Relaxation Dispersion NMR to reveal fast Dynamics in Brønsted Acid Catalysis: Influence of Sterics and H-bond strength on conformations and substrate hopping

N. Lokesh, Johnny Hioe, Johannes Gramüller and Ruth M. Gschwind*

Institute for organic chemistry,
University of Regensburg, D-93053 Regensburg, Germany

E-mail: ruth.gschwind@chemie.uni-regensburg.de

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Experimental data

Deuterated solvents were purchased from Deutero or Sigma Aldrich. Where dry solvents were essential, CD$_2$Cl$_2$ was freshly distilled over CaH$_2$ and Toluene was refluxed over Na/Benzophenone under argon atmosphere. The catalysts were purchased from Sigma Aldrich or STREM chemicals.

High-resolution mass spectra were measured by the central analytics division in the Institute of Organic Chemistry. Gas chromatography coupled with a mass selective detector was performed on an Agilent 6890N Network GC-System.
Synthesis of Imine Substrates

The imines were prepared as described in the literature.\textsuperscript{1–4} The toluene was used either in p.A. quality or was dried by refluxing over sodium. The \textsuperscript{15}N-enriched aniline (if used) was purchased from Euriso-top GmbH and Sigma Aldrich.

(E)-N,1-bis(4-(tert-butyl)phenyl)ethan-1-imine [5]

Molecular sieves 4 Å (4 g) was weighed into a 50 mL Schlenk flask and dried with a heat gun at 350 °C for 30 min under reduced pressure. Under Argon flow, 4-(tert-butyl)aniline (10.0 mmol, 1.49 g, 1.60 mL, 1.0 eq) and 1-(4-(tert-butyl)phenyl)ethan-1-one (10.0 mmol, 1.76 g, 1.83 mL, 1.0 eq.) were added and dissolved in 20 mL anhydrous toluene. Under Argon flow, a reflux condenser was added to the setup and flushed with argon for 3 min. A drying tube filled with CaCl\textsubscript{2} was added to the setup. The solution was refluxed for 24 h. Afterward, the heating bath was removed, and the reaction mixture allowed to cool down. The orange mixture was filtrated, and the solvent was removed under reduced pressure to give an orange-yellow solid. The crude product was washed with methanol to give the product (4.76 mmol, 1.46 g, 48%) as yellow needles predominantly as its \textit{E}-isomer (>99% determined by \textsuperscript{1}H NMR).

\textsuperscript{1}H-NMR (400.1 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta_{\text{H}} = 7.91\) (m, 2H), 7.48 (m, 2H), 7.37 (m, 2H), 6.71 (m, 2H), 2.21 (s, 3H), 1.36 (s, 9H), 1.34 ppm (s, 9H).

\textsuperscript{13}C-NMR (100.6 MHz): \(\delta_{\text{C}} = 164.8, 153.7, 149.2, 145.8, 137.0, 126.8, 125.7, 125.2, 119.0, 34.7, 34.1, 31.2, 31.0, 16.9\) ppm.

HR-MS (ESI, m/z): found 307.2289 (M)+ (calculated for 307.2300 for C\textsubscript{22}H\textsubscript{29}N); Diff(ppm) = -1.92 ppm.
Sample preparation

*Preparation of binary complexes in CD$_2$Cl$_2*

The catalyst was dried for 30 min at 150°C under reduced pressure. Ketimine and catalyst were directly weighed into a 5 mm NMR tube under an inert argon atmosphere. CD$_2$Cl$_2$ (0.6 ml; freshly destilled over CaH$_2$) and 1.0 ml of tetramethylsilane atmosphere were added to the tube. The sample was stored in an -80°C freezer. A 1:1 ratio of catalyst/ketimine was used for all samples unlike stated otherwise. A concentration of 0.25 – 100 mM was used, as indicated specifically.
NMR experiments were performed on Bruker Avance III HD 400 MHz spectrometer, equipped with 5 mm BBO BB-1H/D probe head with Z-Gradients and a Bruker Avance III HD 600 MHz spectrometer, equipped with a 5 mm CPPBBO BB-1H/19F. The temperature was controlled in the VT-experiments by BVT 3000 and BVTE 3900. For NMR measurements employing standard NMR solvents 5 mm NMR tubes were used, if not otherwise noted. NMR Data were processed, evaluated and plotted with TopSpin 3.2 software. Further plotting of the spectra was performed with Corel Draw X14 – X17 software. ¹H,¹³C chemical shifts were referenced to TMS or the respective solvent signals. The heteronuclei ¹⁹F and ³¹P were referenced, employing \( \nu(X) = \nu(TMS) \times \Xi_{\text{reference}} / 100 \% \) according to Harris et al.⁵ The following frequency ratios and reference compounds were used: \( \Xi(¹⁹F) = 94.094011 \) (CCl₃F), \( \Xi(³¹P) = 40.480742 \) (H₃PO₄).

