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Experimental details

The mutarotation of glucose was measured for 24.8mg 99% α -D(+)-glucose (Acros Organics) in 0.6 ml D₂O at 27°C. The interleaved sel-SHARPER and MR-sel-SHARPER spectra used a Δ value of 0.011 ms (134 points), with a total of 122 data chunks collected, yielding a 5.199 s FID with a 15.7511 ppm spectral width. This was calculated to be the optimal experimentally available Δ value by the scripts provided in the Supporting information. Spectra were zero-filled to 64k data-points, apodised by a 0.2 Hz exponential function and baseline corrected (polynomial order 5) before measurement of integrals. For the ¹H 1D spectrum it was necessary to fit the anomeric protons and water signal to produce accurate integrals (MNova 14.0.0 Line Fitting tool using a generalised Lorentzian line shape). The protodeboronation of **1** was measured for 4.9 mg of 2,6-difluoro-4-methoxyphenylboronic acid, **1** (provided by Lloyd-Jones research group, University of Edinburgh) in 0.7 ml 1:1 water:1,4-dioxane solvent with a final concentration of 0.2 M potassium hydroxide at 27 °C. The protodeboronation reaction was measured approximately every 67 seconds alternating MR-SHARPER and 1D ¹⁹F spectra. The largest contribution to the dead time at the start of the reaction was the time required to transport the sample from the lab where the reaction was started, to the NMR spectrometer, whilst following The University of Edinburgh COVID one-way system. The MR-SHARPER experiments used a Δ value of 11.36 ms (298 points), 34.8295 ppm spectral width, with a total of 176 data chunks collected, yielding a 4 s FID. This was calculated to be the optimal experimentally available Δ value between 7.5 ms and 12.5 ms that would yield a spectral width between 10ppm and 100ppm. The ¹⁹F pulse-acquire and MR-sel-SHARPER spectra were zero-filled to 128k data-points, apodisation with a 0.3 Hz exponential was used and all were spectra baseline corrected (polynomial order 3) before measurement of integrals.

MR SHARPER pulse sequences

MR SHARPER pulse sequence for Bruker (Avance III), tested using TS 3.6

```
;Multi Resonance SHARPER
;1D sequence
;
;
;ZG Options for SHARPER loop using Hard/broadband pulses:
;
; Gradients: -Dgrad
;     Switches on the gradients flanking the 180deg pulses
;     This also works for the selective sequences.
;
; Phase Cycle: -Dalt
;     Changes 90x - [180-y - 180-y]n to 90x - [180-y - 180y]n
;     This also works for the selective sequences.
;
;ZG Options for sel-SHARPER:
;
; Selective excitation: -Dselex
;     Using a selective pulse for excitation (either 90 or 270)
;     When this is used 180 must be added to PH0 (whether PH0 = 0 or PH0 = 90)
;
; SPFGSE: -DSPFGSE
;     Single pulse field gradient spin echo for selection.
;     The gradients here should not be switched off
;
; DDPFGSE: -DDPFGSE
;     Double pulse field gradient spin echo for selection.
;     The gradients here should not be switched off
;
; Selective refocussing: -Dselre
;     Uses selective 180deg shaped pulses for refocussing in the SHARPER loop
;     -Dgrad as described above can be used to include gradients
;     -Dalt as described above can be used to change phase cycle
;
; Additional ZG Options:
;
; Pre-saturation of single signal: -DPresat
;     Simple 2 second pre-saturation of single signal power level set with p19.
; Placed at the end of D1 and withing the D1 period (D1>2s)
; Uses offset switching (cnst23 and cnst24) to allow
; the pre-saturation to occur before moving back to the signal of interest
;
;Further development of the sequence from:
; SHARPER reaction monitoring: generation of a narrow linewidth NMR
; singlet, without X-pulses, in an inhomogeneous magnetic field.
; A.B.Jones, G.C.Lloyd-Jones, D. Uhrin, Anal. Chem. 2017,
; DOI:10.1021/acs.analchem.7b02437

;$CLASS=HighRes
;$DIM=1D
;$TYPE=
```

```

;$SUBTYPE=
;$COMMENT=

#include <Avance.incl>
#include <Grad.incl>
#include <Delay.incl>
#include <De.incl>

"p2=p1*2"
"p29=300u"

"d9=2"
"d11=30m"
"d12=20u"
"d62=dw*l2"
;"d62=aq/(l0*2+0.5)"
"d63=d62/2"

#ifdef presat
"DELTA=d1-d11-d9-d12*4"
#else
"DELTA=d1-d11"
#endif

"l0=(aq/d62-0.5)/2"
"l31=l0+4"

"acqt0=-p1*2/Pl"

dwellmode explicit

1 ze
2 d11

        4u BLKGRAD
        DELTA

#ifdef presat
d12 fq=cnst23(bf):f1 ;water offset in Hz
d12 pl9:f1
d9 cw:f1 ph29
4u do:f1
d12 pl1:f1
d12 fq=cnst24(bf):f1 ; final offset in Hz
#endif

        50u UNBLKGRAD
#ifdef selex
d12 pl0:f1
(p11:sp1 ph1):f1
#else
d12 pl1:f1

