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

Contents

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 ($C_5D_5NH_2$; 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_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was washed with Et_2O 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.

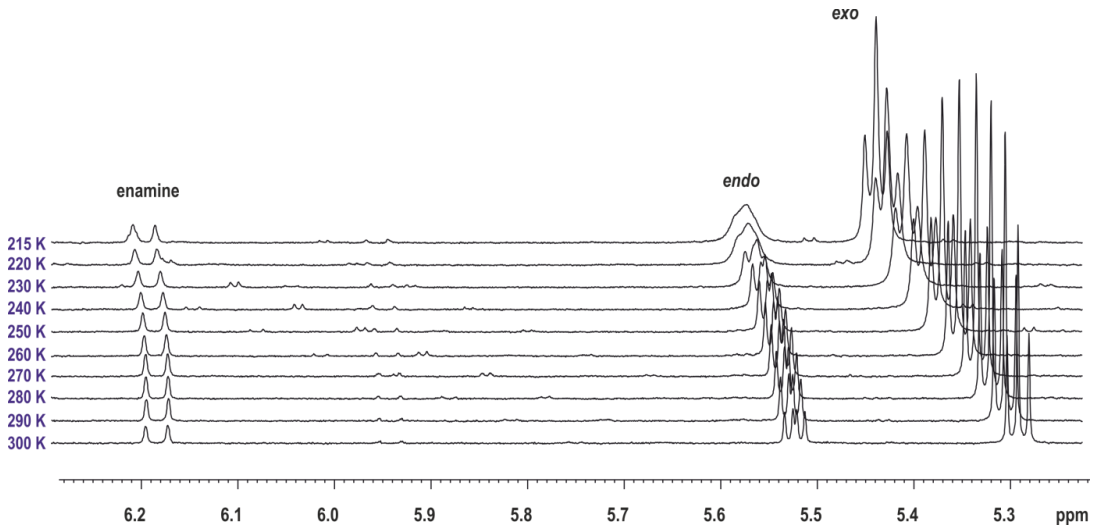
^{1}**H-NMR** (400MHz, DMSO-d_6) [ppm]: 6.96 (s, H_{arom}), 7.27 (s, H_{arom}), 7.44 (s, H_{arom}), 8.66 (s, 2H, NH)

^{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)

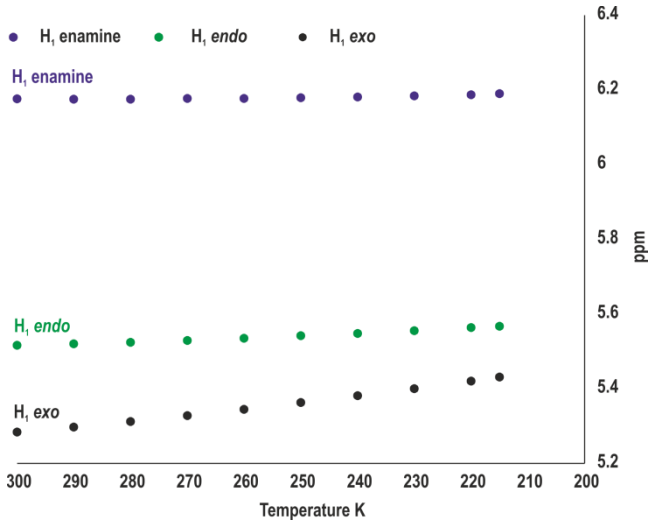
3. Sample preparation

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.

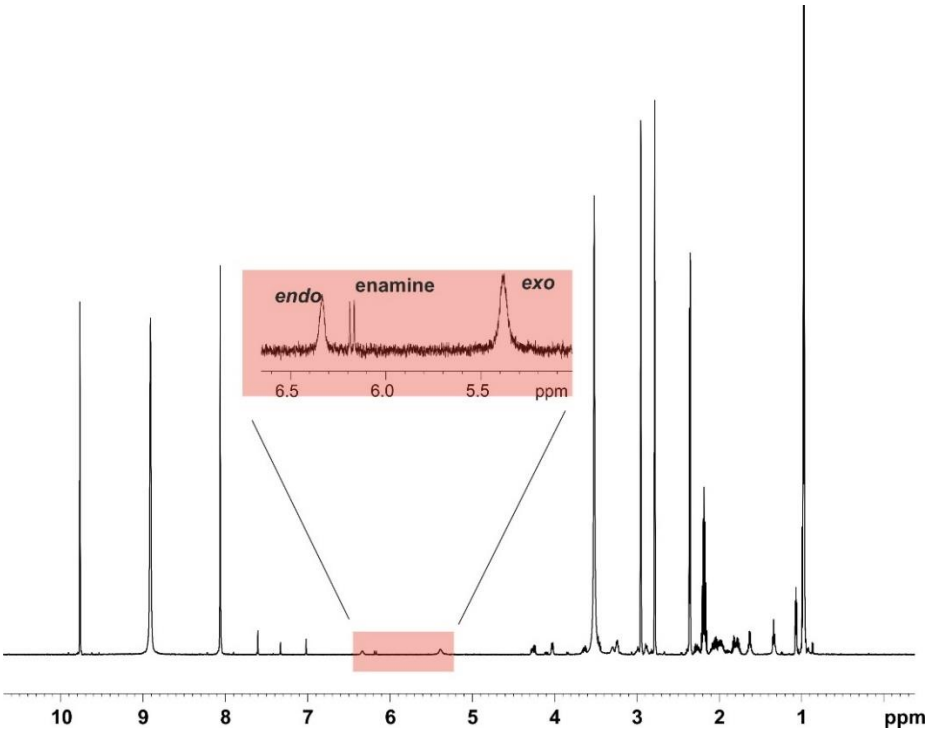


S 1: Stacked part of the 1D ^{1}H spectra of the reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d_7 at 300-215 K, showing H_1 proton chemical shift of intermediates *exo*-, *endo*-oxazolidinone and enamine.