**Pulse programs**

All pulse programs used are standard Bruker NMR pulseprograms except for the \( R_{1,\delta} \) measurements.

**Acquisition Parameters**

**¹H NMR:** Pulse program: zg; Relaxation delay = 2 – 3 s, Acquisition time = 2.48 s, SW = 22.0 ppm, TD = 64k, NS = 8 – 64; zg30; Relaxation delay = 2 s, Acquisition time = 2.48 s, SW = 22.0 ppm, TD = 64k, NS = 8 – 64;

**2D-¹H,¹H NOESY:** Pulse program: noesygpph/noesygpphpp; Relaxation delay = 5 - 8 s, NS = 8-32, mixing time (D8) = 300.00 ms; TD = 4096; increments = 512 - 1k;

**2D-¹H,¹H COSY:** Pulse program: cosygpqf; Relaxation delay = 5 - 8 s, NS = 8-32, TD = 4096; increments = 512 - 1k;

**¹³C NMR:** Pulse program: zgpg30; Relaxation delay = 2.00 s, Acquisition time = 0.80 s, SW = 270.0 ppm, TD = 64k, NS = 1k – 2k;

**2D-¹H,¹³C HSQC:** Pulse program: hsqcedetgpsisp2.3; Relaxation delay = 4 - 8 s, NS = 8-32, \( J_{XH} = 145 \) Hz; TD = 4096; increments = 512 - 1k;

**2D-¹H,¹³C HMBC:** Pulse program: hmbcgplpndqf; Relaxation delay = 4 - 8 s, NS = 8-32, \( J_{XH} = 145 \) Hz, \( J_{XH}(\text{long range}) = 10 \) Hz; TD = 4096; increments = 512 - 1k;

**2D-¹H,³¹P HMBC:** Pulse program: inv4gplmdqf; Relaxation delay = 4 - 8 s, NS = 8-32, TD = 4096; increments = 256 - 1k;

**¹⁵N NMR:** Pulse program: zg; Relaxation delay = 10.00 s, Acquisition time = 0.54 s, SW = 502.8 ppm, TD = 32k, NS = 256 – 2048;

**2D-¹H,¹⁵N HMBC:** Pulse program: inv4gplmdqf; Relaxation delay = 5 - 8 s, NS = 16-32, delay for evolution of long range couplings (D6) = 20.00 ms; TD = 4096; increments = 128 - 512;

**¹⁹F-NMR:** Pulse program: zg30; Relaxation delay = 2 – 3 s, Acquisition time = 11.60 s, SW = 10.0 ppm, TD = 128k, NS = 8 – 64;
2D-\textsuperscript{1}H,\textsuperscript{19}F HOESY: Pulse program: hoesyph; Relaxation delay = 5 - 8 s, NS = 16-32, mixing time (D8) = 500.00 ms; TD = 4096; increments = 1k;
1D $^1$H off-resonance $R_{1\rho}$

**Pulse Sequence**

The recent reported 1D $^1$H off-resonance $R_{1\rho}$ pulse sequence is adopted with slight modification for our measurement.$^6$\textsuperscript{,7}

![Pulse Sequence Diagram]

$$R_{1\rho} = -\frac{1}{T} \ln \frac{I}{I_0}$$

**Figure 1:** Applied pulse sequence and mathematical relation to measure $R_{1\rho}$ experimentally. The applied angle ($\theta$) is 35°. A spinlock period (t) of 100 ms is applied. The filled (black) and unfilled rectangular pulses respectively indicate 90° and 180° hard pulses. The gradient pulses of $G_1 = 70\%$ and $G_2 = 40\%$ of the maximum were applied. $I_0$ is the intensity without any spinlock period and I is the intensity with spinlock period measured over a multiple effective magnetic field.

**Parameter Optimization**

The spinlock period (t) was incremented in 10 ms steps with maximum spinlock power ($\approx 20$ kHz). At each step, the temperature was monitored (sample heating can occur due to application of high intensity spinlock field over an extended time). Around 120 ms, temperature oscillation was observed. To avoid any influence of temperature changes on the measurement, the spinlock period of 100 ms was applied in all our measurements.