```

```

        (p1 ph1):f1
#ifdef SPFGSE
        p28:gp1
        d16 pl0:f1
        (p14:sp4 ph4):f1
        p28:gp1
        d16
#endif
#ifdef DPFGESE
        p28:gp1
        d16 pl0:f1
        (p14:sp4 ph4):f1
        p28:gp1
        d16
        p28:gp2
        d16 pl0:f1
        (p14:sp4 ph4):f1
        p28:gp2
        d16
#endif
#endif

        ACQ_START(ph30,ph31)

        0.1u REC_UNBLK
        0.05u DWL_CLK_ON
        d63
        0.05u DWL_CLK_OFF
        0.1u REC_BLK

#ifdef selre
#ifdef grad
4        p29:gp0
        d16 pl0:f1
#else
4        d12 pl0:f1
#endif
        (p12:sp2 ph2):f1
#ifdef grad
        p29:gp0
        d16
#else
        d12
#endif
#else
#ifdef grad
4        p29:gp0
        d16 pl1:f1
#else
4        d12 pl1:f1
#endif
        (p2 ph2):f1

```

```

#ifdef grad
    p29:gp0
    d16
#else
    d12
#endif
#endif

    0.1u REC_UNBLK
    0.05u DWL_CLK_ON
    d62
    0.05u DWL_CLK_OFF
    0.1u REC_BLK

```

```

# ifdef selre

```

```

#ifdef grad
    p29:gp0*-1
    d16 pl0:f1
#else
    d12 pl0:f1
#endif
    (p12:sp2 ph3):f1

```

```

#ifdef grad
    p29:gp0*-1
    d16
#else
    d12
#endif

```

```

#else
#ifdef grad
    p29:gp0*-1
    d16 pl1:f1
#else
    d12 pl1:f1
#endif
    (p2 ph3):f1

```

```

#ifdef grad
    p29:gp0*-1
    d16
#else
    d12
#endif
#endif

```

```

    0.1u REC_UNBLK
    0.05u DWL_CLK_ON
    d62
    0.05u DWL_CLK_OFF
    0.1u REC_BLK

```

```

lo to 4 times l31

```

```

d63

rcyc=2
30m mc #0 to 2 F0(zd)
exit

#ifdef alt
ph1=0
ph2=1
ph3=3
ph4=1
ph29=0
ph30=(360) 0
ph31=0
#else
ph1=0
ph2=1
ph3=1
ph4=1
ph29=0
ph30=(360) 0
ph31=0
#endif

;p11 : f1 channel - power level for pulse (default)
;p1 : f1 channel - 90 degree high power pulse
;p2 : f1 channel - 180 degree high power pulse
;p11 : f1 channel - selective excitation shaped pulse (90 or 270 degree)
;p12 : f1 channel - SHARPER loop: selective refocussing shaped pulse (180 degree)
;p14 : f1 channel - SPFGSE or DDPFGSE: selective refocussing shaped pulse (180 degree)
;p19 : f1 channel - power level for presaturation
;p29: gradient pulse 0 [300 usec]
;p28: gradient pulses 1 and 2 [300-1000us]

;d1 : relaxation delay [1-5 * T1]
;d11: delay for disk I/O [30ms]
;d9: length of presaturation [2s]
;d16: delay for homospoil/gradient recovery
;d62: length of block between decoupling pulses : approx = aq/I0 [< 20-25ms]
;d63: = d62/2, length of initial half chunk

;sp1 : shaped pulse for selective excitation [Gauss270 or EBURP2]
;sp2 : shaped pulse for selective refocussing [Gauss180, ReBURP, RSNOB, ...]
;sp4 : shaped pulse for selective refocussing [Gauss180, ReBURP, RSNOB, ...]

;cnst23: water (presat) offset [Hz]
;cnst24: chosen offset [Hz]

;zgoptns: Gradients: -Dgrad, Phase Cycle: -Dalt, Selective excitation: -Dselex, -DSPFGSE or -DDPFGSE, Selective
refocussing: -Dselre, Presaturation: -Dpresat

;l0 : number of blocks during acquisition time adjust to get d62 as required
;l2 : number of points in full chunk from 2 * 1/2 chunk from python scripts

```

;ns: 1
;ds: 0 (4)

;for z-only gradients:

;gpz0: 1%

;gpz1: 11-30% smaller than gpz2

;gpz2: 11-31% larger than gpz1

;use gradient files:

