Supplementary Material

Measuring rapid hydrogen exchange in the homodimeric 36 kDa HIV-1 integrase catalytic core domain

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Running Title: Hydrogen exchange rates in the HIV-1 integrase CCD

Supporting information contains 16 pages, 1 table and 1 figure.

Derivation of Equation 1

Consider two proton spins I and W that undergo dipolar cross relaxation and chemical exchange. The cross relaxation rate is σ, and the chemical exchange rate is k:

$$I \xleftrightarrow{\text{k, }\sigma} W$$

If I_z (≡ $<I_z>$) is the average longitudinal magnetization per I spin and W_z (≡ $<W_z>$) is the analogous value for spin W, and R_1 and and R_{1W} are the longitudinal relaxation rates of the I and W spins, respectively, the Solomon equation for $\dot{I}_z$, modified to include chemical exchange, can be written as

$$\dot{I}_z = -R_1(I_z - I_0) - \sigma(W_z - W_0) - k(I_z - W_z) \tag{S1}$$

where I_0 and W_0 are bulk magnetization at equilibrium for I and W, respectively. If there are N equivalent W spins, W_1, W_2, … W_N, each of which cross relaxes and exchanges with I with rates $\sigma_i = \sigma$, $k_i = k$, for $i = 1, \ldots, N$, then

$$\dot{I}_z = -R_1(I_z - I_0) - \sum_{i=1}^{N}\sigma_i(W_{z,i} - W_{0,i}) - \sum_{i=1}^{N}k_i(I_z - W_{z,i}) \tag{S2}$$

All W spins are equivalent, so

$$\begin{aligned} \dot{I}_z &= -R_1(I_z - I_0) - N\sigma_i(W_z - W_0) - Nk_i(I_z - W_z) \\ \dot{I}_z &= -R_1(I_z - I_0) - \sigma_{IW}(W_z - W_0) - k_{IW}(I_z - W_z) \end{aligned} \tag{S3}$$

where $\sigma_{IW} = N\sigma_i$, $k_{h2o} = Nk_i$.

The pulse scheme is designed as an interleaved experiment, where water is alternately either inverted ($W_z(0) = W_z^{\downarrow}(0)$) or left along +z ($W_z(0) = W_z^{\uparrow}(0)$). Note that equilibrium values of I_o and W_o are identical, regardless of the initial conditions. Define $I_z^{\Delta} \equiv I_z^{\uparrow} - I_z^{\downarrow}$ and $W_z^{\Delta} \equiv W_z^{\uparrow} - W_z^{\downarrow}$. Then

$$\begin{aligned} \dot{I}_Z^{\uparrow} &= -R_1(I_Z^{\uparrow} - I_0) - \sigma_{IW}(W_z^{\uparrow} - W_0) - k_{h2o}(I_z^{\uparrow} - W_z^{\uparrow}) \\ \dot{I}_Z^{\downarrow} &= -R_1(I_Z^{\downarrow} - I_0) - \sigma_{IW}(W_z^{\downarrow} - W_0) - k_{h2o}(I_z^{\downarrow} - W_z^{\downarrow}) \end{aligned} \tag{S4}$$

or

$$\begin{aligned} \dot{I}_Z^{\Delta} &= -R_1(I_Z^{\Delta}) - \sigma_{IW}(W_z^{\Delta}) - k_{h2o}(I_z^{\Delta} - W_z^{\Delta}) \\ &= -(R_1 + k_{h2o})I_Z^{\Delta} + (-\sigma_{IW} + k_{h2o})W_z^{\Delta} \end{aligned}. \tag{S5}$$

Since the W spins represent water protons, W_z^{Δ} relaxes independently of I_z, according to the following equation:

$$W_z^{\Delta}(t) = 2W_0(\Delta f)e^{-R_{1W}T} = 2I_0(\Delta f)e^{-R_{1W}T} \tag{S6}$$

where $\Delta f = \left[W_z^{\uparrow}(0) - W_z^{\downarrow}(0)\right]/2W_0$. Eq S5 can then be rewritten as

$$\frac{I_z^{\Delta}(t)}{2I_0} = \frac{\Delta f(k_{h2o} - \sigma_{IW})e^{-R_{1W}T}}{R_1 + k_{h2o} - R_{1W}}\left[1 - e^{-(R_1 + k_{h2o} - R_{1W})T}\right] \tag{S7}$$