The normal relaxation period ($T-t$) in the absence of the spinlock is tested for 3 delays (50 ms, 100 ms and 150 ms). For all three different relaxation periods ($T-t$), we found similar exchange rates within the experimental errors. To minimise signal loss due to relaxation, ($T-t$) of 50 ms was used in all our measurements.
Method testing

To test the applicability of the $R_{1\rho}$ method, we applied the above described pulse sequence with optimized parameters on the known peak in the spectrum (para-methyl protons of the hydrolyzed imine ketone part), which does not experience any chemical exchange process (on a ms-µs timescale) and on the same proton for the CPA/imine complex which experiences chemical exchange. The measured rate for the hydrolyzed ketone showed a nearly straight line (no offset-Lorentzian decay with increasing effective field $\omega_{\text{eff}}$), which was expected for non exchanging protons. For the same proton in the binary CPA/imine complex, an offset-Lorentzian decay was observed, which demonstrates the presence of chemical exchange on a ms-µs timescale.

Figure 2: To test the method, we selected the proton peak of the $p$-methyl group in the hydrolyzed ketone moiety (red shaded) and the proton peak of the $p$-methyl imine in the TRIP/imine binary complex (green shaded) within the same sample (to maintain identical conditions). The hydrolyzed ketone does not undergo any chemical exchange on a ms-µs timescale. The corresponding measured $R_{1\rho}$ data at 180 K with incremental effective field showed a near horizontal line, proving the absence of chemical exchange (left side). On the other hand, the imine inside the catalyst undergoes $E_{\text{I}} \rightleftharpoons E_{\text{II}}$ exchange and thus the corresponding $R_{1\rho}$ data at 185, 180 and 175 K with incremental effective field showed offset-Lorentzian decays for the $p$-methyl protons in the TRIP/imine complex. This confirms the presence of chemical exchange process and hence validates our method for chemical exchange detection in ms-µs range.
Curve fitting

In order to analyze the $R_{1\rho}$ measurements, the signal intensities (integrals) are determined for every effective field strength $\omega_{\text{eff}}$ (i.e. every different spinlock power) and normalized to the reference integral (spinlock power = 0 W). Initially, to extract $k_{\text{ex}}$, the measured experimental points are curve fitted to the following theoretically described equation by using MATLAB (see literature for further details):

$$\frac{R_{\text{eff}}}{\sin^2 \theta} = R_2 - R_1 + \frac{(\Delta \omega)^2 P_A P_B \tau_{\text{ex}}}{1 + \frac{2}{k_{\text{ex}} \omega_{\text{eff}}}}$$  \hspace{1cm} (Eq. 1)

Here

- $R_2$ is the transverse relaxation rate constant
- $R_1$ is the longitudinal relaxation rate constant
- $\Phi = (\Delta \omega)^2 P_A P_B \tau_{\text{ex}}$ encodes both chemical shift difference and population of the minor ($P_B$) and major ($P_A$) exchange species

$\Phi$ and the average isotropic chemical shift $\Omega$ (in ppm) are related by

$$\Phi = -\Omega^2 + a\Omega + b$$ \hspace{1cm} (Eq. 2)

Here,

- $a = 2\Omega_A - \Delta \omega$
- $b = \Omega_A (\Delta \omega - \Omega_A)$.

These can be rearranged as

$$\Delta \omega = (a^2 + 4b)^{1/2}, \text{ and } \Omega_{A,B} = \left\{ a \pm ; \left( a^2 + 4b \right)^{1/2} \right\}/2$$ \hspace{1cm} (Eq. 3)

$\Phi$ and $\Omega$ can be obtained experimentally at different temperatures. Assuming the chemical shift difference $\Delta \omega$ between major (A) and minor (B) species is constant, one can calculate $\Delta \omega$. From $\Delta \omega$ value and $\Phi$ values, populations can be extractable.

Directionality

For the chemical exchange between A and B, the exchange rate constant $k$ is: $k_{\text{ex}} = k_A + k_B$. By using populations and $k_{\text{ex}}$ one can extract rate constants $k_A$ and $k_B$ on both sides.
If a temperature independence within the varied range of 10 K is assumed, then the coefficients $a$ and $b$ can be determined by least squares optimization. Subsequently, $\Delta \omega$ is calculated by $\Delta \omega = (a^2 + 4b)^{1/2}$, and $\Omega_{A,B} = [a \pm (a^2 + 4b)^{1/2}]/2$. Once $\Delta \omega$ is known, $P_A$, $P_B$, $k_A$ and $k_B$ are obtained from $\Phi_{ex}$ and $k_{ex}$ at each temperature.

Hence, in order to separate the populations and chemical shift difference from the term $\phi$, it requires additional experimental $R_{1p}$ measurements at more than one temperature. Therefore we measured $R_{1p}$ experiments for each sample at two or three temperatures (185 K, 180 K and 175 K).