;gpnam0: SMSQ10.100 or SINE.100

;gpnam1: SMSQ10.100 or SINE.100

;gpnam2: SMSQ10.100 or SINE.100

MR SHARPER pulse sequence for Bruker (Avance Neo), tested using TS 4.0

```
;Multi Resonance SHARPER
;1D sequence
;
;
;ZG Options for SHARPER loop using Hard/broadband pulses:
;
; Gradients: -Dgrad
;     Switches on the gradients flanking the 180deg pulses
;     This also works for the selective sequences.
;
; Phase Cycle: -Dalt
;     Changes 90x - [180-y - 180-y]n to 90x - [180-y - 180y]n
;     This also works for the selective sequences.
;
;ZG Options for sel-SHARPER:
;
; Selective excitation: -Dselex
;     Using a selective pulse for excitation (either 90 or 270)
;     When this is used 180 must be added to PH0 (whether PH0 = 0 or PH0 = 90)
;
; SPFGSE: -DSPFGSE
;     Single pulse field gradient spin echo for selection.
;     The gradients here cannot be switched off
;
; DPFGE: -DDPFGE
;     Double pulse field gradient spin echo for selection.
;     The gradients here cannot be switched off
;
; Selective refocussing: -Dselre
;     Uses selective 180deg shaped pulses for refocussing in the SHARPER loop
;     -Dgrad as described above can be used to include gradients
;     -Dalt as described above can be used to change phase cycle
;
; Additional ZG Options:
;
; Presaturation of single signal: -DPresat
;     Simple 2 second presaturation of single signal power level set with pl9.
; Placed at the end of D1 and withing the D1 period (D1>2s)
; Uses offset switching (cnst23 and cnst24) to allow
; the presaturation to occur before moving back to the signal of interest
;

; Development of the sequence from:
; SHARPER reaction monitoring: generation of a narrow linewidth NMR
; singlet, without X-pulses, in an inhomogeneous magnetic field.
; A.B.Jones, G.C.Lloyd-Jones, D. Uhrin, Anal. Chem. 2017,
; DOI:10.1021/acs.analchem.7b02437

;$CLASS=HighRes
;$DIM=1D
```

```

;$TYPE=
;$SUBTYPE=
;$COMMENT=

#include <Avance.incl>
#include <Grad.incl>
#include <Delay.incl>
#include <De.incl>

"p2=p1*2"
"p29=300u"

"d9=2"
"d11=30m"
"d12=20u"
"d62=dw*12"
;"d62=aq/(l0*2+0.5)"
"d63=d62/2"

#ifdef presat
"DELTA=d1-d11-d9-d12*4"
#else
"DELTA=d1-d11"
#endif

"l0=(aq/d62-0.5)/2"
"l31=l0+4"

"acqt0=-p1*2/Pl"

dwellmode explicit
1 ze
2 d11

        4u BLKGRAD
        DELTA

#ifdef presat
d12 fq=cnst23(bf):f1 ;water offset in Hz
d12 pl9:f1
d9 cw:f1 ph29
4u do:f1
d12 pl1:f1
d12 fq=cnst24(bf):f1 ; real offset in Hz
#endif

        50u UNBLKGRAD
#ifdef selex
d12 pl0:f1
(p11:sp1 ph1):f1
#else
d12 pl1:f1
(p1 ph1):f1

```

```

#ifdef SPFGSE
    p28:gp1
    d16 pl0:f1
    (p14:sp4 ph4):f1
    p28:gp1
    d16
#endif
#ifdef DPFGESE
    p28:gp1
    d16 pl0:f1
    (p14:sp4 ph4):f1
    p28:gp1
    d16
    p28:gp2
    d16 pl0:f1
    (p14:sp4 ph4):f1
    p28:gp2
    d16
#endif
#endif

    ACQ_START(ph30,ph31)
    0.1u REC_UNBLK
    0.05u START_NEXT_SCAN
    d63
    0.05u DWELL_HOLD
    0.1u REC_BLK

# ifdef selre
#ifdef grad
4    p29:gp0
    d16 pl0:f1
#else
4    d12 pl0:f1
#endif
    (p12:sp2 ph2):f1
#ifdef grad
    p29:gp0
    d16
#else
    d12
#endif
#else
#ifdef grad
4    p29:gp0
    d16 pl1:f1
#else
4    d12 pl1:f1
#endif
    (p2 ph2):f1
#ifdef grad
    p29:gp0

