Chemical Exchange Saturation Transfer in Chemical Reactions: A Mechanistic Tool for NMR Detection and Characterization of Transient Intermediates.

N. Lokesh, Andreas Seegerer, Johnny Hioe and Ruth M. Gschwind*.

Institute of Organic Chemistry, University of Regensburg, D-93053 Regensburg, Germany

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1. General information

The chemicals for this study were purchased from Sigma Aldrich and Deutero and were used without further purification. DPU-d_{10} was synthesized according to the following procedure. All NMR experiments were performed at 213-300 K on a Bruker Avance III Nanobay 400 and a Bruker Avance III 600 (600.25 MHz) with a fluorine selective TBIF probe or a phosphorous selective TBIP probe. All spectra were processed and evaluated with Bruker Topspin 3.2.

2. Synthesis of DPU-d_{10}

In a flame dried Schlenk flask, under argon atmosphere triphosgene (0.1 equiv., 617.3 mg, 2.1 mmol) was dissolved in THF (20 ml) and was cooled to 0 °C. A mixture of aniline-d_{5} (C_{6}D_{5}NH_{2}; 1.0 equiv., 2.15 g, 21.9 mmol) and NEt_{3} (1.5 equiv., 4.5 ml, 32.5 mmol) in THF (20 ml) was added drop wise. After stirring the reaction mixture for 30 minutes at 0 °C, it was allowed to warm up to room temperature. After 1 h white precipitate was formed. The solution was washed with an aqueous NaHCO_{3} solution (sat.) and the organic phase was separated. The aqueous phase was washed with EtOAc. The combined organic phases were dried over Na_{2}SO_{4}, filtered and the solvent was removed under reduced pressure. The crude product was washed with Et_{2}O and dried under vacuum to give the white product (1.1 g, 78%). Due to the partial incomplete deuteration of the aromatic protons, small signals for the aromatic protons could be detected. The amine protons showed higher signal intensities.

{^1}H-NMR (400MHz, DMSO-d_{6}) [ppm]: 6.96 (s, H_{arom}), 7.27 (s, H_{arom}), 7.44 (s, H_{arom}), 8.66 (s, 2H, NH)

{^{13}}C-NMR (100MHz, DMSO-d_{6}) [ppm]: 117.7 (C_{arom}), 127.9 (C_{arom}), 128.2 (C_{arom}), 139.5 (C_{arom}), 152.4 (C=O)

3. Sample preparation

All samples in this study were prepared by dissolving L-proline (1 equiv.; 50 or 100 mM), 3-methylbutanal (1 equiv.) and diphenylurea (DPU) in 0.6 ml DMF-d_{7} in a 5 mm standard NMR tube. If not otherwise indicated 1 equiv. of DPU or DPU-d_{10} was used.

4. NMR spectroscopic investigations in the absence of DPU at 300-215 K.

S1: Stacked part of the 1D {^1}H spectra of the reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d_{7} at 300-215 K, showing H_{1} proton chemical shift of intermediates exo-, endo-oxazolidinone and enamine.
5. **NMR spectroscopic investigations in the presence of DPU**

S 2: Plot of temperature dependent shift for H$_1$ protons of *endo*- and *exo*-oxazolidinone and enamine in a reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d$_7$ at 300-215 K. In the absence of DPU the shift is not significant.

S 3: 1D $^1$H spectrum of the reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d$_7$ at 300 K in presence of DPU-d$_{10}$ (1 equivalent). The highlighted region shows the corresponding H$_1$ protons of all detectable intermediates, *exo*-, *endo*-oxazolidinone and enamine.
S 4: DPU concentration dependent shift for the H\textsubscript{1} protons of endo-, exo-oxazolidinone and enamine in a reaction mixture of L-proline (1 equiv.), 3-methylbutanal (1 equiv.) and the indicated amount of DPU (10-100%; 100% = 1 equiv.) in DMF-d\textsubscript{7} at 300 K.