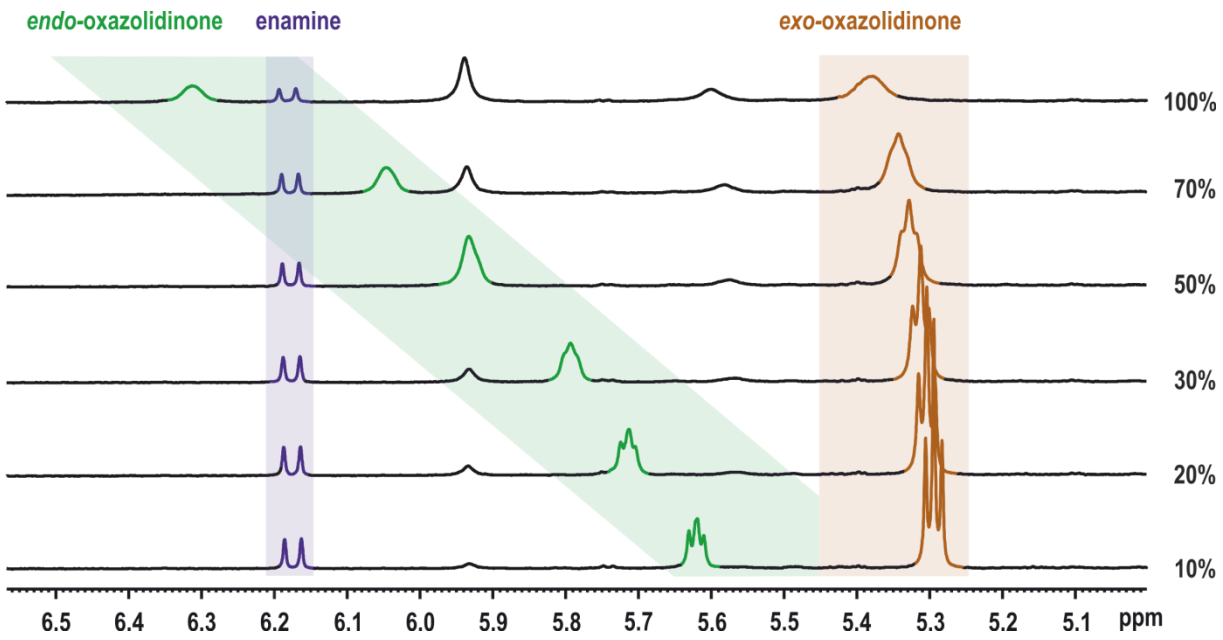


S 2: Plot of temperature dependent shift for H_1 protons of *endo*-, *exo*-oxazolidinone and enamine in a reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d_7 at 300-215 K. In the absence of DPU the shift is not significant.

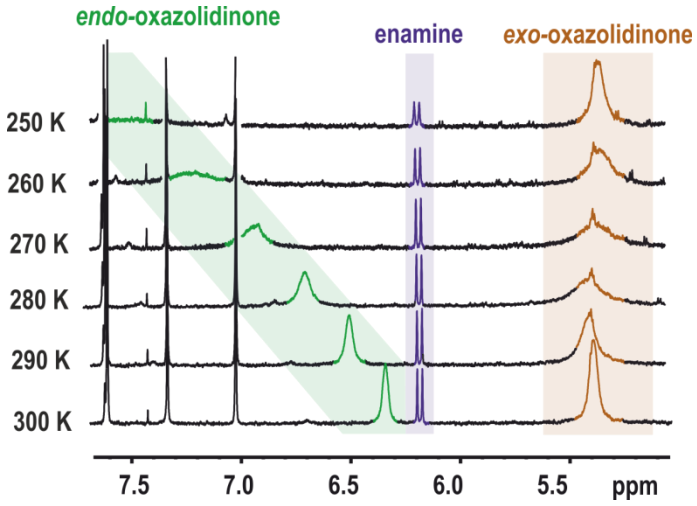
5. NMR spectroscopic investigations in the presence of DPU



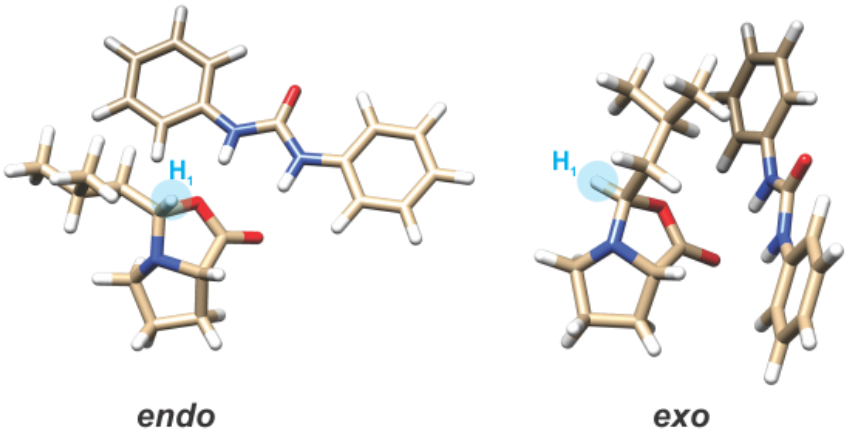
S 3: 1D ^{1}H spectrum of the reaction mixture of L-proline (1 equiv.) and 3-methylbutanal (1 equiv.) in DMF-d_7 at 300 K in presence of DPU-d_{10} (1 equivalent). The highlighted region shows the corresponding H_1 protons of all detectable intermediates, *exo*-, *endo*-oxazolidinone and enamine.



S 4: DPU concentration dependent shift for the H_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_7 at 300 K.