```

```

        d16
#else
        d12
#endif
#endif

        0.1u REC_UNBLK
        0.05u DWELL_RELEASE
        d62
        0.05u DWELL_HOLD
        0.1u REC_BLK

# ifdef selre
# ifdef grad
        p29:gp0*-1
        d16 pl0:f1
# else
        d12 pl0:f1
# endif
        (p12:sp2 ph3):f1
# ifdef grad
        p29:gp0*-1
        d16
# else
        d12
# endif

# else
# ifdef grad
        p29:gp0*-1
        d16 pl1:f1
# else
        d12 pl1:f1
# endif
        (p2 ph3):f1
# ifdef grad
        p29:gp0*-1
        d16
# else
        d12
# endif
#endif
#endif

        0.1u REC_UNBLK
        0.05u DWELL_RELEASE
        d62
        0.05u DWELL_HOLD
        0.1u REC_BLK

        lo to 4 times l31
        d63
0.05u DWELL_RELEASE

```

```

rcyc=2
30m mc #0 to 2 F0(zd)
4u BLKGRAD
exit

#ifdef alt
ph1=0
ph2=1
ph3=3
ph4=1
ph29=0
ph30=(360) 0
ph31=0
#else
ph1=0
ph2=1
ph3=1
ph4=1
ph29=0
ph30=(360) 0
ph31=0
#endif

;p1 : f1 channel - power level for pulse (default)
;p1 : f1 channel - 90 degree high power pulse
;p2 : f1 channel - 180 degree high power pulse
;p11 : f1 channel - selective excitation shaped pulse (90 or 270 degree)
;p12 : f1 channel - SHARPER loop: selective refocussing shaped pulse (180 degree)
;p14 : f1 channel - SPFGSE or DDPFGSE: selective refocussing shaped pulse (180 degree)
;p19 : f1 channel - power level for presaturation [~55-65dB for water]
;p29: gradient pulse 0 [300 usec]
;p28: gradient pulses 1 and 2 [300-1000 usec]

;d1 : relaxation delay [1-5 * T1]
;d11: delay for disk I/O [30 msec]
;d9: length of presaturation [2 s]
;d16: delay for homospoil/gradient recovery
;d62: length of block between decoupling pulses : = aq/l0 [< 20-25msec]
;d63: = d62/2, length of initial half chunk

;sp1 : shaped pulse for selective excitation [Gauss270 or EBURP2]
;sp2 : shaped pulse for selective refocussing [Gauss180, ReBURP, RSNOB etc]
;sp4 : shaped pulse for selective refocussing [Gauss180, ReBURP, RSNOB etc]

;cnst23: water (presat) offset [Hz]
;cnst24: chosen offset [Hz]

;zgoptns: Gradients: -Dgrad, Phase Cycle: -Dalt, Selective excitation: -Dselex, -DSPFGSE or -DDPFGSE, Selective
refocussing: -Dselre, Presaturation: -Dpresat

;l0 : number of blocks during acquisition time adjust to get d62 as required
;l2 : number of points in full chunk from 2 * 1/2 chunk from python scripts

```

;ns: 1
;ds: 0 (4)

;for z-only gradients:

;gpz0: 1%

;gpz1: 11-30% smaller than gpz2

;gpz2: 11-31% larger than gpz1

;use gradient files:

;gpnam0: SMSQ10.100 or SINE.100

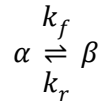
;gpnam1: SMSQ10.100 or SINE.100

;gpnam2: SMSQ10.100 or SINE.100

Mutarotation of glucose

Rate equations and equilibrium constant

The mutarotation of glucose is a reversible, pseudo-first-order process given by references 14 and 15.



[1]

Where α and β indicate α -D-glucose and β -D-glucose respectively, k_f is the forward rate constant and k_r the reverse rate constant.

$$-\frac{d[\alpha]_t}{dt} = \frac{d[\beta]_t}{dt} = k_f[\alpha]_t - k_r[\beta]_t$$

[2]

Where $[\alpha]_t$ is the concentration of α -D-glucose at time, t and $[\beta]_t$ is the concentration of β -D-glucose at time t .

Therefore at equilibrium (when the rate of change of concentration is 0):

$$k_f[\alpha]_{eq} = k_r[\beta]_{eq}$$

[3]

Giving the equilibrium constant, K :

$$K = \frac{k_f}{k_r} = \frac{[\beta]_{eq}}{[\alpha]_{eq}}$$

[4]

The equilibrium constant K was determined from six integrals measured after 400 min, Table 1 (main paper) for each pulse sequence tested.

The reaction rate, k :

$$k = k_f + k_r$$

[5]

Requires three assumptions for determination from $[\alpha]_t$ or $[\beta]_t$ as a function of time:

1. $[G] = [\alpha]_t + [\beta]_t$, the total concentration of glucose $[G]$ is the sum of the α and β concentrations at time t .
2. $[\alpha]_0 = [G]$ and $[\beta]_0 = 0$, the concentration of α -D-glucose at time 0 is the same as the total concentration of glucose, while the concentration of β -D-glucose is 0.
3. $[\alpha]_\infty = [\alpha]_{eq}$ and $[\beta]_\infty = [\beta]_{eq}$, as time tends to infinity the concentration of α and β glucose reach their equilibrium concentrations.