S 5: Temperature dependent shift for the H\textsubscript{1} protons of endo-, exo-oxazolidinone and enamine in a reaction mixture of L-proline (1 equiv.), 3-methylbutanal (1 equiv.) and DPU (1 equiv.) in DMF-d\textsubscript{7} at 300-250 K. The continued line broadening and downfield shift for H\textsubscript{1} of endo indicates fast exchange regime for endo-oxazolidinone$\leftrightarrow$E-Iminium and narrower-broader-narrower profile for H\textsubscript{1} of exo shows shifting from fast exchange to slow exchange regime for exo-oxazolidinone$\leftrightarrow$Z-Iminium.
S 6: Most stable calculated structures of \textit{endo-} and \textit{exo-}oxazolidinone in complexation with DPU. The calculations did not reveal any deshielding effect of the aryl moieties of the DPU on the H$_1$ protons of \textit{endo-} or \textit{exo-}oxazolidinone. However the calculations (see Charge and Bond Length Analysis) showed a C$_1$-O bond elongation causing a shift of H$_1$. The shift of H$_1$ is more pronounced in \textit{endo-}oxazolidinone.
6. Charge and bond length analysis

S 7: Calculated NBO charges for *exo-* and *endo-*oxazolidinone along the C1-O bond with and without DPU. The resulting bond elongation is translated to change in chemical shift for the H1 protons, explaining the stronger shift in case of H1 of *endo-*oxazolidinone (see manuscript).
7. Effect of temperature on E-Iminium population in presence of DPU (1 equivalent).

Possible reasons for the shift of the H1 signal of endo-oxazolidinone at 300 K in presence of DPU, shown above (S4), were discussed in detail in the manuscript. Decrease in temperature enhanced E-Iminium ion population causing continued downfield shift for H1 of endo-oxazolidinone peak. For Z-iminium ion and exo-oxazolidinone quantitative data regarding exchange rates and thermal population were obtained directly from CEST (see manuscript). Unlike the Z-iminium ion, it is not possible to analyze the kinetic and thermodynamics by CEST due to the fast exchange (k ≥ Δν) between E-iminium ion and endo-oxazolidinone. At 300 K, the EXSY measurements (data shown below) showed similar exchange rates for interconversion between exo↔endo, indicating equivalent thermal stability for E- and Z-iminium ion. The CEST measurement showed that Z-iminium ion is located +8.1 kJ/mol above the exo-oxazolidinone at 250 K, and is expected to be even higher at room temperature. Due to the similar thermal stability of E/Z-iminium, the E-iminium ion is located at least +6.1 kJ/mol above the endo-oxazolidinone (considering the ΔG300 of 2.0 kJ/mol between exo and endo). This means, the population effect of iminium species at 300 K is negligible.

The decrease of temperature results a continuous shift for the endo peak, which allows us to extract the population of E-iminium ion. However, the downfield due to the C1-O bond polarization must be discounted for all measurements at all temperature. The obtained relative population plots are shown below.

S 8: Plot of [E-iminium]/[endo-oxazolidinone] population dependency on temperature (A); Variation of difference in free energy between endo-oxazolidinone and E-iminium structure with temperature, the – ΔS suggest more ordered structure for E-iminium:DPU than endo-oxazolidinone:DPU (B).

Upon decreasing temperature to 250 K, the energy gap diminishes, and the interconversion process enters towards slow exchange regime (broadening of signals). Furthermore, the plot ΔG(E/endo) vs. temperature yields a negative ΔS (−139 J/(mol K)), which implicates a more ordered state of E-iminium relative to endo-oxazolidinone in presence of DPU. This is rather surprising because it is usually assumed that the oxazolidinone is more rigid than the iminium. The more ordered state at E-iminium side would mean that DPU associates stronger with the zwitterionic species than the neutral oxazolidinone.
8. 1D $^1$H EXSY studies to obtain rate constants and free energy barriers at 300 K

A series of 1D $^1$H EXSY experiments were measured by exciting $^1$H protons of exo-, endo-oxazolidinone and enamine for different mixing time. The plot of intensity versus mixing time directly provides rate exchange from the slope, which can be used to extract rate constant and hence the free energy barrier.