Results of the $R_{1p}$ measurements

**TRIP/3**

![Spectrum and data table]

Figure 3: $R_{1p}$ measurement for the TRIP/3 complex. The proton H$_1$ of the catalyst (marked in the spectrum, red shaded) was selected as probe. The offset-Lorentzian decay indicates the
presence of chemical exchange \(k_{\text{ex}} \approx 18000 \text{ s}^{-1} \text{ at } 180 \text{ K}\). With experimental data obtained at two different temperatures, the populations and directionality were extracted.

TRIP/2

Figure 4: \(R_{1p}\) measurement for TRIP/2 complex. The proton \(H_1\) of the catalyst (shaded in red) and the fluorine signals of the imine-CF\(_3\) group (shaded in green) were selected as probes. The offset-Lorentzian decay indicates presence of chemical exchange \(k_{\text{ex}} \approx 3-5 \times 10^3 \text{ s}^{-1} \text{ at } 180 \text{ K}\). With experimental data obtained at three different temperatures, the populations and directionality were extracted.
Figure 5: $R_{1p}$ measurement for TiPSY/1 complex, (to avoid signal overlap, the sample was prepared with nearly exclusive population of the $E$-complex; see above for sample preparation). The proton $H_1$ of the catalyst (shaded in red) was selected as probe. The offset-Lorentzian decay indicates presence of chemical exchange ($k_{ex} \approx 9$ ks$^{-1}$ at 180 K).
**Figure 6:** $R_{1p}$ measurements for TRIM/2 and TRIM/3 complexes. For TRIM/2, the CF$_3$ group of the imine was used as a probe (shaded in green) and for TRIM/3 the proton H$_1$ of the catalyst (shaded in red) was selected as probe. The offset-Lorentzian decay in both system indicates the presence of chemical exchange ($k_{ex} \approx 2000-3000$ s$^{-1}$ at 180 K).

For TRIM/2 and TRIM/3, the offset-Lorentzian decay fit does not match the experimental decay as precisely as for the other systems. Hence, a larger experimental error is expected. However, the $R_{1p}$ measurements for TRIM/2 and TRIM/3 complexes indicate, that similar exchange rates ($k_{ex} \approx 2000-3000$ s$^{-1}$ at 180 K) are obtained for TRIM/1-3 regardless of the hydrogen bond strength.
NMR-Structural analysis of CPA/imine complexes

The investigated complexes TRIP/1-3, TiPSY/1 and TRIM/1-3 were already described in the previous work. The NMR-structural analysis of TRIM/4 is described below. In addition, the backbone splitting of TiPSY/1 is discussed in detail below.

Chemical Shift assignment of TRIM/4

The $^1$H (black) and $^{13}$C (green) chemical shifts (in ppm) of all investigated complexes were assigned with standard 2D NMR experiments ($^1$H,$^1$H COSY, $^1$H,$^1$H TOCSY, $^1$H,$^1$H NOESY, $^1$H,$^{13}$C HSQC, $^1$H,$^{13}$C HMBC) at 180 K. The $^{31}$P (orange) chemical shift (in ppm) was assigned by $^1$H,$^{31}$P HMBC. Due to signal overlap and lacking resolution and intensity of 2D correlations, not all signals could be assigned.

In accordance with our previous analysis of hydrogen bond strengths, the $^1$H chemical shift of the hydrogen bond strength reflects the H-bond strength (in our system, higher chemical shifts correlate with stronger H-bonds). Hence, the H-bond strength of TRIM/4E (16.09 ppm) is in between TRIM/1E (16.26 ppm) and TRIM/3E (15.80 ppm).

Identification of Type I E and Type II E

Analogous to our previous work, for the Type I E structure, the tert-butyl group of the ketone part of the imine (marked in blue) is placed above the BINOL backbone. The blue NOE cross signals A and B to the Naphthyl backbone reveal the presence of the Type I E structure (Figure 7) for TRIM/4E. The NOE cross signal D (black) is a result of overlapping NOE signals between the tert-butyl group and the naphthyl backbone and the tert-butyl group and the attached...
phenyl ring (backbone: 8.00 ppm, phenyl ring of imine: 7.98 ppm). For the Type II E structure, the tert-butyl group of the aniline part of the imine is placed above the BINOL backbone and thus the red NOE cross signals A-D reveal the presence of the Type II E structure.