Determination of k from $[\alpha]_t$ as a function of time starts from:

$$-\frac{d[\alpha]_t}{dt} = k_f[\alpha]_t - k_r[\beta]_t \quad [6]$$

Using [5] and assumption 1:

$$\frac{d[\alpha]_t}{dt} = (-k)[\alpha]_t + k_r[G] \quad [7]$$

Which has the general solution,

$$[\alpha]_t = \frac{k_r[G]}{k} + Ce^{-kt} \quad [8]$$

Where C is a constant.

Using assumption 2 when t = 0:

$$C = \frac{k_r[G]}{k} - [G] \quad [9]$$

Using assumption 3 when t → ∞:

$$[\alpha]_{eq} = \frac{k_r[G]}{k} \quad [10]$$

Therefore,

$$[\alpha]_t = [\alpha]_{eq} + ([\alpha]_{eq} - [G])e^{-kt} \quad [11]$$

Which can be rearranged to extract k as the gradient by linear regression, from a plot of $f([\alpha]_t)$ against time:

$$\ln([\alpha]_t - [\alpha]_{eq}) = \ln([\alpha]_{eq} - [G]) - kt \quad [12]$$

The same process for determination of k from $[\beta]_t$ starts from:

$$\frac{d[\beta]_t}{dt} = k_f[\alpha]_t - k_r[\beta]_t \quad [13]$$

Resulting in the solution:

$$[\beta]_t = [\beta]_{eq} - [\beta]_{eq}e^{-kt} \quad [14]$$

Which can be rearranged to extract k as the gradient by linear regression, from a plot of $f([\beta]_t)$ against time:

$$\ln(1 - [\beta]_t / [\beta]_{eq}) = -kt$$

[15]

The forward (k_f) and reverse (k_r) rate constants can be determined using the equilibrium constant K and the rate constant k : $k_r = k/(1+K)$ and $k_f = k/(1+K^{-1})$.

Determination of rate constant, k

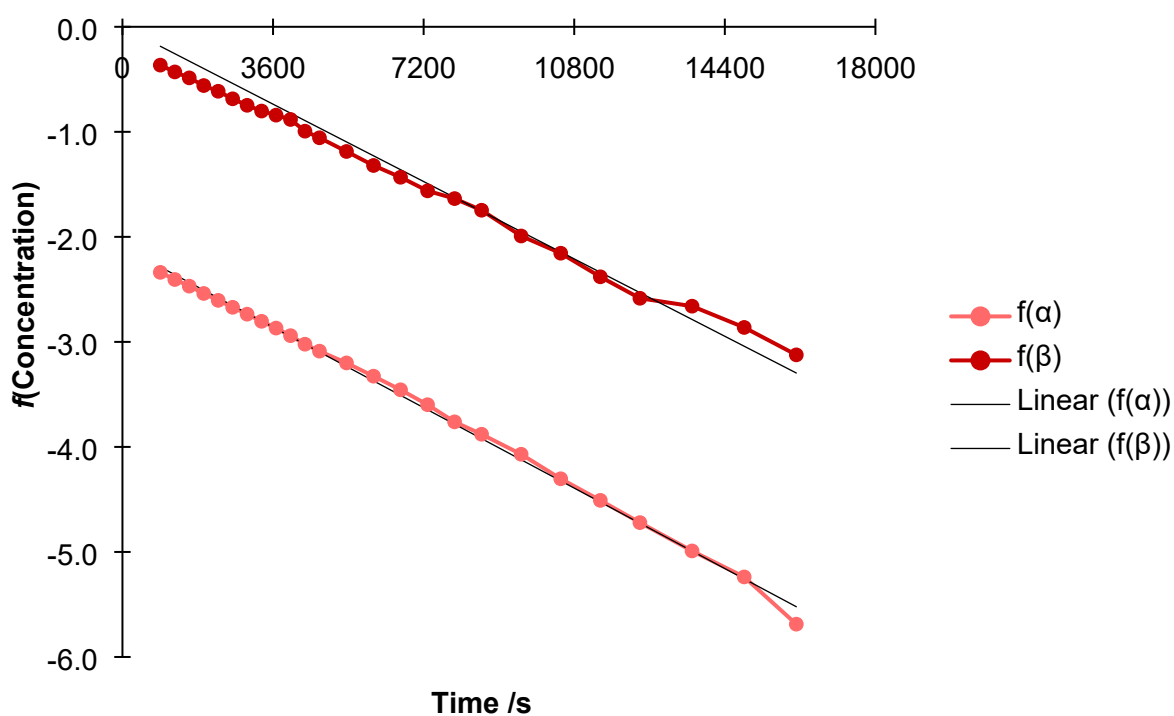


Figure S1 Analysis of concentrations determined from anomeric protons in 1D ^1H spectra. The rate constant, k , given by the gradient of the linear regressions as determined using equation [12] for α -D-glucose and [15] for β -D-glucose. Data measured after 17000 s was not used to determine k due to the concentrations approaching the equilibrium values.