Prior derivations[1, 2] assumed a negligible σ_{IW} term, and for most situations this approximation holds, especially when mixing times, T, are short and $I_z^{\Delta}(t)$ is approximately linear. The $\sigma_{IW} \approx 0$ approximation also holds in cases where the NOE contribution is removed, i.e in the CLEANEX-PM scheme.[3] Applying the $\sigma_{IW} \approx 0$ approximation to long mixing times, however, will introduce an error in the observed parameters k_{h2o} and R_1. In this case, since $\sigma_{IW} < 0$, k_{h2o} would be overestimated because of the additional term, and R_1 would be underestimated, since

$$\frac{I_z^{\Delta}(t)}{2I_0} = \frac{\Delta f(k_{h2o} - \sigma_{IW})e^{-R_{1W}T}}{(R_1 + \sigma_{IW}) + (k_{h2o} - \sigma_{IW}) - R_{1W}}\left\{1 - e^{-[(R_1 + \sigma_{IW}) + (k_{h2o} - \sigma_{IW}) - R_{1W}]T}\right\} \tag{S8a}$$

The parameters used in fitting would be $R_1^{'} = R_1 + \sigma_{IW}$ and $k_{obs}^{'} = k_{h2o} - \sigma_{IW}$, or

$$\frac{I_z^{\Delta}(t)}{2I_0} = \frac{\Delta f\, k_{obs}e^{-R_{1W}T}}{R_1^{'} + k_{obs} - R_{1W}}\left\{1 - e^{-\left[R_1^{'} + (k_{h2o} - \sigma_{IW}) - R_{1W}\right]T}\right\} \tag{S8b}$$

Thus, an identical model can be fit to situations where the $\sigma_{IW} \approx 0$ approximation does not apply; however, the parameters $R_1^{'}$ and k_{obs} must be corrected to account for the NOE contribution. In our experiments, we use the pH-independence of the NOE to determine the size of the correction.

Adding another proton, S, which can cross-relax with I as well as exchange with water, will affect the initial expression for $\dot{I}_Z^{\Delta}$ in the following way:

$$\dot{I}_Z^{\Delta} = -R_1(I_Z^{\Delta}) - \sigma_{IW}(W_z^{\Delta}) - k_{h2o}(I_z^{\Delta} - W_z^{\Delta}) - \sigma_{IS}(S_z^{\Delta}) \tag{S9}$$

A closed-form solution is still possible as long as S exchanges very rapidly with water compared to the k_{h2o} exchange rate (e.g. for an OH group), i.e. $S^{\Delta}_z(T) \approx W^{\Delta}_z(T)$. In this case,

$$\frac{I_z^{\Delta}(T)}{2I_0} = \frac{\Delta f(k_{h2o} - \sigma_{IW} - \sigma_{IS})e^{-R_{1W}T}}{R_1^{'} + (k_{h2o} - \sigma_{IW} - \sigma_{IS}) - R_{1W}}\left\{1 - e^{-\left[R_1^{'} + (k_{h2o} - \sigma_{IW} - \sigma_{IS}) - R_{1W}\right]T}\right\} \tag{S10}$$

If we define $k_{noe} \equiv -\sum_j \sigma_{I,j}$, where the summation extends over every nearby rapidly exchanging proton, j, and if we let $k_{obs} = k_{h2o} + k_{noe}$, we are left with the simple expression presented in the main text (eq 1b):

$$S(T) = \frac{I_z^{\Delta}(T)}{2I_0} = \frac{\Delta f\, k_{obs}e^{-R_{1W}T}}{R_1^{'} + k_{obs} - R_{1W}}\left[1 - e^{-(R_1^{'} + k_{obs} - R_{1W})T}\right] \tag{S11}$$

where $R_1^{'} = R_1 - k_{noe}$.

The error introduced by neglecting cross-relaxation in deriving eq S11 was tested by fitting the equation to simulated signal intensity, *S(T)*, profiles calculated ($T_{\mathrm{max}} = 0.5$s) with inclusion of proton-proton cross-relaxation (σ_{IS}) terms. The best fitted values of k_{h2o} or k_{noe} obtained were found to be systematically slightly smaller than the values used to generate *S(T)*.

For values of $\sigma < 3$ (corresponding to a proton-proton separation > 2.6Å) the error introduced is less than 10%.