**exo-oxazolidinone $\rightarrow$ endo-oxazolidinone**

The Intensity $I_0$ (exo) is relative intensity of $^1$H proton of exo-oxazolidinone at 0 s

By Eyring equation $k = \dfrac{k_BT}{\hbar} e^{-\Delta G^\ddagger / RT}$

For $k= 1.26 \text{ s}^{-1}$ the free energy barrier for exo$\rightarrow$endo is $\Delta G^\ddagger = 72.9 \text{ kJ/mol}$

**endo-oxazolidinone $\rightarrow$ exo-oxazolidinone**

The Intensity $I_0$ (endo) is relative intensity of $^1$H proton of endo-oxazolidinone at 0 s

By Eyring equation, $k = \dfrac{k_BT}{\hbar} e^{-\Delta G^\ddagger / RT}$

For rate constant $k= 1.5 \text{ s}^{-1}$ the free energy barrier for endo$\rightarrow$exo is $\Delta G^\ddagger = 72.5 \text{ kJ/mol}$. The values suggests similar thermal stability for E and Z-iminium, since C=N rotation is the rate measurement step

**exo-oxazolidinone $\rightarrow$ enamine**

The Intensity $I_0$ (enamine) is relative intensity of $^1$H proton of enamine at 0 s

By Eyring equation $k = \dfrac{k_BT}{\hbar} e^{-\Delta G^\ddagger / RT}$

For rate constant $k= 0.113 \text{ s}^{-1}$ the free energy barrier for exo$\rightarrow$enamine is $\Delta G^\ddagger = 79 \text{ kJ/mol}$

S 9: 1D selective EXSY build-up curve for exo$\rightarrow$endo exchange. The dashed line represents the initial slope, which is used for rate approximation.

S 10: 1D selective EXSY build-up curve for endo$\rightarrow$exo exchange. The dashed line represents the initial slope, which is used for rate approximation.

S 11: 1D selective EXSY build-up curve for exo$\rightarrow$enamine exchange. The dashed line represents the initial slope, which is used for rate approximation.
endo-oxazolidinone → enamine

Due to near frequency separation between H$_1$ of endo and enamine, the quantitative EXSY data was not possible. In endolexo-oxazolidinone to enamine conversion, the rate determining step is conversion from E/Z-iminium to enamine. At 300 K, the thermal stability of E and Z are similar, assuming similar free energy barrier for both E-iminium to enamine and Z-iminium to enamine. The derived endo-oxazolidinone to enamine free energy barrier is 78.6 kJ/mol.

9. $^1$H CEST pulse sequence

![Graphical representation of CEST pulse sequence](image)

S 12: CEST pulse sequence

Graphical representation of applied CEST pulse sequence consists of initial continuous saturation pulse, followed by a 90° pulse. In all our experiments the saturation is applied for 0.75 s with $B_1 \approx 45$ Hz RF strength. Acquisition time $A_q = 1$ s, and inter scan delay time $d_1 = 3$ s are used.

The saturation offset scanned with incremental step of 50 Hz, from up field to down field, while monitoring H$_1$ peak intensity of exo-oxazolidinone. The data, intensity of marked H$_1$ peak in exo-oxazolidinone vs. saturation offset (CEST profile) was plotted for further analysis.
10. Possible intermediate probes to detect iminium ion in the system

In principle it is possible to observe the decreased intensity in CEST on saturation of H₁ proton of iminium ion (≈ 9 ppm) in all three intermediates exo-, endo-oxazolidinone and enamine. Since all these three intermediates exchanges with iminium ion as shown in figure S13. However at room temperature due to very less concentration of iminium ion even in presence of DPU, it could not be detected in CEST. On decrease in temperature to stabilize iminium ion, the exchange of iminium ion with enamine freezes and iminium ion exchange happens only with oxazolidinones. Therefore at low temperature the saturation effect on iminium ion can be observed only in oxazolidinone. Further it was observed that at 250 K, the slow exchange regime is achieved only for exo ↔ Z-iminium ion, which is necessary condition in CEST experiment.
11. Bloch-McConnell equations for two site exchange