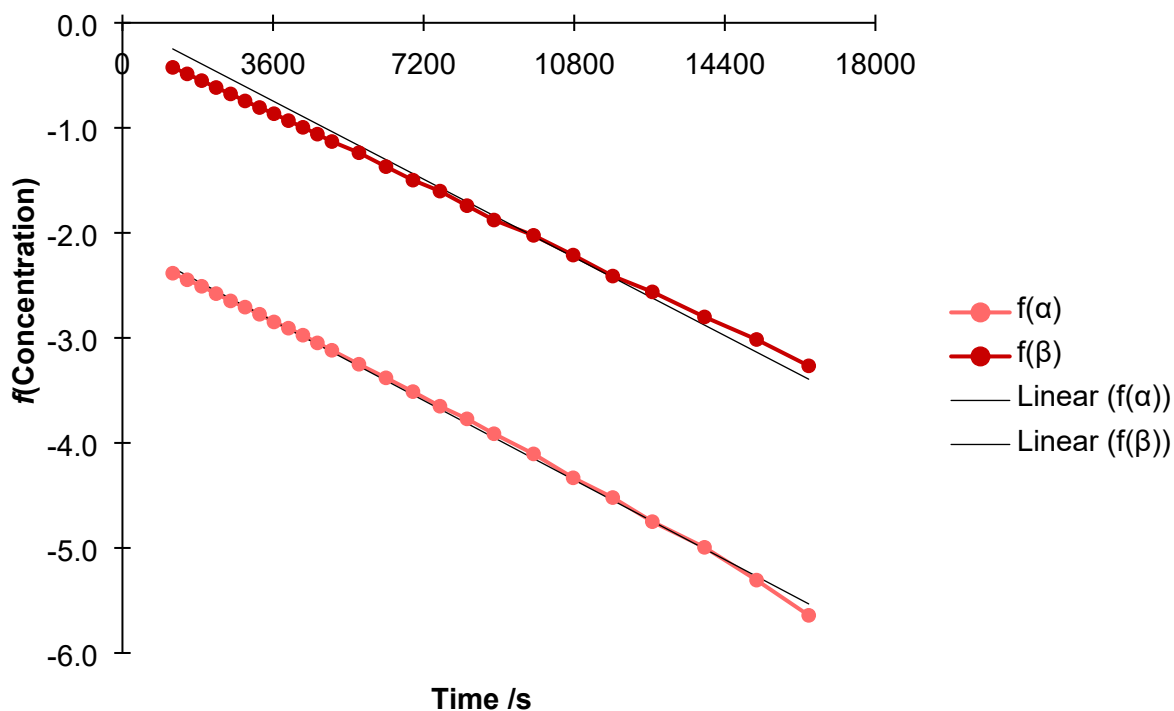


Figure S2 Analysis of concentrations determined from anomeric protons in 1D SPFGSE spectra (doubly selective 50 ms Gaussian 180° pulse used). The rate constant, k , given by the gradient of the linear regressions as determined using equation [12] for α -D-glucose and [15] for β -D-glucose. Data measured after 17000s was not used to determine k due to the concentrations approaching the equilibrium values.