Pulse Sequence Code (for Bruker DRX/Avance-II Consoles)

```
#include "bits.nt"

;
; title:   trosy-fb_h2oex2df.ncf
; summary: H2O-exchange utility program
; author:  Nick Fitkzee (nfitzkee@nih.gov)
; date:    July 2, 2010
;
; pulse lengths and amplifier configuration (DRX, 800 MHz):
;
; * Proton Channel (H=f1, carrier on H2O)
;   p1    =  90 deg (10us)   pulse @ pl1
;   p9    = 180 deg (2ms)    pulse @ sp10 (Sinc1.1000)
;   p2    =  90 deg (1.2ms)  pulse @ sp9  (Sinc1.1000, phcor21)
;         =  90 deg (1.2ms)  pulse @ sp0  (Sinc1.1000, phcor11)
;         =  90 deg (1.2ms)  pulse @ pl12 (phcor10)
;   p25   =  90 deg (1ms)    pulse @ sp1  (Sinc1.1000, phcor22=phcor23)
;         =  90 deg (1ms)    pulse @ sp2  (Sinc1.1000, phcor20)
;   p29   =  ~1 deg (1us)    pulse @ pl20 (spy pulse)
;
; * Nitrogen Channel (N=f2, carrier on ~117.5 ppm, in0 = 0.5/sw, loop l3)
;   p7    = 90 deg (50us)    pulse @ pl7
;
; * Carbon Channel (C1=f4 carrier on 56ppm, C2=f5 carrier on 176ppm)
;   p4    = 180 deg (17.8us) pulse @ pl4 (C1) or pl6 (C2)
;   pcpd5 = garp decoupling (1.5 kHz field) @ pl31
;
; For Avance systems or system with one 13C amplifier, you must
; modify the pulse program so that the carrier is on 176 ppm and
; the Ca decoupling pulse uses a shaped pulse with an offset.
;
; * Gradient pulses
;   p20   =     2m  -> gp10
;   p21   =     1m  -> gp2, gp3
;   p22   = 101.3u  -> gp4
;   p23   =   500u  -> gp5, gp6
;
;   gp0   (  5% z)  (gron)      : On during HX mixing time
;   gp1   (  1% z)  (gron)      : Suppress radiation damping during INEPT
;   gp2   (-10% z)  (sine.50)   : S3E refocussing
;   gp3   ( 30% z)  (sine.50)   : S3E refocussing
;   gp4   ( 60% z)  (sine.20)   : Decoding gradient
;   gp5   (-60% z)  (sine.20)   : 1/2 encoding gradient
;   gp6   ( 60% z)  (sine.20)   : 1/2 encoding gradient
;   gp10  (0.5% z)  (sine.100)  : ZZ crusher
;
; The vdlist controls the length of the mixing times.
; Each entry in vdlist is multiplied by two, so if vdlist specifies
; 10 ms, the actual time will be 20 ms.

; delays and phasing

"d11=50m"
"d21=2.4m-10u"
"d22=2.3m-p21-p25"
"d23=2.3m-p21"
"d26=d23+p7-p2-p1*0.818+p22*0.5+de*0.5+5u"
"d27=d23+p7-p2-p1*1.182-p22*0.5-de*0.5-15u"

; Uncomment for 15N 0,0 phasing
```

```
;"d25=200u"
;"d0=d25*0.5+p7*0.637-p4*2-p1*0.5-2u"

; Uncomment for 15N -90,180 phasing
"d25=200u"
"d0=in0*0.5+d25*0.5+p7*0.637-p4*2-p1*0.5-2u"

;- Pulse Program Control ---------------------------------------------------

; When using spy pulses, TD = l8 = ~8, ns = 1, d1 ~ 2.0 s.  Read the water
; peak from the final FID.

; To measure W0/ W+, uncomment the following lines:
;#define SPY_PULSE
;#define SPY_REFERENCE

; To measure W-, uncomment the following lines:
;#define SPY_PULSE
;#define SPY_INVERSION


; For the reference experiment, TD = l3 * 2, ns >= 8, d1 >= 8.0 s.
; To measure the reference experiment (I0/M0), uncomment the following line:
;#define REFERENCE

; Leave all of the above commented to measure the actual HX measurement.
; For the HX experiment, TD = l3*l6*4, ns >= 8, d1 ~ 2.0.

; Water flip backs may be tuned at any of the goto 777 lines.

;- End Pulse Program Control -----------------------------------------------

"p29=1u"
"d9=p9"

#ifdef REFERENCE
#define PLUS_Z
#endif

#ifdef PLUS_Z
"l5=2"
#else
"l5=1"
#endif

"l7=1"

1       ze
        1m RESET
2       100u do:C2 do:N
        900u LOCK_ON
        d11
3       1m
4       1m
5       1m
6       1m
        d1

        1m LOCK_OFF
        10u pl1:H
        10u pl7:N
        10u pl6:C2
        10u pl4:C1
```

```
#ifdef SPY_REFERENCE
        if "l7==l8" goto 770
#endif

#ifndef REFERENCE

;-- Water flip phase: +/- z -------------------------------

20     3u pl0:H
        3u
        if "l5==1" goto 30
        d9               ; No flipback applied