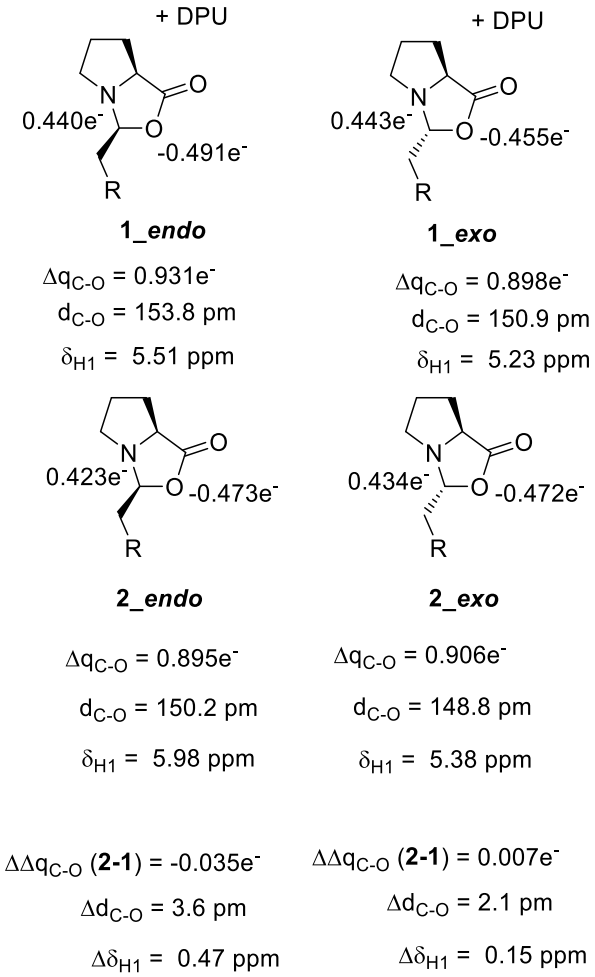


S 5: Temperature dependent shift for the H_1 protons of *endo*-, *exo*-oxazolidinone and enamine in a reaction mixture of L-proline (1 equiv.), 3-methylbutanal (1 equiv.) and DPU (1 equiv.) in DMF-d_7 at 300-250 K. The continued line broadening and downfield shift for H_1 of *endo* indicates fast exchange regime for *endo*-oxazolidinone↔*E*-Iminium and narrower-broader-narrower profile for H_1 of *exo* shows shifting from fast exchange to slow exchange regime for *exo*-oxazolidinone↔*Z*-Iminium.



S 6: Most stable calculated structures of *endo*- and *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 *endo*- or *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 *endo*-oxazolidinone.

6. Charge and bond length analysis

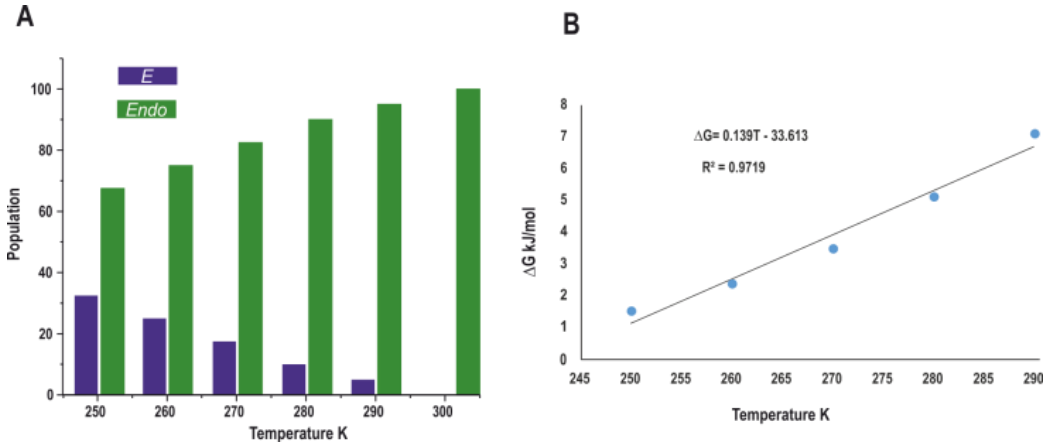


S 7: Calculated NBO charges for *exo*- and *endo*-oxazolidinone along the C_1-O bond with and without DPU. The resulting bond elongation is translated to change in chemical shift for the H_1 protons, explaining the stronger shift in case of H_1 of *endo*-oxazolidinone (see manuscript).

7. Effect of temperature on *E*-Iminium population in presence of DPU (1 equivalent).

Possible reasons for the shift of the H_1 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 H_1 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 ($k \geq \Delta\nu$) 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 ΔG_{300} 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 C_1-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 $\Delta G_{E/endo}$ 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

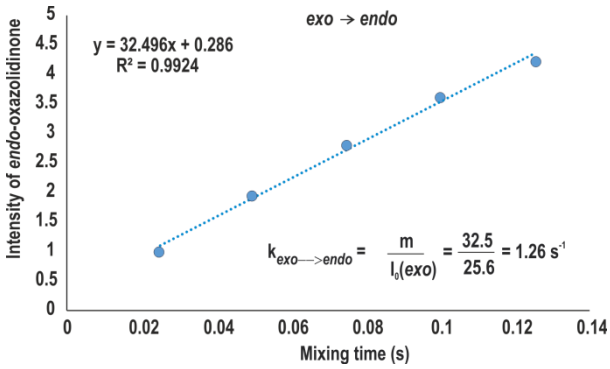
A series of 1D ^{1}H EXSY experiments were measured by exciting ^{1}H protons of *exo*-, *endo*-oxazolidinone and enamine for different mixing time. The plot of intensity versus mixing time directly provides rate exchange from the slope, which can be used to extract rate constant and hence the free energy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

<u>*exo*-oxazolidinone → *endo*-oxazolidinone</u>

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

By Eyring equation $k = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger}}{RT}}$

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



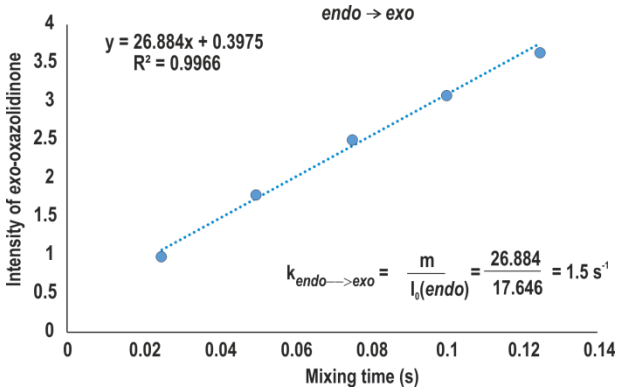
S 9: 1D selective EXSY build-up curve for *exo*→*endo* exchange. The dashed line represents the initial slope, which is used for rate approximation.

<u>*endo*-oxazolidinone → *exo*-oxazolidinone</u>

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

By Eyring equation, $k = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger}}{RT}}$

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



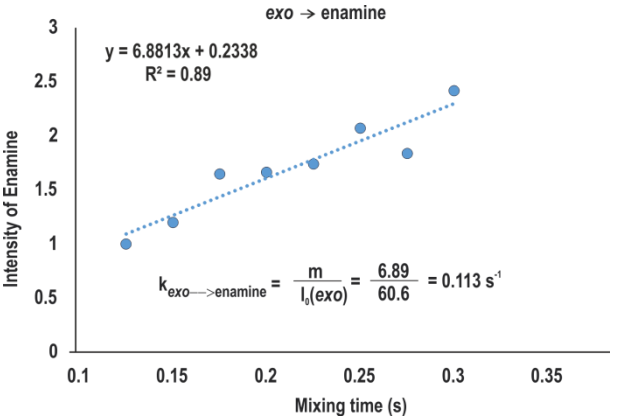
S 10: 1D selective EXSY build-up curve for *endo*→*exo* exchange. The dashed line represents the initial slope, which is used for rate approximation.