For our two site exchange system, here between exo-oxazolidinone and Z-iminium ion, the equations are

\[
\frac{dM_x^{\text{exo}}}{dt} = -\Omega_{im} M_y^{\text{im}} - R_2^{\text{exo}} M_x^{\text{exo}} - k_{\text{exo} \rightarrow Z} M_x^{\text{im}} + k_{Z \rightarrow \text{exo}} M_x^{\text{im}} \quad \text{[1]}
\]

\[
\frac{dM_y^{\text{im}}}{dt} = -\Omega_{im} M_y^{\text{im}} - R_2^{\text{im}} M_y^{\text{im}} - k_{Z \rightarrow \text{exo}} M_y^{\text{im}} + k_{Z \rightarrow \text{im}} M_x^{\text{im}} \quad \text{[2]}
\]

\[
\frac{dM_x^{\text{im}}}{dt} = -\Omega_{im} M_x^{\text{im}} - R_2^{\text{im}} M_y^{\text{im}} - k_{Z \rightarrow \text{exo}} M_y^{\text{im}} + k_{Z \rightarrow \text{im}} M_y^{\text{im}} - \omega_1 M_x^{\text{im}} \quad \text{[3]}
\]

\[
\frac{dM_y^{\text{exo}}}{dt} = -R_1^{\text{exo}} (M_x^{\text{exo}} - M_y^{\text{exo}}) - k_{\text{exo} \rightarrow Z} M_x^{\text{exo}} + k_{Z \rightarrow \text{exo}} M_y^{\text{exo}} + \omega_1 M_y^{\text{exo}} \quad \text{[4]}
\]

\[
\frac{dM_x^{\text{im}}}{dt} = -R_1^{\text{im}} (M_x^{\text{im}} - M_y^{\text{im}}) - k_{Z \rightarrow \text{exo}} M_y^{\text{im}} + k_{Z \rightarrow \text{im}} M_y^{\text{im}} + \omega_1 M_y^{\text{im}} \quad \text{[5]}
\]

Here,

\(M_x^{\text{exo}}, M_y^{\text{im}}, M_x^{\text{im}}, M_y^{\text{exo}}\) and \(M_x^{\text{im}}, M_y^{\text{im}}\) are magnetization of exo-oxazolidinone and Z-iminium ion.

\(k_{Z \rightarrow \text{exo}}\) and \(k_{\text{exo} \rightarrow Z}\) are rate constants.

\(\Omega_{im}\) = offset frequency of iminium proton (H1)

\(\Omega_{exo}\) = offset frequency of exo-oxazolidinone proton (H1)

\(R_2^{\text{exo}} = \frac{1}{T_2^{\text{exo}}}, R_2^{\text{im}} = \frac{1}{T_2^{\text{im}}}, R_1^{\text{exo}} = \frac{1}{T_1^{\text{exo}}} \quad \text{and} \quad R_1^{\text{im}} = \frac{1}{T_1^{\text{im}}}\)

T_{2exo} and T_{2im} are spin-spin relaxation times for H1 proton of exo-oxazolidinone and iminium ion.

T_{1exo} and T_{1im} are spin-lattice relaxation times for H1 proton of exo-oxazolidinone and iminium ion.
12. CEST spectra (profile) simulation details

CEST spectra are simulated using numerical solutions of above Bloch-McConnell equations. Simulations are carried out in MATLAB as described in earlier reports.\(^1\)\(^-\)\(^3\) The used initial input parameters are \(M_{0\text{exo}}\), \(M_{0\text{imi}}\), \(\omega_1\), \(T_{1\text{exo}}\), \(T_{1\text{imi}}\) and \(k_{Z\text{exo}}\).