        goto 40
30     (p9:sp10 ph6):H   ; Flip to -z
40     3u
        3u pl4:C1 pl1:H
;goto 777

#ifdef SPY_INVERSION
#ifndef PLUS_Z
        if "l7!=l8" goto 45
       (p1*2 ph0):H
        3u
#endif  ;-- PLUS_Z
#endif  ;-- SPY_INVERSION

#ifdef SPY_PULSE
45      10u gron0         ; eliminate radiation damping
        10m
        500u groff
#else
45      5u gron0
        vd                ; must not exceed 400 ms
        5u groff
        10u
        5u gron0
        vd                ; must not exceed 400 ms
        5u groff
        500u
#endif
#ifdef SPY_INVERSION
        if "l7==l8" goto 770
#endif  ;-- SPY_INVERSION

#endif  ;-- ifndef REFERENCE

;-- Start INEPT to 15N ------------------------------------

60      5u pl1:H
        5u
       (p1 ph0):H
        5u gron1
        d21
        5u groff
       (center (p1*2 ph0):H (p7*2 ph0):N)
        5u gron1
        d21
        5u groff
       (p1 ph1):H
        3u pl0:H
        3u
        if "l5==1" goto 70
```

```
       (p2:sp9 ph21:r):H     ; Water starts +z: std flip
        goto 80
70     (p2:sp0 ph11:r):H     ; Water starts -z: inv flip
80      3u
        3u pl1:H

;goto 777
        p20:gp10
85      200u

;-- TROSY Evolution and back transfer ---------------------

        if "l1==1" goto 88
       (p7 ph17):N
        105u
        p23:gp6
        d25
       (p7*2 ph17):N
        p23:gp5
        goto 89

88     (p7 ph7):N
        105u
        p23:gp5
        d25
       (p7*2 ph7):N
        p23:gp6

89      105u
        d0
       (p4*2 ph0):C1
        4u
       (p4*2 ph0):C2
        d0

        if "l1==1" goto 78
       (p1 ph2):H
        3u
        2u pl2:H
       (p25:sp1 ph22:r):H
        goto 79

78     (p1 ph12):H
        3u
        2u pl0:H
       (p25:sp1 ph23:r):H

79      3u
        2u pl1:H
;goto 777
        p21:gp2
        d22
        300u
       (center (p1*2 ph0):H (p7*2 ph0):N)
        p21:gp2
        d22
        305u pl0:H
       (p25:sp2 ph20:r):H
        3u
        2u pl1:H
        if "l1==1" goto 98
       (p1 ph0):H (p7 ph4):N     ;DOUBLE 90
        goto 99
```

```
98     (p1 ph0):H (p7 ph14):N    ;DOUBLE 90
99      5u
;goto 777
        p21:gp3
        295u pl12:H
       (left (d26 p2 ph10:r 3u 2u pl1 p1*2 ph0 3u 2u pl12 p2 ph10:r d27):H
             (d23 p7*2 ph0 d23):N)
        5u pl1:H
;goto 777
        p21:gp3
        295u pl31:C2
       (p7 ph0):N

#ifdef SPY_FINAL
        if "l7==l8" goto 770
#endif

        goto 776
770     3u
        2u pl20:H
       (p29 ph30):H
        goto 777

776     p22:gp4
777     10u pl31:C2
        go=2 ph31 cpds5:C2
        100u do:N do:C2
        100u LOCK_ON
        d11 wr #0 if #0 zd

#ifdef SPY_PULSE
        800u iu7
        lo to 3 times l8
#else
        800u iu5
#ifndef REFERENCE
        lo to 3 times 2
#endif
#endif

        500u ru5
        500u ivd

#ifndef SPY_PULSE
#ifndef REFERENCE
        lo to 4 times l6
#endif
#endif

        100u iu1
        900u

#ifndef SPY_PULSE
        lo to 6 times 2
#endif

        100u id0
        100u ru1
        100u ip31*2     ; generally needed to move streak at 15N
        100u ip7*2      ; carrier to edge of spectrum, since d1
        100u ip17*2     ; is less than H2O T1.
        500u
```

```
#ifndef SPY_PULSE
        lo to 6 times l3
#endif SPY_PULSE

        1m rd0
1m do:C2 do:N
1m LOCK_ON
1m RESET
1m
exit

ph0=0
ph1=1 1 1 1 3 3 3 3     ;original setting
                        ;phase cycled to remove Boltzmann
ph30=0 2 2 0 1 3 3 1
ph2=3                   ;original setting
ph4=3                   ;original setiing
ph5=1

ph6=0
ph16=2

ph15=1
ph10=2
ph20=0
ph22=1
ph23=3
ph11=2
ph21=0

ph12=1                  ;original seting
ph7=1 0 3 2
ph17=1 2 3 0
ph14=1                  ;original setting

#ifdef SPY_PULSE
ph31=0 2 2 0 1 3 3 1
#else
ph31=1 2 3 0 3 0 1 2
#endif
```