<u>*exo*-oxazolidinone → enamine</u>

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

By Eyring equation $k = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger}}{RT}}$

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

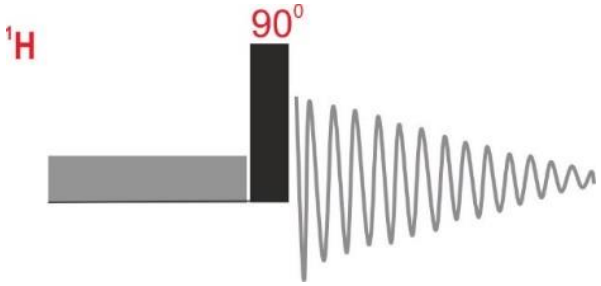


S 11: 1D selective EXSY build-up curve for *exo*→enamine exchange. The dashed line represents the initial slope, which is used for rate approximation.

***endo*-oxazolidinone → enamine**

Due to near frequency separation between H_1 of *endo* and enamine, the quantitative EXSY data was not possible. In *endo*/*exo*-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

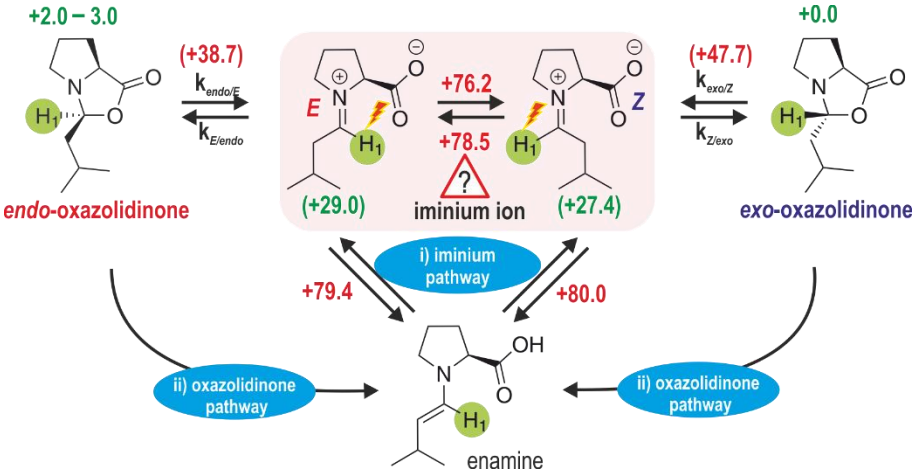


S 12: CEST pulse sequence

Graphical representation of applied CEST pulse sequence consists of initial continuous saturation pulse, followed by a 90^0 pulse. In all our experiments the saturation is applied for 0.75 s with $B_1 \approx 45$ Hz RF strength. Acquisition time Aq = 1 s, and inter scan delay time d1= 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

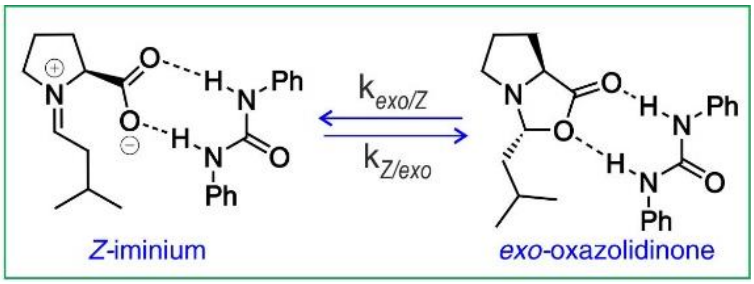
10. Possible intermediate probes to detect iminium ion in the system



S 13: possible equilibria in the reaction system between the intermediates

In principle it is possible to observe the decreased intensity in CEST on saturation of H_1 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



S 14: Two side exchange equilibrium between *Z*-iminium ion and *exo*-oxazolidinone.

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

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

$$\frac{dM_x^{im}}{dt} = -\Omega_{im}M_y^{im} - R_2^{im}M_x^{im} - k_{Z\to exo}M_x^{im} + k_{exo\to Z}M_x^{exo} \quad [2]$$

$$\frac{dM_y^{exo}}{dt} = -\Omega_{exo}M_x^{exo} - R_2^{exo}M_y^{exo} - k_{exo\to z}^{exo}M_y^{exo} + k_{Z\to exo}M_y^{im} - \omega_1 M_Z^{exo} \quad [3]$$

$$\frac{dM_y^{im}}{dt} = -\Omega_{im}M_x^{im} - R_2^{im}M_y^{exo} - k_{z\to exo}^{im}M_y^{im} + k_{exo\to Z}M_y^{exo} - \omega_1 M_Z^{exo} \quad [4]$$

$$\frac{dM_z^{exo}}{dt} = -R_1^{exo}(M_z^{exo} - M_0^{exo}) - k_{exo\to Z}M_z^{exo} + k_{Z\to exo}M_z^{im} + \omega_1 M_y^{exo} \quad [5]$$

$$\frac{dM_z^{im}}{dt} = -R_1^{im}(M_z^{im} - M_0^{im}) - k_{Z\to exo}M_z^{im} + k_{exo\to Z}M_z^{exo} + \omega_1 M_y^{im} \quad [6]$$

Here,

$M_{x,y,z}^{exo}$ and $M_{x,y,z}^{exo}$ are magnetization of *exo*-oxazolidinone and iminium ion.

$k_{Z\to exo}$ and $k_{exo\to z}$ are rate constants .

Ω_{im} = offset frequency of iminium proton (H_1)

Ω_{exo} = offset frequency of *exo*-oxazolidinone proton (H_1)

$R_2^{exo} = \frac{1}{T_{2exo}}$, $R_2^{im} = \frac{1}{T_{2im}}$, $R_1^{exo} = \frac{1}{T_{1exo}}$ and $R_1^{im} = \frac{1}{T_{1im}}$

T_{2exo} and T_{2im} are spin-spin relaxation times for H_1 proton of *exo*-oxazolidinone and iminium ion.