Here, 
\(M_{0\text{exo}}\) is initial magnetization of \(\text{exo}\) oxazolidinone at equilibrium;  
\(M_{0\text{imi}}\) is initial magnetization of \(Z\)-iminium ion at equilibrium;  
\(\omega_1\) is strength of RF saturation in Hz;  
\(T_{1\text{exo}}\) and \(T_{1\text{imi}}\) are longitudinal relaxations of chosen proton in \(\text{exo}\)-oxazolidinone and \(Z\)-iminium ion respectively;  
\(k_{Z\text{exo}}\) is rate of ring closing from \(Z\)-iminium to \(\text{exo}\)-oxazolidinone.

In all simulated spectra, we used \(M_{0\text{exo}} = 1\) and \(\omega_1 = 45\) Hz. The \(T_{1\text{exo}}\) values are experimentally obtained by inversion recovery experiment while saturating at 9.12 ppm. \(M_{0\text{imi}}\) and \(k_{Z\text{exo}}\) are varied to match simulation spectra with that of experimental data via multi parameter optimization.

Case 1. At 250 K:

\[ M_0(\text{exo}) = 1, \ \omega_1 = 45\ \text{Hz and } T_{1\text{exo}} = T_{1\text{imi}} = 1.8 \ \text{s are fixed.} \]

Case 2. At 213 K:

\[ M_0(\text{exo}) = 1, \ \omega_1 = 45\ \text{Hz and } T_{1\text{exo}} = T_{1\text{imi}} = 0.8 \ \text{s are fixed.} \]
13. Details of theoretical calculations

Extrapolation procedure

The total energy at DLPNO-CCSD(T)/CBS level of theory were extrapolated according to the extrapolation formula Eq. 1-4.

\[ E_{\text{SCF}}^X = E_{\text{SCF}}^\infty + Ae^{-a\sqrt{X}} \]  \hspace{1cm} \text{Eq. 1}

\[ E_{\text{corr,MP2}}^\infty = \frac{X^\beta E_{\text{corr,MP2}}^X - (X-1)^\beta E_{\text{corr,MP2}}^{X-1}}{X^\beta - (X-1)^\beta} \]  \hspace{1cm} \text{Eq. 2}

\[ E_{\text{MP2}}^\infty = E_{\text{SCF}}^\infty + E_{\text{corr,MP2}}^\infty \]  \hspace{1cm} \text{Eq. 3}

\[ E_{\text{CCSD(T)}}^\infty = E_{\text{CCSD(T)}}^{d\text{efZ-TZVPP}} + E_{\text{MP2}}^\infty - E_{\text{MP2}}^{d\text{efZ-TZVPP}} \]  \hspace{1cm} \text{Eq. 4}

\[ \Delta G_{\text{gas}} \text{ CCSD(T)/CBS (Boltzmann averaged)} + \Delta G_{\text{soln}} \text{ (PCPM) in a.u.} \]

| Ground states                  |          |
|-------------------------------|----------|
| \textit{exo-oxazolidinone}    | -1282.024904 |
| \textit{endo-oxazolidinone}   | -1282.023829 |
| Z-iminium                     | -1282.022150 |
| \textit{E-iminium}            | -1282.022783 |

| Transition states (Ring Opening) |          |
|----------------------------------|----------|
| \textit{exo-oxazolidinone}       | -1282.006070 |
| \textit{endo-oxazolidinone}      | -1282.010202 |

\textbf{Geometry of stationary points (most stable conformations)}

\textit{exo-oxazolidinone} + DPU

1\%:GINC-WORKER1\%:Opt\%:RTPSSTPSS\%:def2SVP/W06\%:C23H29N3O3\%:JH10E:09-May-20
17/0/\%: tpsstppss/def2svp/w06 empiricaldispersion=gd3 scrf=(pcpm,solve
nt=n,-DiMethylFormamide,read) opt=int=ultrafine\%:title\%:0,1\%:C,.-1.8931
520135,1.9076239109,-0.3230357501\%:C,-1.6467014096,4.2107435123,0.199111
26099\%:C,-3.0520489729,4.0445277726,-0.3912125564\%:H,-2.301196548,0.9891
057102,0.13974275265\%:H,-1.5920048449,4.93159841,1.0233454106\%:H,-0.93407
184134,5.349658706,-0.5990810733\%:H,-3.7895229206,3.9922810108,0.428483
19421\%:H,-3.3347971572,4.8733515737,-1.0597245779\%:C,0.0487240683,2.49952
endo-oxazolidinone + DPU