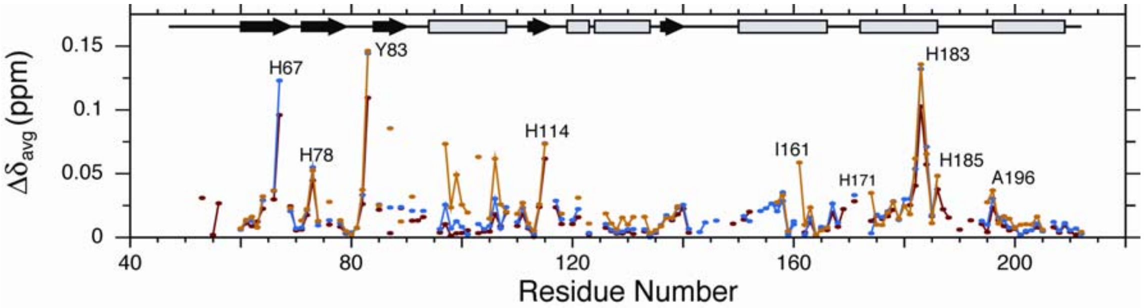

Figure S1. Chemical shift differences as a function of pH in IN$^{50-212}$. Weighted mean changes in chemical shift[4] are plotted as $\Delta\delta_{avg} = \sqrt{\frac{1}{2}(\Delta\delta_{HN}^2 + \frac{1}{25}\Delta\delta_N^2)}$, where $\Delta\delta_N$ and $\Delta\delta_{HN}$ are the respective changes in nitrogen and amide proton chemical shifts. Chemical shift changes are generally small with the exceptions of His residues, which titrate in the range from pH 6.4-9.2. Residues proximal to His side chains (Y83, A196) also show larger than average chemical shift changes. Chemical shift differences are shown relative to pH 6.4 for pH 7.35 (red), 8.3 (blue) and 9.2 (orange).

Table S1 – Hydrogen Exchange Parameters for IN$^{50\text{-}212}$

Residue		N_k[1]	k_{h2o} (s^{-1})[2]	σ_{h2o} (s^{-1})[3]	k_{noe} (s^{-1})	σ_{noe} (s^{-1})	N_{R1}[4]	R_1 (s^{-1})	σ_{h2o} (s^{-1})	log(*P*)[5]
52	GLY	1	24.5	0.3	N.D.[6]	N.D.	0	N.D.	N.D.	0.1
53	GLU	2	2.37	0.06	3.02	0.08	2	9	4	-0.1
54	VAL	1	1.36	0.01	N.D.	N.D.	0	N.D.	N.D.	-0.4
55	ASP	2	2.18	0.07	0.8	0.2	2	4	1	-0.1
56	SER	2	2.9	0.4	3.1	0.5	2	9	3	0.4
57	SER[7]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
58	PRO	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
59	GLY	1	11.5	0.4	N.D.	N.D.	0	N.D.	N.D.	-0.4
60	ILE[8]	4	< 0.0048	0.0004	5.4	0.1	4	7.1	0.3	2.4
61	TRP	4	< 0.001	N.D.	0.60	0.05	0	N.D.	N.D.	≥ 3.0
62	GLN	4	< 0.001	N.D.	1	2	1	4	2	≥ 3.6
63	LEU	3	0.131	0.009	0.7	0.5	2	4	1	1.1
64	ASP	4	< 0.001	N.D.	0.7	0.2	0	N.D.	N.D.	≥ 3.1
65	CYS[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
66	THR	4	< 0.001	N.D.	0.99	0.01	2	1.4	0.2	≥ 4.0
67	HIS	3	0.24	0.02	9.2	0.2	3	14	2	2.0
68	LEU	3	< 0.001	N.D.	1.14	0.03	0	N.D.	N.D.	≥ 3.7
69	GLU	2	1.02	0.03	1.00	0.06	2	4	1	-0.1
70	GLY	2	1.4	0.1	0.6	0.2	3	10	10	0.6
71	LYS[7]	4	< 0.0030	0.0002	1.60	0.05	2	3.2	0.3	3.3
72	VAL	4	< 0.001	N.D.	0.48	0.01	2	1.2	0.4	≥ 3.0
73	ILE	4	< 0.001	N.D.	0.7	0.1	0	N.D.	N.D.	≥ 2.8
74	LEU	4	< 0.001	N.D.	0	1	0	N.D.	N.D.	≥ 2.8
75	VAL[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
76	ALA	4	< 0.001	N.D.	0.4	0.8	0	N.D.	N.D.	≥ 3.5
77	VAL[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
78	HIS	4	< 0.001	N.D.	0.42	0.04	0	N.D.	N.D.	≥ 4.0
79	VAL	4	< 0.001	N.D.	2.62	0.09	4	4.3	0.4	≥ 3.5
80	ALA	4	0.0033	0.0003	4.6	0.2	4	7.7	0.4	3.0
81	SER	4	0.001	0.002	1	2	1	4	2	4.0
82	GLY	4	< 0.001	N.D.	0.90	0.05	1	1.5	0.3	≥ 4.2
83	TYR	4	< 0.001	N.D.	1.2	0.3	1	1.8	0.4	≥ 3.5
84	ILE[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
85	GLU	4	0.0071	0.0009	0.4	0.3	1	8	1	2.0
86	ALA[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
87	GLU	4	< 0.001	N.D.	0.51	0.02	0	N.D.	N.D.	≥ 3.1
88	VAL	3	0.0016	0.0009	3.23	0.09	3	5.1	0.7	2.6
89	ILE	4	< 0.001	N.D.	0.00	0.01	0	N.D.	N.D.	≥ 2.8