T_{1exo} and T_{1im} are spin-lattice relaxation times for H_1 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_{0exo}, M_{0im}, ω_1, T_{1exo}, T_{1imi} and $k_{Z/exo}$.

Here,

M_{0exo}, is initial magnetization of *exo* oxazolidinone at equilibrium;

M_{0imi}, is initial magnetization of *Z*-Iminium ion at equilibrium;

ω_1 is strength of RF saturation in Hz ;

T_{1exo} and T_{1imi} are longitudinal relaxations of chosen proton in *exo*-oxazolidinone and *Z*-iminium ion respectively;

$k_{Z/exo}$ is rate of ring closing from *Z*-iminium to *exo*-oxazolidinone.

In all simulated spectra, we used M_{0exo} = 1 and ω_1= 45 Hz. The T_{1exo} values are experimentally obtained by inversion recovery experiment while saturating at 9.12 ppm. M_{0imi} and $k_{Z/exo}$ are varied to match simulation spectra with that of experimental data via multi parameter optimization.

Case 1. At 250 K:

M_0(*exo*) =1, ω_1 = 45 Hz and T_{1exo} = T_{1im} = 1.8 s are fixed.

Case 2. At 213 K:

M_0(*exo*) =1, ω_1 = 45 Hz and T_{1exo} = T_{1im} = 0.8 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.

$$E_{SCF}^{X} = E_{SCF}^{\infty} + Ae^{-a\sqrt{X}} \quad \text{Eq. 1}$$

$$E_{corr,MP2}^{\infty} = \frac{X^{\beta}E_{corr,MP2}^{X} - (X-1)^{\beta}E_{corr,MP2}^{X-1}}{X^{\beta} - (X-1)^{\beta}} \quad \text{Eq. 2}$$

$$E_{MP2}^{\infty} = E_{SCF}^{\infty} + E_{corr,MP2}^{\infty} \quad \text{Eq. 3}$$

$$E_{CCSD(T)}^{\infty} = E_{CCSD(T)}^{def2-TZVPP} + E_{MP2}^{\infty} - E_{MP2}^{def2-TZVPP} \quad \text{Eq. 4}$$

ΔG_{268} CCSD(T)/CBS (Boltzmann averaged) + ΔG_{solv} (CPCM) in a.u.

Ground states	
exo-oxazolidinone	-1282.024904
endo-oxazolidinone	-1282.023829
Z-iminium	-1282.022150
E-iminium	-1282.022783
Transition states (Ring Opening)	
exo-oxazolidinone	-1282.006070
endo-oxazolidinone	-1282.010202

Geometry of stationary points (most stable conformations)

***exo*-oxazolidinone + DPU**

1\1\GINC-WORKER1\FOpt\RTPSSTPSS\def2SVP/W06\C23H29N3O3\JHIOE\09-May-20
17\0\\#p tpsstpss/def2svp/w06 empiricaldispersion=gd3 scrf=(cpcm,solve
nt=n,n-DiMethylFormamide,read) opt int=ultrafine\\title\\0,1\C,-1.8931
520135,1.9076239109,-0.3230357501\C,-1.6467014096,4.2107435123,0.19111
26099\C,-3.0520489729,4.0445277726,-0.3912125564\H,-2.301196548,0.9891
057102,0.1397425265\H,-1.5920048449,4.93159841,1.0233454106\H,-0.93407
18413,4.5349658706,-0.5990810733\H,-3.7895229206,3.9922810108,0.428483
1942\H,-3.3347971572,4.8733515737,-1.0597245779\C,0.0487240683,2.49952

69207,0.8140310867\N,-1.345341637,2.8430183047,0.6823200963\O,0.445130
8612,1.931027115,-0.5266256479\C,-0.6624100671,1.5012013627,-1.1384848
142\O,-0.6293939681,0.8542057589,-2.1815149904\C,0.3218568015,1.429059
5633,1.869058646\H,0.0760835776,1.8808071035,2.8487488111\C,1.75795745
58,0.8646757994,1.8811427304\H,1.9690588203,0.487420029,0.8652044228\H
,-0.3973260467,0.6029878368,1.7140006903\C,-2.9697974335,2.6864756844,
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3.2102575344\H,3.8231962226,1.4910763507,2.215844592\C,1.8475621164,-0
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H,-1.1090521202,-1.0517052617,-1.6279187432\N,1.2308662255,-1.24094844
11,-1.2435746847\H,0.8186144361,-0.5196263554,-1.8478480539\C,2.617822
6997,-1.1196610841,-1.0473264285\C,3.2579816615,-0.0103354934,-1.64939
58292\C,3.3871803482,-2.0270815911,-0.2850215422\C,4.6326747261,0.1902
603821,-1.487043576\H,2.6610365755,0.704399133,-2.2262794995\C,4.76360
75982,-1.8076534784,-0.1284816355\H,2.8979608263,-2.8784051806,0.18792
75585\C,5.398185861,-0.7051698631,-0.7212558663\H,5.1062810863,1.05884
97882,-1.9575975523\H,5.3463991647,-2.5169422089,0.4699404098\H,6.4732
981917,-0.5450907315,-0.5898496741\C,-2.1712586723,-2.2071613063,-0.30
11788121\C,-3.38097299,-1.6547231738,-0.7883946995\C,-2.2230058882,-3.
1582834981,0.743255168\C,-4.6098717021,-2.0386509177,-0.2410184218\H,-
3.3493129561,-0.9200154059,-1.6015025671\C,-3.4641899697,-3.5296544698
,1.280839416\H,-1.295238079,-3.5898444045,1.1188465802\C,-4.6626151803
,-2.9789096843,0.8013039585\H,-5.5317781549,-1.5960810946,-0.633754295
7\H,-3.4878771239,-4.267005533,2.0911668909\H,-5.6240328451,-3.2786870
6,1.2307751164\H,0.6731146383,3.3947546426,0.949821062\\Version=ES64L-
G09RevD.01\State=1-A\HF=-1283.2813331\RMSD=5.862e-09\RMSF=5.445e-06\Di
pole=-1.2930581,3.0343326,0.0427922\Quadrupole=5.2194012,0.5990893,-5.
8184905,-2.1630566,2.8182429,-1.81857\PG=C01 [X(C23H29N3O3)]\\@