**Figure 7:** Excerpt of the \(^1\)H,\(^1\)H NOESY spectrum of TRIM/4 at 180 K and 600 MHz (100 mM sample) in CD\(_2\)Cl\(_2\). The blue NOE cross signals indicate the presence of the Type I E structure, while the red NOE signals indicate the presence of the Type II E structure.
**DOSY measurements of TRIM/4**

To prove, that the observed species in TRIM/4 are monomers of the binary complexes, DOSY measurements (Diffusion ordered spectroscopy) were performed to derive the molecular radii of the present species.

The DOSY measurements were performed with the convection suppressing DSTE (double stimulated echo) pulse sequence developed by Jerschow and Müller in a pseudo 2D mode. TMS was used to reference the viscosity of the solvent at 180 K. The diffusion time delay was set to 45 ms. The gradient pulse lengths (p16, SMSQ10.100 pulse shape) were optimized for each species to give a sigmoidal signal decay for varying gradient strengths. Optimal pulse lengths of 3.0 ms and 6.0 ms were found for TMS and TRIM/4, respectively. For each species, twenty spectra with linear varying gradient strength of 5% - 95% have been measured. The used probe signals for the analysis are listed in table 1. The signal intensities of the respective groups were analyzed as a function of the gradient strength by Bruker TopSpin 3.2 software T1/T2 relaxation package by employing the Stejskal-Tanner equation. No line broadening occurred for increasing gradient strength. The sigmoidal fit provided the translational self-diffusion coefficients $D_i$ listed in Table 1. The molecular radii were derived by the Stokes-Einstein equation using Chens correction.

$$D_i = \frac{k_B T}{6\pi \eta r_H} \cdot (1 + 0.695 \cdot \left(\frac{r_{\text{solv}}}{r_H}\right)^{2.234}) \quad (Eq. 4)$$

$D_i$ is the self-diffusion coefficient derived by the measurement, $\eta$ is the viscosity of the solvent, $r_H$ is the hydrodynamic radius of the observed molecule and $r_{\text{solv}}$ the radius of the solvent. No form factor correction was applied. The viscosity was determined by measuring the diffusion coefficient of the reference tetramethylsilane (TMS) and solving the equation for $\eta$ with the literature value of the radius of 2.96 Å. The solvent radius of CD$_2$Cl$_2$ (2.46 Å) was taken from the reference.

**Table 1**: Probe signals, measured diffusion coefficients and derived molecular radii for TRIM/5.

| Entry | Species | $p16$ [ms] | Observed signal [ppm] | $D_i$ [m$^2$/s] · 10$^{-12}$ | Averaged | $r_H$ [Å] |
|-------|---------|------------|----------------------|-----------------------------|----------|----------|
| 1     | TMS     | 3.10       | 0.00                 | 21.32                       |          |          |
| 2     | TRIM/4E | 6.00       | 1.16                 | 4.76                        |          |          |
| 3     | TRIM/4E | 6.00       | 2.64                 | 4.80                        | 4.69     | 9.54     |
| 4     | TRIM/4E | 6.00       | 7.77                 | 4.50                        |          |          |

The derived molecular radius (9.54 Å) is similar to the one reported previously for TRIM monomers. Thus, the DOSY measurements showed, that the species investigated by the $R_{1p}$ measurement is the binary TRIM/4E complex.
A general rotational correlation time of 10-50 ns was estimated for the investigated binary complexes of chiral phosphoric acids and imines with their hydration shell. Stokes Law (Eq. 5) was used to calculate the rotational correlation time based on the results of the DOSY measurements of TRIM/4E.

\[ \tau_c = \frac{4\pi \eta r^3}{3kT} \]  
(Eq. 5)

The radius of the binary complex of TRIM/4 with its hydration shell was determined by DOSY measurements (see respective chapter) and a radius of 9.54 Å was determined for the complex with its hydration shell. The viscosity \((3.05 \times 10^{-2} \text{ kg m}^{-1} \text{ s}^{-1})\) of the solution at 180 K was determined by Equation 4 based on the DOSY measurement on TMS. A rotational correlation time of 44.6 ns was calculated for TRIM/4E with its hydration shell. Given the bulkiness of the two tert-butyl substituents of imine 4, it is expected that the other investigated complexes have smaller radii, resulting in smaller rotational correlation times. Hence, a general rotational correlation time around 10 – 50 ns was estimated.
In the TiPSY/1 complex, the backbone splitting could not be resolved at 180 K and 600 MHz in CD$_2$Cl$_2$ (see figure). However, in our previous investigations we observed, that the backbone splitting in TiPSY complexes is very small and could often not be resolved sufficiently (see SI of literature). Goodman et al. demonstrated, that the binding pocket for TiPSY is significantly smaller than for TRIP (no rotation possible). The biggest binding pocket for the investigated CPAs was determined for TRIM (rotation possible). Hence, a rotation of the imine inside the binding pocket of TiPSY can be excluded, even if the backbone splitting can not be resolved sufficiently.