\%GINC-LOGIN\%FOpt\%RTPSSTPSS\%def2SVP\%W06\%C23H29N3O3\%ROOT\%09-May-2017\%
0\%
#tpstps\%def2svp\%w06 empiricaldispersion=gd3 scrf=(cpcm,solvent=DiMethylFormamide,read) opt int=ultrafine\%title\%0\%C1.1.45388161
| Z-iminium + DPU |
|-----------------|
| 1\1\GINC-LOGINF|Opt\RTPSSTPS\def2SVP/W06C23H29N3O3\ROOT09-May-2017\ |
| 01\pt\stpsst\def2svp/w06.scr=(cpem.solvent=n.n-DiMethylFormamide.re |
| ad\empiricaldispersion=gd3 opt=int ultrafine\title\01\C,-2.3260180 |
| 861,1\3.9324174,-0.8691349996\C,-3.9229533122,-0.6043165819,-2.4142404 |
| 112\C,-3.7703378109,-2.0783081257,-2.7901326004\H,-2.527925009,-2.1805 |
| 29862,0\0.01735814\H,-4.947469437,-0.2082594559,-2.4366952536\H,-3.26 |
| 30898891,0\0.0249741568,-3.0189200003\H,-4.5963410882,-2.6609829028,-2.3 |
| 466737406\H,-3.7854468108,-2.2264941341,-3.880847516\C,-3.8257959832, |
| 0.2250585321,-0.0989363669\H,-4.604205196,0.9332970021,-0.4144258147\N, |
| -3.4055569729,-0.5859086659,-1.0178670774\O,-0.9167528236,0.29705856 |
| 8,-0.2908478671\C,-0.9269434316,-0.9088133549,-0.6681784381\O,0.051403 |
| 0244,-1\6.6813525,-0.8840572503\C,-3.4217803866,0.2390544647,1.32916940 |
| 86\H,-2.6203022658,-0.4848262498,1.5393054356\C,-4.642796221,0.0089715 |
| 307,2\2.62998607\H,-5.4100319976,0.7666733108,2.0164535121\H,-3.0037024 |
| 716,1\2.45335629,1.5224707147\C,-2.4209225505,-2.4573780524,-2.15005488 |
| 74\H,-2.3465558115,-3.5293650871,-1.9160389141\H,-1.5826433541,-2.2033 |
| 211269,-2\8.17732111\C,-5.2515930252,-1.3882893655,0.611424743\H,-5.5 |
| 893934757,-1.5384337395,1.0195759216\H,-4.5127625125,-2.1767903068,2.2 |
| 959483127\H,-6.123886477,-1.5332075808,2.7216620301\C,-4.21308730,0.2 |
| 284054909,3\7.285516018\H,-3.8115401719,1.2455642994,3.8804501401\H,-5. |
| 0728725468,0.0919634878,4.4073815209\H,-3.430924499,0.496400382,4.01 |
| 97380622\C,2.7728441691,0.7305387645,0.0677275797\O,3.8870096138,1.219 |
| 1648011,0.3033132743\N,2.5195740506,-0.6319167424,-0.0092830322\H,1.57 |
| 5171353,-0.9374003934,-0.3400768336\N,1.6247447786,1.478128412,-0.1533 |
| 688976\H,7.141443018,0.9671686466,-0.2315013193\C,1.5084142239,2.8722 |
| 782803,-0.2336408352\C,-0.2067923704,3.3956733468,-0.4506873213\C,2.592 |
| 480579,3\7.7773469748,0.1224511928\C,-0.000620633,4.7754278243,-0.5492 |
| 010086\H,-0.6326152966,2.6983049408,-0.5415315863\C,2.3642417715,5.157 |
| 623966,-0.2262519956\H,3.5951978528,3.851807924,0.0477736619\C,1.0758 |
| 773753,5.6724528306,-0.4382052161\H,-1.016264065,5.152224166,-0.71628 |
| 18877\H,3.2170977289,5.8407635031,-0.1371640238\O,0.9120636206,2.35251 |
| 2368,-0.5156198357\C,3.4073921826,-1.6836589862,0.2448630958\C,2.9067 |
| 137697,-3.0026463336,0.0666065405\C,4.7481542178,-1.5233742721,0.67213 |
| 97076\C,3.721068336,-1.1143448487,0.305860425\H,1.8695405988,-3.13073 |
| 87509,-0.2606486811\C,5.5482280606,-2.6511543899,0.9088479773\H,5.1432 |
| 979729,-0.5165556747,0.8076186483\C,5.0513534222,-3.951456563,0.729896 |
| 2608\H,3.3091112639,-5.1194849346,0.1596605416\H,6.5831022027,-2.50291 |
| 45314,1.239129358\H,5.6878455771,-4.8228656538,0.9167108914\Version=E |
E-iminium + DPU