***endo*-oxazolidinone + DPU**

1\1\GINC-LOGIN\FOpt\RTPSSTPSS\def2SVP/W06\C23H29N3O3\ROOT\09-May-2017\
0\\#p tpsstpss/def2svp/w06 empiricaldispersion=gd3 scrf=(cpcm,solvent=
n,n-DiMethylFormamide,read) opt int=ultrafine\\title\\0,1\C,1.45388161

83,-3.0315153584,0.2390818279\C,3.3463521724,-2.1535086269,1.339562582
2\C,3.1025692677,-3.5341685474,1.9554293038\H,1.1634017382,-3.63353683
14,-0.6426277988\H,4.4124227251,-1.8967277512,1.2387984942\H,2.8540910
054,-1.3658007814,1.9504888015\H,3.8138454697,-4.260015475,1.525351314
4\H,3.2291068245,-3.5330610132,3.0496264078\C,2.3178326125,-1.11524645
96,-0.6949415884\N,2.717348006,-2.2988987854,0.0009054616\O,0.94964755
04,-0.7592635581,-0.0902054299\C,0.4237340617,-1.8997880938,0.38230526
93\O,-0.7048502503,-1.9588062497,0.849291508\C,3.2214712848,0.09704328
08,-0.6081321064\H,2.6984051067,0.9361286706,-1.1009758779\C,4.6087905
046,-0.0993806008,-1.2637609705\H,5.1072185003,-0.9477688803,-0.756222
8482\H,3.3479902469,0.376479168,0.4523385859\C,1.6587917607,-3.8781927
847,1.5178582705\H,1.5223729256,-4.9516156368,1.3190419035\H,0.9196063
206,-3.5826837843,2.280997662\C,4.510602859,-0.4377524394,-2.761804062
5\H,3.9985058403,-1.4002242987,-2.9361258625\H,3.958573964,0.349589675
7,-3.3083260102\H,5.5186075249,-0.5146642667,-3.2057764828\C,5.4617198
075,1.1600177699,-1.0332174078\H,5.563471822,1.3833965459,0.0438457513
\H,6.4743456078,1.0314378995,-1.4541796372\H,4.9998863925,2.0395179256
,-1.5194634657\C,-2.372490514,1.35923812,0.0245016125\O,-3.183301147,2
.2650812381,-0.1953696034\N,-2.6925113943,0.0105315751,0.0641289712\H,
-1.9544437234,-0.6425193497,0.3734197145\N,-1.0198166211,1.5729113199,
0.2679836104\H,-0.4161742038,0.7470710662,0.3230170335\C,-0.3424660024
,2.7953981047,0.4111696461\C,1.0041602625,2.734600878,0.8447890926\C,-
0.917305421,4.0600085069,0.1453839362\C,1.761610049,3.9010762239,0.992
1500044\H,1.4472975608,1.7595907533,1.0697825853\C,-0.1462783972,5.220
7056928,0.3084322246\H,-1.9544271155,4.1157038557,-0.1854311227\C,1.19
23537946,5.1576274359,0.7255506438\H,2.8032187578,3.8236467461,1.32334
80043\H,-0.6068472111,6.1926285604,0.0975977092\H,1.7827635215,6.07220
86106,0.8431655959\C,-3.9274084271,-0.5968025676,-0.2161949641\C,-3.99
48799442,-2.0060858216,-0.0804405372\C,-5.0847786371,0.1054729049,-0.6
276175331\C,-5.1848620402,-2.6909004929,-0.3486149561\H,-3.100945274,-
2.5538017317,0.2370822755\C,-6.268333155,-0.5990247246,-0.8935787258\H
,-5.0427586912,1.1899417841,-0.7288200373\C,-6.3342668551,-1.994261220
6,-0.7586519464\H,-5.2112478927,-3.7805489948,-0.2360435034\H,-7.15496
0757,-0.0384649248,-1.2114761577\H,-7.2652943402,-2.5311353283,-0.9684
021525\H,2.0600635488,-1.3648449327,-1.7377810149\\Version=ES64L-G09Re
vD.01\State=1-A\HF=-1283.277155\RMSD=7.249e-09\RMSF=5.030e-06\Dipole=4
.2797189,-2.4622704,0.1116238\Quadrupole=-2.0894392,3.244179,-1.154739
8,2.1717863,3.4398831,-2.1816851\PG=C01 [X(C23H29N3O3)]\\@

***Z*-iminium + DPU**

1\1\GINC-LOGIN\FOpt\RTPSSTPSS\def2SVP/W06\C23H29N3O3\ROOT\09-May-2017\
0\\#p tpsstpss/def2svp/w06 scrf=(cpcm,solvent=n,n-DiMethylFormamide,re
ad) empiricaldispersion=gd3 opt int=ultrafine\\title\\0,1\C,-2.3260180
861,-1.59324174,-0.8691349996\C,-3.9229533122,-0.6043165189,-2.4142404
112\C,-3.7703378109,-2.0783081257,-2.7901326004\H,-2.527925009,-2.1805
29862,0.0417350314\H,-4.9476469437,-0.2082594559,-2.4366952536\H,-3.26
30898891,0.0429741568,-3.0189200003\H,-4.5963410882,-2.6609829028,-2.3
466737406\H,-3.7854468108,-2.2264941341,-3.8808475116\C,-3.8257959832,
0.2250585321,-0.0989363669\H,-4.604205196,0.9332970021,-0.4142158147\N
,-3.4055566927,-0.5859086659,-1.0178670774\O,-0.9167528236,0.291705856
8,-0.2908478671\C,-0.9269434316,-0.9088133549,-0.6681784381\O,0.051403
0244,-1.66813525,-0.8840572503\C,-3.4217803866,0.2390546447,1.32916940
86\H,-2.6203022658,-0.4848262498,1.5393054356\C,-4.642796221,0.0089715
307,2.269298607\H,-5.4100319976,0.7666733108,2.0164535121\H,-3.0037024
716,1.245335629,1.5224707147\C,-2.4209225505,-2.4573780524,-2.15005488
74\H,-2.3465558115,-3.5293650871,-1.9160389141\H,-1.5826433541,-2.2033
211269,-2.8187327111\C,-5.2515930252,-1.3882893655,2.0611424743\H,-5.5
893934757,-1.5384337395,1.0195759216\H,-4.5127625125,-2.1767903068,2.2
959483127\H,-6.123886477,-1.5332075808,2.7216620301\C,-4.213083703,0.2
284054909,3.7285516018\H,-3.8115401719,1.2455642994,3.8804501401\H,-5.
0728725468,0.0919634878,4.4073815209\H,-3.430924499,-0.4964400382,4.01
97380622\C,2.7728441691,0.7305387645,0.0672727597\O,3.8870096138,1.219
1648011,0.3033132743\N,2.5195740506,-0.6319167424,-0.0092830332\H,1.57
5171353,-0.9374003934,-0.3400768836\N,1.6247447786,1.478128412,-0.1533
688976\H,0.7141443018,0.9671686466,-0.2135013139\C,1.5084142239,2.8722
782803,-0.2336408352\C,0.2067923704,3.3956733468,-0.4506873213\C,2.592
4805729,3.7773469748,-0.1224511928\C,-0.000620633,4.7754278243,-0.5492
010086\H,-0.6326125966,2.6983049408,-0.5415315863\C,2.3642417715,5.157
623966,-0.2262519956\H,3.5951797852,3.3851807924,0.0477736619\C,1.0758
773753,5.6724528306,-0.4382052161\H,-1.016264065,5.1522242166,-0.71628
18877\H,3.2170977289,5.8407635031,-0.1371642023\H,0.9120636202,6.75251
23638,-0.5156198357\C,3.4073921826,-1.6863589862,0.2448630958\C,2.9067
137697,-3.0026463336,0.0666065405\C,4.7481542178,-1.5233742721,0.67213
97076\C,3.7210968336,-4.1143448487,0.305860425\H,1.8695405988,-3.13073
87509,-0.2606486811\C,5.5482280606,-2.6511543899,0.9088847973\H,5.1432
979729,-0.5165556747,0.8076186483\C,5.0513534222,-3.951456536,0.729896
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