---

[1] Number of pH values where k_{h2o} could be determined

[2] k_{h2o} values are reported at the reference pH 6.4

[3] Uncertainties (σ) are reported as the standard deviations of Monte-Carlo simulations (see Material and Methods).

[4] Number of experiments (at different pH values) where R_1 could be determined accurately ($\sigma_{R1}/R_1 < 0.5$).

[5] $\log_{10}$ of the protection factor, plotted in figure 5

[6] Not determined.

[7] This residue could not be resolved in the 2-D spectrum.

[8] A poor fit of $k_{obs}(pH)$ was observed, indicating a pH-dependent NOE contribution, discussed in the text. k_{h2o} is an upper bound for these residues.

Residue		N_k[1]	k_{h2o} (s^{-1})[2]	σ_{h2o} (s^{-1})[3]	k_{noe} (s^{-1})	σ_{noe} (s^{-1})	N_{R1}[4]	R_1 (s^{-1})	σ_{h2o} (s^{-1})	log(*P*)[5]
90	PRO	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
91	ALA	4	0.0034	0.0001	0.51	0.02	2	1.4	0.3	2.9
92	GLU	2	3.2	0.2	2.5	0.4	1	4.3	0.4	-0.4
93	THR	3	0.12	0.01	1.8	0.1	2	4.1	0.6	1.3
94	GLY[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
95	GLN	1	20	1	N.D.	N.D.	0	N.D.	N.D.	-0.4
96	GLU	3	0.08	0.01	4.0	0.2	2	7.4	0.7	1.4
97	THR	4	0.014	0.004	3	2	1	6	2	2.3
98	ALA	4	0.0020	0.0002	0.96	0.03	2	2.0	0.3	3.5
99	TYR	4	< 0.001	N.D.	0.67	0.12	0	N.D.	N.D.	≥ 3.4
100	PHE	4	< 0.001	N.D.	0.52	0.03	0	N.D.	N.D.	≥ 3.4
101	LEU	4	< 0.001	N.D.	0.41	0.03	0	N.D.	N.D.	≥ 3.1
102	LEU	2	< 0.001	N.D.	0.58	0.02	1	1.15	0.09	≥ 2.8
103	LYS	4	0.0015	0.0004	0.57	0.04	3	2	1	3.2
104	LEU	3	0.0016	0.0008	0.62	0.05	0	N.D.	N.D.	3.0
105	ALA	4	< 0.001	N.D.	0.72	0.02	0	N.D.	N.D.	≥ 3.4
106	GLY	4	< 0.001	N.D.	2.4	0.2	3	4.7	0.6	≥ 3.9
107	ARG	4	< 0.001	N.D.	1.45	0.08	3	2.9	0.6	≥ 3.9
108	TRP	4	< 0.001	N.D.	1.25	0.07	2	2.2	0.6	≥ 3.4
109	PRO	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
110	VAL	4	0.0074	0.0003	1.07	0.06	4	2.5	0.4	1.8
111	LYS	4	0.0049	0.0004	0.65	0.06	2	1.7	0.4	2.8
112	THR	4	0.0043	0.0001	0.77	0.06	3	1.7	0.4	3.0
113	VAL	4	< 0.001	N.D.	0.46	0.02	1	1.3	0.3	≥ 3.1
114	HIS	4	< 0.001	N.D.	0.65	0.08	1	5	1	≥ 4.0
115	THR	4	0.0012	0.0003	2.19	0.09	4	3.9	0.3	4.1
116	ASP	1	3.6	0.3	N.D.	N.D.	0	N.D.	N.D.	-0.0
117	ASN	3	0.21	0.01	1.7	0.1	3	3.4	0.9	1.6
118	GLY	4	0.042	0.001	2.3	0.1	2	3.7	0.3	2.6
119	SER	1	37	4	N.D.	N.D.	0	N.D.	N.D.	-0.4
120	ASN	3	0.32	0.03	2.8	0.3	2	4.8	0.8	1.9
121	PHE	4	0.015	0.001	2.18	0.09	3	3.4	0.7	2.5
122	THR	2	0.001	0.004	6	3	1	8	3	3.6
123	SER	4	0.0061	0.0003	2.9	0.1	4	4.4	0.6	3.4
124	THR[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
125	THR[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
126	VAL	4	0.064	0.005	3.4	0.2	4	8	4	1.3
127	LYS	4	0.0035	0.0004	1.43	0.06	4	2.5	0.5	2.9
128	ALA[7]	4	< 0.001	N.D.	0.7	0.2	1	1.18	0.08	≥ 3.7
129	ALA[7]	4	< 0.001	N.D.	0.3	0.1	0	N.D.	N.D.	≥ 3.6
130	CYS	4	< 0.001	N.D.	0.44	0.03	1	3.7	0.5	≥ 4.2
131	GLU	3	< 0.001	N.D.	0.2	0.3	1	7	3	≥ 3.6
132	TRP	2	< 0.001	N.D.	0.55	0.04	2	4	1	≥ 3.1
133	ALA	3	< 0.001	N.D.	0.3	0.6	0	N.D.	N.D.	≥ 3.5
134	GLY	4	< 0.001	N.D.	0.1	0.3	0	N.D.	N.D.	≥ 3.9
135	ILE	3	< 0.001	N.D.	0.1	0.3	0	N.D.	N.D.	≥ 3.1
136	LYS	4	< 0.001	N.D.	0.33	0.02	1	1.8	0.7	≥ 3.4
137	GLN	4	0.0233	0.0005	0.04	0.03	2	3	1	2.4
138	GLU	4	< 0.001	N.D.	1.47	0.02	4	2.8	0.5	≥ 3.3
139	PHE	4	0.058	0.003	0.07	0.08	3	3	3	1.5