The sample was prepared with an exclusive population of the $E$-imine. To achieve that, the sample was prepared according to the general procedure described above. However, before adding the solvent, the NMR-tube with TiPSY and 1 was cooled to -90 °C in acetone/liquid N$_2$ and the precooled solvend was added to the tube. The low temperature suppressed $E \rightarrow Z$ isomerization of the imine.

**Figure 8**: Excerpt of the $^1$H,$^{31}$P HMBC spectrum of TiPSY/1 (E-only, 25 mM, TiPSY:1 = 1:1) at 180 K and 600 MHz in CD$_2$Cl$_2$. The sample was prepared with an exclusive population of $E$-imine species.
Exchange with free imines

Typically, in 1:1 complexes of TRIP, TRIM and TiPSY, the complexation of the imine was incompletely (≈ 25 % free imine present). Thus, for complexes with imines 1-3, the assignment of the free imines was done for the CPA/imine samples. For imine 4, a NMR sample with the imine only (50 mM, CD₂Cl₂, 180 K and 600 MHz) was measured and compared to the chemical shifts in the CPA/4 sample. For TRIM/4, no free imine was observed in the binary complex sample.

As the free imines 1-4 gave chemical shifts well separated from the respective CPA/E-imine complexes (see figure 9 for free imines and assignments of the binary complex in literature²), the exchange between free and complexated imine is slow on the NMR time scale. Thus, the exchange pathway via dissociation and re-association causing averaging of the BINOL backbone can be excluded to significantly contribute to the measured exchange rates in the R₁σ measurements.

Figure 9: Chemical shift assignment of the free imines 1-4 at 180 K in CD₂Cl₂.
Additional fitting of TRIM/1E

Due to the strong signal decay within the first few percent of the horizontal axis for TRIM/1E (Figure 6B in the manuscript), fewer data points are in the decay region relevant for the fit, which could affect the quality of the fit and thus the precision of the extracted rate. However, the fit curves for lower (500 s$^{-1}$) and higher (10 000 s$^{-1}$) exchange rates as the optimized one (2500 s$^{-1}$) significantly deviate from the data set (Figure 10).

Figure 10: Additional curve fitting for the signal decay of TRIM/1E with different exchange rates at a concentration of 5 mM. The determined exchange rate of 2500 s$^{-1}$ fits the data set best, while lower or higher exchange rates result in a significant offset. Other parameters, e.g. the population of $E$-I and $E$-II were not changed.

In addition, a TRIM/1E sample at different concentration (0.25 mM) was measured with more $\omega_{\text{eff}}$ increments. The extracted exchange rate of 2500 s$^{-1}$ is identical to the previous one and the fit for lower or higher exchange rates does not match the data set (Figure 11).

Hence, the quality of the fit for TRIM/1E is adequately precise to reveal, that the exchange rate for TRIM/1E is significantly lower than for TRIP/1E ($\approx$10 000 s$^{-1}$).
Figure 10: Additional curve fitting for the signal decay of TRIM/1E with different exchange rates at a concentration of 0.25 mM and additional $\omega_{\text{eff}}$ increments. The determined exchange rate of 2500 s$^{-1}$ fits the data set best, while lower or higher exchange rates result in a significant offset. Other parameters, e.g. the population of $E$-I and $E$-II were not changed.
**Computational Details**

All structures were optimized at TPSS/def2-SVP\(^{17}\) level of theory using D3\(^{18}\) correction in continuum of CH2Cl2 (SMD\(^{19}\)). The dielectric constant was adapted to 16.20 to mimic low temperature condition in the experiment. Vibrational and thermochemical analyses were performed at the same level of theory as the geometry optimization. Subsequently, single point calculations at SCS-MP2/CBS\(^{20}\) level of theory were conducted. Def2-SVP and def2-TZVP basis sets were used for extrapolation to approach complete basis set. Solvent and thermochemical corrections were added to the single point energy. Software used for the geometry optimization, frequency analysis and solvent correction was Gaussian 09 version D.01.\(^{21}\) For single point calculation, ORCA 4.1.1 was used.\(^{22}\) Constant temperature (NVT) molecular dynamic was done using semi-empirical xtb software in DCM.\(^{23}\)

**Extrapolation procedure**

The CBS basis set extrapolation proceeds under the two point extrapolation procedure as in implemented in ORCA 4.1.1 with the basis set Def2-SVP and Def2-TZVP.