S64L-G09RevD.01\State=1-A\HF=-1283.2799569\RMSD=4.595e-09\RMSF=2.408e-
06\Dipole=-8.8073483,-1.2745358,-0.8234744\Quadrupole=14.2329333,-12.0
585813,-2.174352,1.2655675,6.7214813,2.1674415\PG=C01 [X(C23H29N3O3)]\
\@

***E*-iminium + DPU**

1\1\GINC-LOGIN\FOpt\RTPSSTPSS\def2SVP/W06\C23H29N3O3\ROOT\15-May-2017\
0\\#p tpsstpss/def2svp/w06 scrf=(cpcm,solvent=n,n-DiMethylFormamide,re
ad) empiricaldispersion=gd3 opt int=ultrafine\\title\\0,1\C,-1.6794133
038,-2.1765674288,-0.6773847147\C,-3.8331286825,-1.6322643894,-1.73074
70518\C,-3.236839848,-2.8695251536,-2.408290754\H,-1.6264268756,-2.984
5488408,0.072082728\H,-4.889250092,-1.7326442303,-1.4442241286\H,-3.70
45222072,-0.7217490054,-2.3424846729\H,-3.6486457165,-3.7831468646,-1.
9456219212\H,-3.4663647568,-2.8919273253,-3.4847621258\C,-3.2891007314
,-0.8019331636,0.5473393227\H,-2.5591061814,-0.8421434894,1.3635003042
\N,-2.9887583402,-1.4861957123,-0.5114303377\O,-0.6736810448,-0.080662
2213,0.0461702317\C,-0.461527757,-1.2283338214,-0.4308946805\O,0.64204
07512,-1.7424773756,-0.7493414598\C,-4.5346416951,-0.0095059257,0.7337
665337\H,-4.9948176463,0.2444110386,-0.2366728628\C,-4.3032733453,1.27
15163625,1.577548752\H,-3.8789157739,0.9519555471,2.5496020557\H,-5.25
0473756,-0.6701104226,1.2671084625\C,-1.7345324979,-2.739822096,-2.112
656316\H,-1.189327164,-3.691316263,-2.1888554476\H,-1.264838876,-2.023
6494703,-2.80855341\C,-3.292011796,2.2062753137,0.8932522284\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
0977,1.8450881057\H,-6.3519905164,1.3037489086,2.3678071004\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
9,0.2202420976\N,2.8506432276,-0.267166529,0.1525789317\H,1.9940098137
,-0.7689104427,-0.1815431257\N,1.5824351317,1.6023239086,-0.2247667558
\H,0.7855967994,0.9315618647,-0.1520868835\C,1.2113688029,2.9168378515
,-0.536479513\C,-0.1371014181,3.1251679783,-0.9243712948\C,2.084360415
3,4.0309203846,-0.492414958\C,-0.6006858319,4.405972944,-1.2411915699\
H,-0.8097989164,2.2629841418,-0.9717654908\C,1.6038706232,5.3070549554
,-0.8230570806\H,3.1224997149,3.8796854153,-0.1956565455\C,0.265811007
9,5.5119223409,-1.1945217382\H,-1.6495072112,4.5373460752,-1.531198557
\H,2.2948445134,6.1572190431,-0.782246694\H,-0.0962558855,6.5147406916
,-1.444637854\C,3.9042657173,-1.1067183078,0.5354071303\C,3.6568433849

,-2.5036922347,0.4954281322\C,5.1758517798,-0.6546827761,0.9653558911\
C,4.6491068102,-3.4148725347,0.8716331681\H,2.6733275157,-2.8538833692
,0.1635566313\C,6.157080949,-1.5841426456,1.3411749841\H,5.3777100041,
0.4163731822,0.9918418871\C,5.9104682597,-2.9652630721,1.2993367684\H,
4.4322382711,-4.4884775288,0.8305099015\H,7.134919179,-1.2141172054,1.
6711064966\H,6.6865388357,-3.6797618255,1.5935186905\\Version=ES64L-G0
9RevD.01\State=1-A\HF=-1283.282459\RMSD=7.265e-09\RMSF=3.081e-06\Dipol
e=-8.4933168,-2.798089,-0.466351\Quadrupole=11.8350709,-5.3651327,-6.4
699382,11.0489552,2.782214,3.3642656\PG=C01 [X(C23H29N3O3)]\\@