Residue		N_k[1]	k_{h2o} (s^{-1})[2]	σ_{h2o} (s^{-1})[3]	k_{noe} (s^{-1})	σ_{noe} (s^{-1})	N_{R1}[4]	R_1 (s^{-1})	σ_{h2o} (s^{-1})	log(*P*)[5]
140	GLY	3	0.103	0.009	1.3	0.1	3	2.9	0.4	1.9
141	ILE	3	0.3	0.1	3.9	0.7	3	8	3	0.6
142	PRO	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
143	TYR	2	0.9	0.1	0.7	0.2	2	3	1	0.2
144	ASN	2	1.10	0.04	1.3	0.1	1	3.1	0.2	1.1
145	PRO	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
146	GLN	2	1.92	0.08	0.89	0.09	2	4	2	0.2
147	SER	1	4.3	0.2	N.D.	N.D.	0	N.D.	N.D.	0.6
148	GLN	1	4.9	0.2	N.D.	N.D.	0	N.D.	N.D.	0.3
149	GLY	2	3.2	0.1	0.6	0.2	2	5	2	0.6
150	VAL	1	1.9	0.2	N.D.	N.D.	0	N.D.	N.D.	-0.2
151	ILE	3	0.074	0.003	0.94	0.05	2	2.6	0.7	0.9
152	GLU	3	0.022	0.006	1.25	0.09	2	4	1	1.6
153	SER[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
154	MET	2	0.6	0.1	0.9	0.2	2	3.9	0.9	1.2
155	ASN	2	0.21	0.03	0.3	0.1	1	1.5	0.5	1.9
156	LYS	2	0	3	0	6	0	N.D.	N.D.	1.6
157	GLU	4	0.0183	0.0007	0.8	0.1	4	3.7	0.7	2.0
158	LEU	4	0.003	0.001	0.3	0.7	1	1.2	0.7	2.4
159	LYS	3	0.002	0.001	0.4	0.6	2	1.4	0.7	3.0
160	LYS	2	< 0.001	N.D.	1	2	0	N.D.	N.D.	≥ 3.7
161	ILE[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
162	ILE	2	0.0011	0.0002	0.35	0.08	0	N.D.	N.D.	2.6
163	GLY	4	0.0069	0.0001	0.40	0.06	2	1.9	0.8	2.8
164	GLN	4	0.039	0.002	0.8	0.1	2	2.9	0.6	2.3
165	VAL	4	0.020	0.005	1	3	1	2	3	1.8
166	ARG	4	0.054	0.009	1.6	0.3	2	3.4	0.6	1.8
167	ASP	3	0.29	0.05	0.7	0.3	3	4	2	1.1
168	GLN	3	0.109	0.005	0.90	0.05	2	2.6	0.6	1.5
169	ALA[6]	0	N.D.	N.D.	N.D.	N.D.	0	N.D.	N.D.	N.D.
170	GLU	1	8.4	0.5	N.D.	N.D.	0	N.D.	N.D.	-0.8
171	HIS	3	0.150	0.007	3.7	0.2	2	5.4	0.5	1.8
172	LEU	1	5.0	0.8	N.D.	N.D.	0	N.D.	N.D.	-0.0
173	LYS	1	0	20	N.D.	N.D.	0	N.D.	N.D.	0.1
174	THR	4	0.021	0.002	1.6	0.1	3	4	1	2.3
175	ALA	4	0.0021	0.0009	1.4	0.4	1	2.6	0.5	3.5
176	VAL[7]	4	< 0.001	N.D.	0.8	0.2	0	N.D.	N.D.	≥ 2.9
177	GLN[7]	4	< 0.001	N.D.	0.7	0.1	1	1.0	0.1	≥ 3.5
178	MET	4	< 0.001	N.D.	0.9	0.2	2	1.4	0.3	≥ 3.8
179	ALA	2	< 0.001	N.D.	0.48	0.03	0	N.D.	N.D.	≥ 3.7
180	VAL	3	< 0.001	N.D.	0.57	0.02	0	N.D.	N.D.	≥ 2.9
181	PHE	4	< 0.001	N.D.	1.78	0.07	4	4.6	0.4	≥ 3.2
182	ILE	4	< 0.001	N.D.	0.52	0.04	1	1.7	0.6	≥ 3.0
183	HIS	4	0.00	0.02	0	3	0	N.D.	N.D.	3.7
184	ASN	4	< 0.001	N.D.	0.7	0.7	0	N.D.	N.D.	≥ 4.7
185	LYS	4	< 0.001	N.D.	2.1	0.2	3	6	3	≥ 3.9
186	LYS	4	0.0032	0.0004	1.00	0.06	4	3	1	3.2
187	ARG	2	2.9	0.7	1.0	0.6	2	6	3	0.4
188	LYS	2	3.2	0.2	2.0	0.2	1	3.8	0.2	0.3
189	GLY	1	25.2	0.5	N.D.	N.D.	0	N.D.	N.D.	-0.4