%1\GINC-LOGIN\Opn\RTPSSTPSS\def2SVP/W06/C23H29N3O3\ROOT\15-May-2017\%p
\def2sppss/def2svp/w06 scrf=(cpcm,solvent=n,n-DiMethylFormamide,rc)
\ad empircaldispersion=gd3 opt int=ultrafine\title\0,\0,\0,\1,\1,-\1,6794133
038,-.2.1765674288,-.6773847147\C,-3.8331286825,-1.6322643894,-1.73074
70518\C,-3.236839848,-.2.8695251536,-.2.4802907541\H,-1.6264268756,-2.984
584808,0.072082728\H,-.4.889250092,-1.7326442303,-1.4442241286\H,-.7.30
45222072,-.7.217490054,-.2.3424846729\H,-3.6486457165,-3.7831468646,-1.45
9456219212\H,-3.4663647568,-2.8919273253,-3.4847621258\C,-3.2891007314
-.0.8019331636,0.5473393227\H,-.2.5591061814,-.8.4214343894,1.3655030342
\N,-2.9887583402,-1.4861957123,-0.5114303377\O,-0.6736810448,-0.080662
2213,0.0461702317\C,-0.461527775,-1.2283338214,-0.4308946805\O,0.64204
07512,-1.7424773756,-0.7493414598\C,-.4.5346416951,-.0095059257,0.7337
665337\H,-4.9948176463,0.2444110386,-.2.366728628\C,-.43032733453.1,27
15163625,1.577548752\H,-3.8789157739,0.9519555471,2.5496020557\H,-5.25
4073756,-.670104226,1.2671084625\C,-1.7345324979,-2.739822096,-2.112
6563161\H,-1.1893271643,-.691316263,-.2.1888554476\H,-1.264838876,-2.023
6494703,-.2.80855341\C,-.3.2920117962,2.062755137,0.8932522284\H,-2.3255
041506,1.6989680825,0.7319777365\H,-3.6693278431,2.5393587189,-0.09181
73502\H,-3.1120190524,3.1050871029,1.5082784697\C,-5.6443915193,1.9714
09771,1.8450881057\H,-6.3519950164,1.3037489086,2.3678071004\H,-5.49252
03986,2.8687549385,2.4697263335\H,-6.114333429,2.2936970691,0.89755073
96\C,2.8506345736,1.1173466048,0.0648730995\O,3.8520253889,1.830104126
9,0,2.202420976\N,2.8506432276,-.2.67166529,0.1525789317\H,1.9940098137
-.0.7689104427,-.0.1815431257\N,1.5824351317,1.6023239086,-.2.247667558
\H,-0.7855967994,0.9315618647,-.0.1520868835\C,1.2113688029,2.9168378515
-.0.536479513\C,-.1371014181,3.1251679783,-.9243712948\C,2.0843604015
3.4,0.0309203846,-.4924419583,-.600685319,4.405972944,-1.2411915699
\H,-.8097989164,2.2629841418,-.9717654908\C,1.6038706232,5.3070549554
-.8.230570806\H,3.1224997149,3.8796854153,-.195656555\C,0.265811007
9.5,5.119223409,-1.1945217382\H,-1.6495072112,4.5373460752,-1.531198557
\H,2.294845134,6.1572190431,-.782246694\H,-.0962558855,6.5147406916
-.1.444637854\C,3.9042657173,-1.1067183078,0.5354071303\C,3.6568433849
TS Ring Opening *endo*-oxazolidinone + DPU