\[
E_{\text{SCF}}^X = E_{\text{SCF}}^\infty + Ae^{-\alpha\sqrt{X}}
\]

\[
E_{\text{corr,MP2}}^\infty = \frac{X^\beta E_{\text{corr,MP2}}^X - (X - 1)^\beta E_{\text{corr,MP2}}^{X-1}}{X^\beta - (X - 1)^\beta}
\]

\[
E_{\text{MP2}}^\infty = E_{\text{corr,MP2}}^\infty + E_{\text{SCF}}^\infty
\]

**TRIP/1E Type III.1 and E-III.2 structures (most stable conformations)**

Type E-III.1

Type E-III.2
xtb-MD of TRIP/1E binary complex at 370 K

MD of TRIP/1E complex shows the exchange of E-II and E-I conformations via tilting and switching. The E-II conformation is marked by the close contact between C134 and H10, while the E-I conformation shows close contact between C140 and H25. No rotation is observed during a simulation of 4000 ps at 300 K to 370 K, i.e. C134 never meets H25 or C140 never meets H10. Beyond this temperature, dissociation of complex is observed.
Optimized Geometries

TRIM/1E Type I

Distance trajectory between atom C134 and atom H25

Distance trajectory between atom C134 and atom H10
Conf2

1) GIN WC WORKER 2 SPRTSSTPSvd2SPvC6H6FNP1O4P1

#p tpsstpss/def2svp int=ultrafine empiricaldispersion=gd3 scrf=(sm

title

version=ES64L-G09 evd.01\State=A\HF=-3513.6185302\RMSD=1.979e-09\Dipole=2.4812717,-3.1

21743.4,4842739\Quadropulse=8.3960565,20.8546422,-12.4858565,-15.9093

918.7,33165.2,20.8342641\PC=CD [C6H6FNP1O4P1]@
\[ \text{TRIP/2E Switching TS} \]

Conf0

\{11\} IGN-C-WORKER0/SP/RTSSTPSS/def2SVP/C65H69F3N1O4P1/JHIOE/29-Apr-2019
\title{\text{\#p tpsstpss/def2svp int=ultrafine empiricaldispersion=v3 scrf=(sm S})

\begin{verbatim}
Conf
\end{verbatim}
References

(1) Sorgenfrei, N.; Hioe, J.; Greindl, J.; Rothermel, K.; Morana, F.; Lokesh, N.; Gschwind, R. M. NMR Spectroscopic Characterization of Charge Assisted Strong Hydrogen Bonds in Brønsted Acid Catalysis. J. Am. Chem. Soc. 2016, 138 (50), 16345–16354.

(2) Greindl, J.; Hioe, J.; Sorgenfrei, N.; Morana, F.; Gschwind, R. M. Brønsted Acid Catalysis-Structural Preferences and Mobility in Imine/Phosphoric Acid Complexes. J. Am. Chem. Soc. 2016, 138 (49), 15965–15971.

(3) Aznar, F.; Valde, C. Modular Synthesis of Indoles from Imines and o-Dihalobenzenes or o-Chlorosulfonates by a Pd-Catalyzed Cascade Process. J. Am. Chem. Soc. 2009, 131 (8), 4031–4041.

(4) Schramm, Y.; Barrios-Landeros, F.; Pfaltz, A. Discovery of an Iridacycle Catalyst with Improved Reactivity and Enantioselectivity in the Hydrogenation of Dialkyl Ketimines. Chem. Sci. 2013, 4, 2760–2766.

(5) Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Goodfellow, R.; Granger, P. NMR Nomenclature: Nuclear Spin Properties and Conventions for Chemical Shifts. IUPAC Recommendations 2001. International Union of Pure and Applied Chemistry. Physical Chemistry Division. Commission on Molecular Structure and Spectroscopy. Magn. Reson. Chem. 2002, 40 (7), 489–505.

(6) Trigo-Mouriño, P.; Griesinger, C.; Lee, D. Label-Free NMR-Based Dissociation Kinetics Determination. J. Biomol. NMR 2017, 69 (4), 229–235.

(7) Akke, M.; Palmer, A. G. Monitoring Macromolecular Motions on Microsecond to Millisecond Time Scales by R 1ρ –R 1 Constant Relaxation Time NMR Spectroscopy. J. Am. Chem. Soc. 1996, 118 (4), 911–912.

(8) Palmer, A. G.; Kroenke, C. D.; Loria, J. P. Nuclear Magnetic Resonance Methods for Quantifying Microsecond-to-Millisecond Motions in Biological Macromolecules; Elsevier Masson SAS, 2001; Vol. 339.