TS Ring Opening *endo*-oxazolidinone + DPU

1\1\GINC-WORKER0\FTS\RTPSSTPSS\def2SVP/W06\C23H29N3O3\JHIOE\18-May-201
7\0\\#p tpsstpss/def2svp/w06 empiricaldispersion=gd3 scrf=(cpcm,solven
t=n,n-DiMethylFormamide,read) opt=(ts,calcfc,noeigen) int=ultrafine\\t
itle\\0,1\C,-1.3927084451,-2.943102568,-0.1378541067\C,-3.2766330622,-
2.1916244499,-1.4130789051\C,-2.8871087419,-3.565421572,-1.9688124287\
H,-1.1959483855,-3.5309910499,0.7763862787\H,-4.3624369913,-2.02547861
96,-1.350425941\H,-2.8230906497,-1.3725842823,-2.006384347\H,-3.577980
0829,-4.3298658573,-1.573791313\H,-2.934168427,-3.5945599871,-3.068507
6497\C,-2.5768733853,-1.1584649721,0.7506559706\N,-2.6846334664,-2.237
4451303,-0.0545288293\O,-0.8172012806,-0.6439688787,0.1974312436\C,-0.
3433005819,-1.7888581318,-0.1896928889\O,0.8194989138,-1.9884298503,-0
.5726520124\C,-3.473945366,0.0305491803,0.6136182401\H,-3.0076090301,0
.8646083608,1.165538438\C,-4.9083948065,-0.2069091242,1.1705225558\H,-
5.3553867977,-1.0437124033,0.5999681892\H,-3.5367612502,0.3251824757,-
0.4475147051\C,-1.4586899297,-3.8015315468,-1.4220629376\H,-1.26295907
54,-4.863842986,-1.213598869\H,-0.6895215645,-3.4520949171,-2.13028422
37\C,-4.8999996618,-0.5929162094,2.6594177455\H,-4.375537644,-1.548281
7223,2.8365745474\H,-4.4052242718,0.1883667651,3.2656047123\H,-5.93312
88802,-0.7071328618,3.0309958517\C,-5.7581587341,1.0497778726,0.920137
1482\H,-5.7886554774,1.3068071203,-0.1534488309\H,-6.7948580085,0.8917
281996,1.2653733966\H,-5.3444480002,1.9170596756,1.4670797204\C,2.4350
828116,1.3746212812,-0.0478010765\O,3.2596477526,2.2932383552,0.033193
2989\N,2.7555262918,0.0262317732,-0.0024836033\H,2.0016632155,-0.65558
71001,-0.2216195824\N,1.067449695,1.5717627436,-0.199918264\H,0.454744
582,0.7459296079,-0.1178644238\C,0.3810376549,2.7808348024,-0.39059554
16\C,-1.0116890771,2.6914389149,-0.6370730768\C,0.9837358033,4.0606072
353,-0.3521456169\C,-1.7817301834,3.8435118676,-0.8246791745\H,-1.4766

712084,1.7023933556,-0.6830691597\C,0.1973265428,5.2055204165,-0.55102
61288\H,2.0545369372,4.1397540716,-0.1643462856\C,-1.1838222601,5.1146
410164,-0.7839404345\H,-2.8574997481,3.7428014137,-1.0083449921\H,0.68
1089094,6.1885552045,-0.5172574351\H,-1.7845607221,6.0179968061,-0.932
6471351\C,4.0108275817,-0.554403059,0.234443222\C,4.0809253493,-1.9703
964802,0.1920981769\C,5.1890878579,0.176778164,0.5193823274\C,5.291196
311,-2.6312880392,0.4271346675\H,3.1710645694,-2.5392330527,-0.0270534
541\C,6.3928494697,-0.5042345173,0.7541596549\H,5.1461248933,1.2655747
292,0.5477018192\C,6.4605475627,-1.9053218273,0.7112107474\H,5.3182373
766,-3.7261739675,0.3881073584\H,7.2943657316,0.079615334,0.973361014\
H,7.4074102461,-2.4238691296,0.8949287943\H,-2.1959560468,-1.380192449
9,1.7539522539\\Version=ES64L-G09RevD.01\State=1-A\HF=-1283.2728014\RM
SD=4.182e-09\RMSF=8.548e-07\Dipole=-5.8084804,-2.9534151,0.0952037\Qua
drupole=1.8203083,0.8853617,-2.70567,2.2093804,2.0196214,2.00474\PG=C0
1 [X(C23H29N3O3)]\\@

TS Ring Opening *exo*-oxazolidinone + DPU

1\1\GINC-WORKER1\FTS\RTPSSTPSS\def2SVP/W06\C23H29N3O3\JHIOE\17-May-201
7\0\\#p tpsstpss/def2svp/w06 empiricaldispersion=gd3 scrf=(cpcm,solven
t=n,n-DiMethylFormamide,read) opt=(ts,calcfc,noeigen) int=ultrafine\\t
itle\\0,1\C,-1.7703659025,-2.6077078276,0.2076097901\C,-3.145608726,-2
.7976143297,-1.7540896439\C,-2.8368347734,-4.2233381545,-1.2911684756\
H,-1.9082606443,-2.5783292918,1.3008931271\H,-4.1791738769,-2.64457664
63,-2.0989049517\H,-2.4451203006,-2.4640270181,-2.5444209907\H,-3.7029
671413,-4.6267687517,-0.7387652551\H,-2.6224867203,-4.896635724,-2.135
6126102\C,-2.9109137369,-0.6777055769,-0.502345587\N,-2.9107675283,-2.
0171422581,-0.5137618688\O,-0.9089626324,-0.5645360594,-0.726936359\C,
-0.5691685239,-1.6677677859,-0.1498210563\O,0.5906769363,-2.012923608,
0.1346494929\C,-2.9705175476,0.1394709659,0.7540534309\H,-2.414588257,
-0.3396379286,1.5773671901\C,-4.4406573219,0.4022946908,1.1973586462\H
,-4.9979460625,0.7719739273,0.3137725156\H,-2.4821877939,1.1038914059,
0.5390178526\C,-1.6293129682,-4.0491015826,-0.3412838676\H,-1.62262065
82,-4.7938329318,0.4683802636\H,-0.6742897827,-4.1371080577,-0.8848647
723\C,-5.1275899701,-0.8747966532,1.7077935358\H,-5.1341712557,-1.6705
218575,0.9433722321\H,-4.6036649025,-1.2669291329,2.5993899596\H,-6.17
30945804,-0.663844773,1.9932505105\C,-4.4536797465,1.5125178563,2.2628
020172\H,-4.0040406137,2.4440164365,1.8758846651\H,-5.4879648397,1.733
9595116,2.5795182594\H,-3.8827436329,1.2025611676,3.1574561742\C,2.353

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46584,-0.6881339567\H,-2.6589715489,3.957725351,-1.6628980073\H,0.5459
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