\[ \text{I1GINC-WORKER0} \text{/FTSRTPSSTPSS} \text{def2SVP/W06/C23H29N3O3/JHIOE/18-May-2011} \]

\[ \text{t=n,DiMethylFormamide,read} \text{ opt=(ts,calcfc,noeigen) int=ultrafine} \]

\[ \text{H,7.099382,11.04895901} \]

\[ \text{RMSD=7.265e+06} \]

\[ \text{RMSF=3.081e+06} \]

\[ \text{PG=C01 [X(C23H29N3O3)]} \]
TS Ring Opening $exo$-oxazolidinone + DPU

\[ \text{\#p tspstpp/def2svp/w06 empiricaldispersion=gd3 scrf=(cpcm,solvent=DiMethylFormamide,read) opt=(ts,calcfc,noeigen) int=ultrafine} \]

\[ \text{t=nn-DiMethylFormamide,read) opt=(ts,calcfc,noeigen) int=ultrafine} \]

\[ \text{title}01,1-\text{H,7.2943657316,0.79615334,0.973361014} \]

\[ \text{H,7.4074102461,0.8949287943,0.2195956046,0.380192449} \]

\[ \text{9.1.753952539\text{Version}=ES6\text{G09RevD.01STATE}=-1-AHF=-128.2728014\text{RMSD}=4.182e-09\text{RMSF}=8.548e-07\text{Dipole}=-5.8084804,-2.9534151,0.0952037\text{Quadrupole}=1.8203083,0.8853617,-2.705672,2.093804,2.0196214,0.004743PG=C01} \]

\[ \text{[X(C23H29N3O3)]} \]
6189937,1.3232192903,-0.1335346808
264562N,2.642674329,-0.0286037775,-0.0223494979
39635,-0.395778457N,1.0097253753,1.5472790455,-0.4086348483
086883.07302340084,-0.6037339399C,0.3528148921,2.7839421768,-0.50127
37298C,-0.9274696295,2.7954387823,-1.1092755285C,0.8766314777,3.9988
347334,0.001054213C,-1.6696535202,3.990594532,-1.1922573984H,-1.328
4556941.18638942112,-1.5208062058C,0.1240990052,5.1778982211,-0.0999
88304H,1.8657224232,4.0053706336,0.4596901818C,-1.1507122595,5.18326
46584,-0.6881339567H,-2.6589715489,3.957725351,-1.6628980073H,0.5459
643106.61085863991,0.2965814H,-1.7288844868,6.1106362164,-0.75651800
71C,3.8945728147,-0.6237761077,0.199081223C,3.9160879607,-2.0329676
796,0.3596411908C,5.1181816645,0.0858507016,0.2613852322C,5.12257357
95,-2.7077991794,0.5739153047H,2.9715798502,-2.5849623799,0.316901668
9C,6.3176604412,-0.6088279098,0.4771300781H,5.1111507544,1.169542194
4,0.1453409732C,6.3369793193,-2.0031721421,0.6346759127H,5.110907388
9,-3.7969441673,0.6952106386H,7.2543787779,-0.0411499535,0.5220293205
H,7.2807090808,-2.5326685416,0.8027146422H,-3.3285699748,-0.19949475
41,-1.3996856985\Version=ES64L-G09RevD.01\State=1-AHF=-1283.2697754\RMSD=5.525e-09\RMSF=9.967e-07\Dipole=-6.0005938,-2.775788,-0.457033\Quadropole=1.2382403,1.8582955,-3.0965358,3.0841969,4.5751633,4.9025814\PG=C01 [X(C23H29N3O3)]\}@
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