq}, s^{-1} | ln(k_{eq}/T) seconds^{-1} |
|------|--------|------------------|----------|----------------|-------------------|
| 303  | 0.003300 | 0.0031#          | 5366.301# | 1.79E-08#      |                   |
| 303  | 0.003300 | 0.0032¶          | 5198.604¶ | 1.85E-08¶      |                   |
| 303  | 0.003300 |                |          | 1.83E-08@       | -23.53397577*     |
| 313  | 0.003195 | 0.0132          | 1260.268 | 7.64E-08       | -22.13363178     |
| 323  | 0.003096 | 0.0426          | 390.5055 | 2.47E-07       | -20.99344348     |
| 333  | 0.003003 | 0.3318          | 50.13723 | 1.92E-06       | -18.97125553     |

# unfiltered data
¶ filtered data
@ average of filtered and unfiltered
* obtained by taking an average k_{eq} between filtered and unfiltered data to compute this value, plotted in Figure SI-2
Figure S4. Eyring plot for MRTX1719 HCl salt in 2 M MeOH

*Data for MRTX1719 Free Base in DMSO*

Sample preparation and heating: ~5mg of MRTX1719 free base was dissolved in 1mL DMSO in (corresponding to an initial concentration of ~10 mM) and equilibrated at the given temperature with stirring of 700 rpm for given amount of time.

*Table S6. MRTX1719 free base in DMSO racemization summary*

| Temperature | Time point, hrs | % ee |
|-------------|----------------|------|
| 333K        | 1              | 100.0|
|             | 4              | 98.8 |
|             | 8              | 97.9 |
|             | 24             | 93.8 |
|             | 32             | 88.4 |
| Time point, hrs | % ee  |
|----------------|-------|
| 0              | 100   |
| 1              | 100   |
| 4              | 100   |
| 8              | 100   |
| 24             | 99.1  |
| 48             | 100   |
| 72             | 100   |
| 96             | 100   |
| 120            | 89.6  |
| 144            | 85.9  |

| Temperature | Time point, hrs | % ee  |
|-------------|----------------|-------|
| 323K        | 48             | 86.1  |
|             | 56             | 81.1  |
|             | 72             | 80.9  |
|             | 96             | 68.9  |
|             | 120            | 57    |
|             | 144            | 55.3  |
| Temperature | Time point, hrs | % ee |
|-------------|----------------|------|
| **343K**    |                |      |
| 1           | 100            |      |
| 4           | 98.7           |      |
| 8           | 96.3           |      |
| 24          | 76.8           |      |
| 48          | 58.7           |      |
| 72          | 40.4           |      |
| 96          | 26.2           |      |
| 120         | 19.1           |      |
| 144         | 12.9           |      |
| **353K**    |                |      |
| 1           | 100            |      |
| 2           | 100            |      |
| 4           | 98             |      |
| 6           | 95.2           |      |
| 8           | 92.4           |      |
| 10          | 90.4           |      |
| 24          | 63.4           |      |
| 32          | 52             |      |
| 48          | 36.4           |      |
| 56          | 29.7           |      |
| Temperature | Time point, hrs | % ee |
|-------------|----------------|------|
| 363K        | 1              | 97.6 |
|             | 2              | 96.7 |
|             | 4              | 83.2 |
|             | 6              | 71.7 |
|             | 8              | 60.9 |
|             | 10             | 50.6 |
|             | 24             | 6.9  |
|             | 32             | 1.1  |
| 373K        | 1              | 100  |
|             | 2              | 91.6 |
|             | 4              | 45.9 |
|             | 6              | 28.6 |
|             | 8              | 17.1 |
|             | 10             | 10.8 |
|             | 24             | 0.4  |
a) Racemization kinetics of **MRTX1719 FB** in DMSO at 323K

\[
y = -0.0008x + 4.6208 \\
R^2 = 0.6297
\]

b) Racemization kinetics of **MRTX1719 FB** in DMSO at 333K

\[
y = -0.0043x + 4.6314 \\
R^2 = 0.9711
\]
c) Racemization kinetics of MRTX1719 FB in DMSO at 343K

\[ y = -0.0144x + 4.6795 \]
\[ R^2 = 0.9962 \]

---

d) Racemization kinetics of MRTX1719 FB in DMSO at 353K

\[ y = -0.0298x + 4.8166 \]
\[ R^2 = 0.9304 \]
Figure S5. HPLC-controlled racemization kinetics measured at a) 323K b) 333K c) 343K d) 353K e) 363K f) 373K
Table S7. Summary of MRTX1719 FB in DMSO kinetics data

| T, K   | 1/T     | $k_{rac}$ hrs$^{-1}$ | $k_{rac}$ s$^{-1}$ | ln($k_e/T$) seconds$^{-1}$ |
|--------|---------|----------------------|-------------------|--------------------------|
| 323    | 0.003096| 0.0008               | 2.222E-07         | -21.79038746             |
| 333    | 0.003003| 0.0043               | 1.194E-06         | -20.13911905             |
| 343    | 0.002915| 0.0144               | 0.000004          | -18.96009382             |
| 353    | 0.002833| 0.0298               | 8.278E-06         | -18.26155125             |
| 363    | 0.002755| 0.1428               | 3.967E-05         | -16.72254937             |
| 373    | 0.002681| 0.242                | 6.722E-05         | -16.2223228              |

Figure S6. Eyring plot for MRTX1719 FB in DMSO

Racemization rate in DMSO solution vs solid state

Described methods that investigate racemization kinetics in solution represent the extreme case that exaggerates real life storage conditions of an API. Shelf life of a crystalline solid API is expected to surpass solution API stability. To further demonstrate this we conducted a comparison
of enantiostability under accelerated racemization conditions at 100 °C for DMSO solution (used in one of chromatographic kinetic studies) vs. amorphous solid MRTX1719 HCl salt. Figure SI-4 tracks changes of enantiopurity in heated samples with time and demonstrates that racemization in solution proceeds at much faster rate than in solid form.

**Figure S7.** Racemization of MRTX1719 at 100 °C

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5. When considering activation energies and free energies of activation, it is more correct to speak in terms of enantiomerization, which is a molecular-level process, rather than racemization, which is a macroscopic process. In other words, \( k_e \) should be used rather than \( k_{rac} \). Of course, the two rates only differ by a factor of two (see Eq. (7)), so, in practice, it is easy to convert between the two.

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