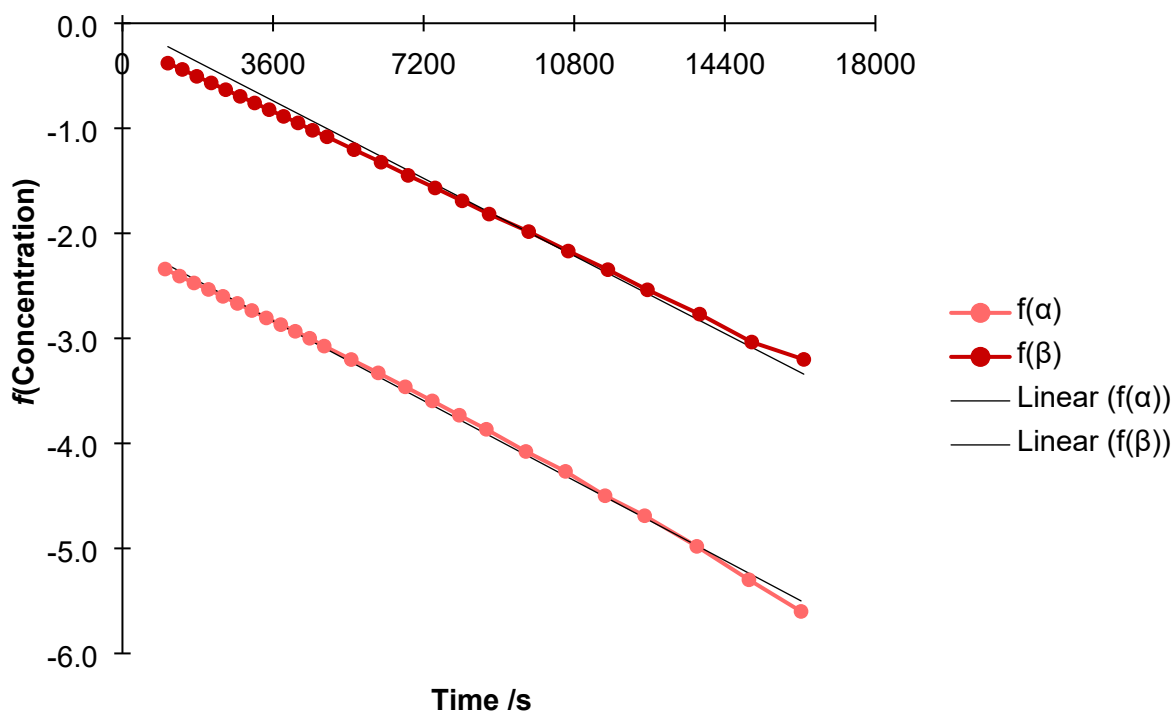


Figure S3 Analysis of concentrations determined from anomeric protons in 1D sel-SHARPER spectra. The rate constant, k , given by the gradient of the linear regressions as determined using equation [12] for α -D-glucose and [15] for β -D-glucose. Data measured after 17000s was not used to determine k due to the concentrations approaching the equilibrium values.

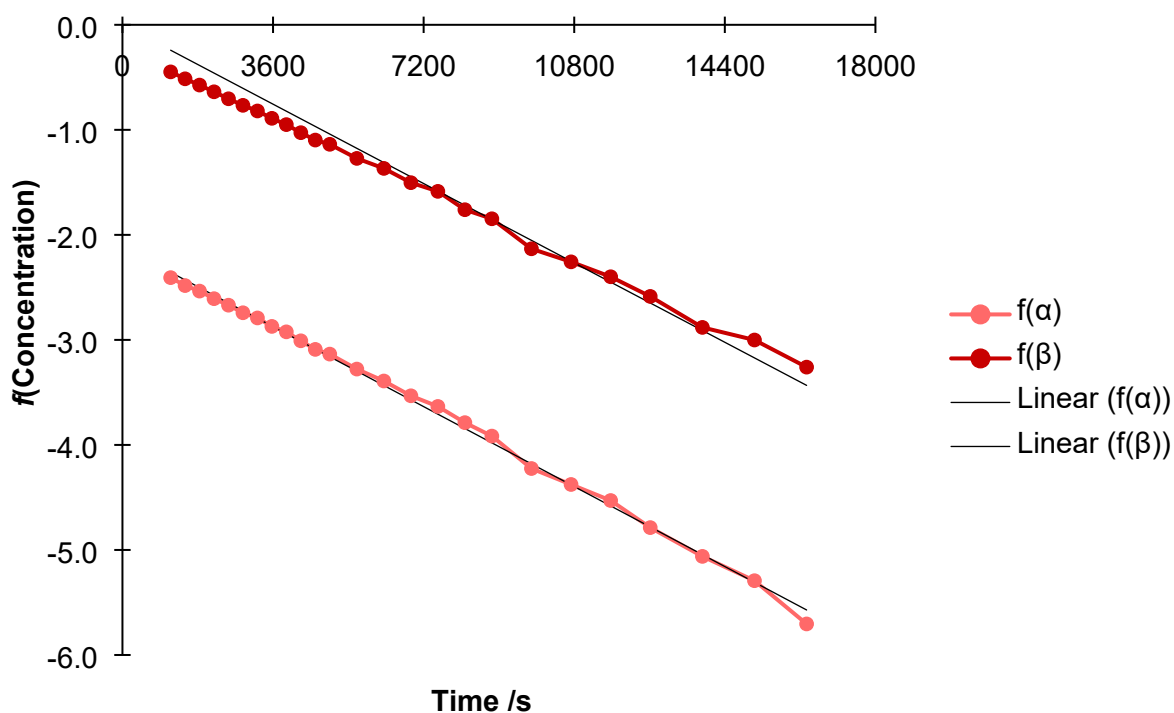


Figure S4 Analysis of concentrations determined from anomeric protons in 1D MR-sel-SHARPER spectra, where integrals were taken only for the “main peak” as described in Figure S 8. The rate constant, k , given by the gradient of the linear regressions as determined using equation [12] for α -D-glucose and [15] for β -D-glucose. Data measured after 17000s was not used to determine k due to the concentrations approaching the equilibrium values.