Residue		N_k[1]	k_{h2o} (s^{-1})[2]	σ_{h2o} (s^{-1})[3]	k_{noe} (s^{-1})	σ_{noe} (s^{-1})	N_{R1}[4]	R_1 (s^{-1})	σ_{h2o} (s^{-1})	log(*P*)[5]
190	GLY	1	10.2	0.4	N.D.	N.D.	0	N.D.	N.D.	0.1
191	ILE	1	4.48	0.08	N.D.	N.D.	0	N.D.	N.D.	-0.6
192	GLY	2	5.7	0.3	2.5	0.4	2	13	8	-0.1
193	GLY	1	1.97	0.05	N.D.	N.D.	0	N.D.	N.D.	0.8
194	TYR	3	0.241	0.002	1.75	0.07	3	4	2	1.1
195	SER	4	0.0156	0.0007	4.2	0.2	3	5.5	0.5	2.8
196	ALA	4	0.0087	0.0007	3.3	0.1	4	5.4	0.5	3.0
197	GLY[7]	4	< 0.0019	0.0004	2.6	0.2	4	4.2	0.4	3.6
198	GLU[7]	4	< 0.0014	0.0001	2.55	0.08	4	3.9	0.3	3.1
199	ARG[7]	4	< 0.0016	0.0002	1.62	0.08	3	3.1	0.3	3.4
200	ILE[7]	4	< 0.0012	0.0001	0.85	0.04	1	1.5	0.2	3.0
201	VAL[7]	4	< 0.0012	0.0002	0.68	0.03	0	N.D.	N.D.	2.6
202	ASP[7]	4	< 0.0015	0.0002	0.78	0.06	3	2.0	0.1	3.0
203	ILE[7]	4	< 0.0011	0.0003	0.80	0.03	1	2.0	0.6	2.7
204	ILE[7]	4	< 0.0016	0.0003	0.90	0.06	1	2.1	0.3	2.5
205	ALA[7]	4	< 0.0021	0.0001	1.23	0.04	3	1.9	0.1	3.1
206	THR	3	0.0098	0.0009	4.8	0.2	3	7.5	0.5	2.6
207	ASP	3	0.21	0.01	1.4	0.1	3	5	3	1.2
208	ILE	3	0.089	0.006	0.71	0.08	1	2.1	0.2	0.8
209	GLU	3	0.28	0.02	1.5	0.1	3	5	4	0.4
210	THR	2	1.62	0.03	1.35	0.05	1	3.35	0.09	0.2
211	LYS	2	2.01	0.04	0.81	0.06	2	5	2	0.5
212	GLU	4	0.066	0.001	0.000	0.003	3	4	4	-0.4

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