(9) Melikian, M.; Gramüller, J.; Hioe, J.; Greindl, J.; Gschwind, R. M. Brønsted Acid Catalysis – the Effect of 3,3′-Substituents on the Structural Space and the Stabilization of Imine/Phosphoric Acid Complexes. Chem. Sci. 2019, 10, 5226–5234.

(10) Jerschow, A.; Müller, N. Suppression of Convection Artifacts in Stimulated-Echo Diffusion Experiments. Double-Stimulated-Echo Experiments. J. Magn. Reson. 1997, 125 (2), 372–375.

(11) Stejskal, E. O.; Tanner, J. E. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time-Dependent Field Gradient. J. Chem. Phys. 1965, 42 (1), 288–292.

(12) MacChioni, A.; Ciancaleoni, G.; Zuccaccia, C.; Zuccaccia, D. Determining Accurate Molecular Sizes in Solution through NMR Diffusion Spectroscopy. Chem. Soc. Rev. 2008, 37 (3), 479–489.

(13) Chen, H. C.; Chen, S. H. Diffusion of Crown Ethers in Alcohols. J. Phys. Chem. 1984, 88 (21), 5118–5121.

(14) Ben-Amotz, D.; Willis, K. G. Molecular Hard-Sphere Volume Increments. J. Phys. Chem. 1993, 97 (29), 7736–7742.

(15) Zuccaccia, D.; Macchioni, A. An Accurate Methodology to Identify the Level of Aggregation in Solution by PGSE NMR Measurements: The Case of Half-Sandwich Diamino Ruthenium(II) Salts. Organometallics 2005, 24 (14), 3476–3486.

(16) Reid, J. P.; Goodman, J. M. Goldilocks Catalysts: Computational Insights into the Role of the 3,3′-Substituents on the Selectivity of BINOL-Derived Phosphoric Acid Catalysts. J. Am. Chem. Soc. 2016, 138 (25), 7910–7917.

(17) J. M. Tao; J. P. Perdew; V. N. Staroverov; G. E. Scuseria. Climbing the density functional ladder: Nonempirical meta-generalized gradient approximation designed for molecules and solids. Phys. Rev. Lett. 2003, 91, 146401.

(18) S. Grimme; J. Antony, S. Ehrlich; H. Krieg. A consistent and accurate ab initio parameterization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. J. Chem. Phys. 2010, 132, 154104.

(19) A. V. Marenich; C. J. Cramer; D. G. Truhlar. Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. J. Phys. Chem. B, 2009, 113, 6378-6396.
(20) S. Grimme. Improved second-order Møller–Plesset perturbation theory by separate scaling of parallel- and antiparallel-spin pair correlation energies. *J. Chem. Phys.*, **2003**, *118*, 9095.

(21) Gaussian 09, Revision D.01, M. J. Frisch; G. W. Trucks; H. B. Schlegel; G. E. Scuseria; M. A. Robb; J. R. Cheeseman; G. Scalmani; V. Barone; B. Mennucci; G. A. Petersson; H. Nakatsuji; M. Caricato; X. Li; H. P. Hratchian; Á. F. Izmaylov; J. Bloino; G. Zheng; J. L. Sonnenberg; M. Hada; M. Ehara; K. Toyota; R. Fukuda; J. Hasegawa; M. Ishida; T. Nakajima; Y. Honda; O. Kitao; H. Nakai; T. Vreven; J. A. Montgomery, Jr.; J. E. Peralta; F. Ogliaro; M. Bearpark; J. J. Heyd; E. Brothers; K. N. Kudin; V. N. Staroverov; R. Kobayashi; J. Normand; K. Raghavachari; A. Rendell; J. C. Burant; S. S. Iyengar; J. Tomasi; M. Cossi; N. Rega; J. M. Millam; M. Klene; J. E. Knox; J. B. Cross; V. Bakken; C. Adamo; J. Jaramillo; R. Gomperts; R. E. Stratmann; O. Yazyev; A. J. Austin; R. Cammi; C. Pomelli; J. W. Ochterski; R. L. Martin; K. Morokuma; V. G. Zakrzewski; G. A. Voth; P. Salvador; J. J. Dannenberg; S. Dapprich; A. D. Daniels; Ö. Farkas; J. B. Foresman; J. V. Ortiz; J. Cioslowski; D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

(22) F. Neese. Software update: the ORCA program system, version 4.0. *WIREs Comput Mol Sci*, **2018**, *8:e1327*. doi: 10.1002/wcms.1327

(23) S. Grimme; C. Bannwarth; P. Shushkov. A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent Interactions of Large Molecular Systems Parametrized for All spd-Block Elements (Z=1–86). *J. Chem. Theory Comput.*, **2017**, *13*, 1989.