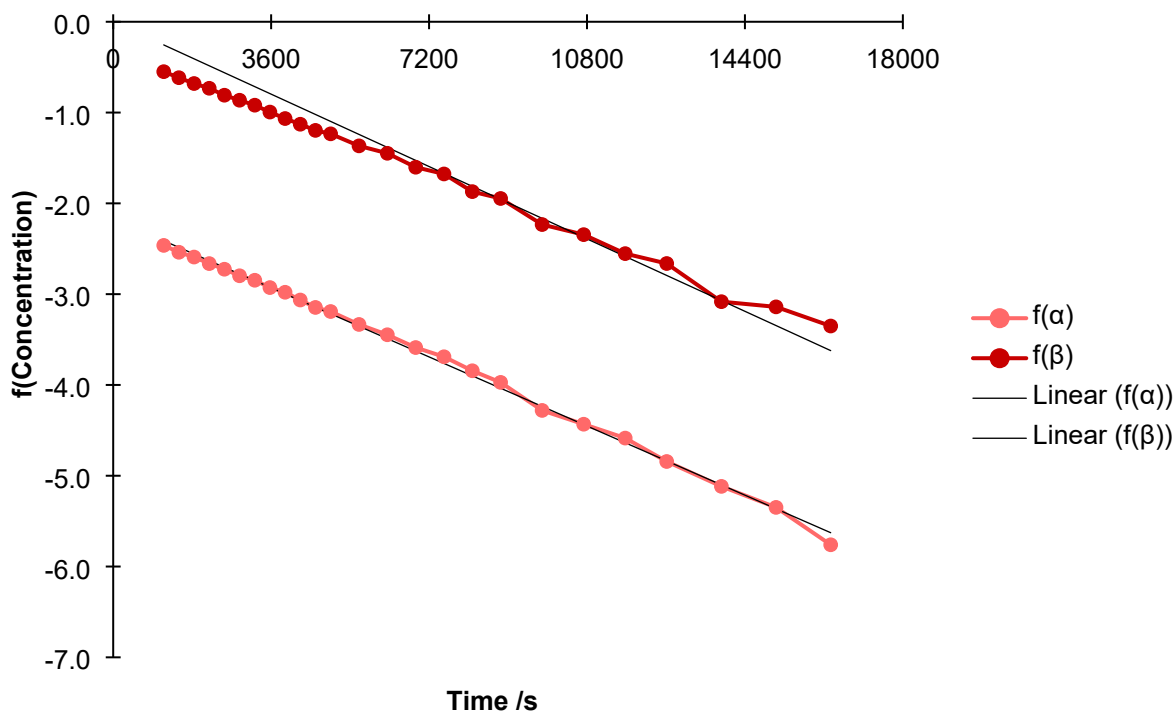


Figure S5 Analysis of concentrations determined from anomeric protons in 1D MR-sel-SHARPER spectra, where “wide” integrals were taken from the β anomeric proton as described in Figure S8. The rate constant, k , given by the gradient of the linear regressions as determined using equation [12] for α -D-glucose and [15] for β -D-glucose. Data measured after 17000 s was not used to determine k due to the concentrations approaching the equilibrium values.

The effect of signal quantification on data analysis

At the end of the experiment when equilibrium is established there is a discrepancy between the ratios measured by MR-sel-SHARPER (f) and the other techniques (a), (d) and (e) in Figures S6 and expanded in Figure S7. To investigate this the data were processed in two ways differing in the size of the integration regions for the off-resonance β anomeric proton: (i) including only the main SHARPER peak, and (ii) including also the contributions from the first sidebands (Figure S8, resulting in the data in Figure S6 (g) and 7 (g)). These choices are based on the results of our preliminary experiments, where we found that the inclusion of the first sidebands improved accuracy of the results. In case of glucose, and due to the small chemical shift difference between the α and β anomeric protons (235.0 Hz), the chunking artefacts/sidebands from the two signals affect each other. Therefore, at the beginning of the experiment, when the α anomeric signal is most intense, using a wider integral region for the off-resonance β signal affects the accuracy of integrals due to the interference from the α proton artefacts resulting in higher error in the rate constant, k (Table 1, main text). Once the off-resonance β signal is dominating the spectrum, the integral accuracy improves resulting in an accurate equilibrium constant, K (Table 1, main text). The reverse follows for the narrower “main peak” integral region.

Only the main peak was used to monitor the α anomeric proton. This peak was selected to be on-resonance when measuring the spectra, due to its dominance in the initial spectra. This results in less intense artefacts around the α signal in comparison to the off-resonance β anomeric proton. Therefore, the main peak is sufficient for measuring the absolute intensity without interference from the β anomeric proton as it increases in intensity. The use of a wider integral range for the α anomeric proton is only likely to lead to (a small) improvement in accuracy in the case of a greater frequency difference between the two signals of interest.

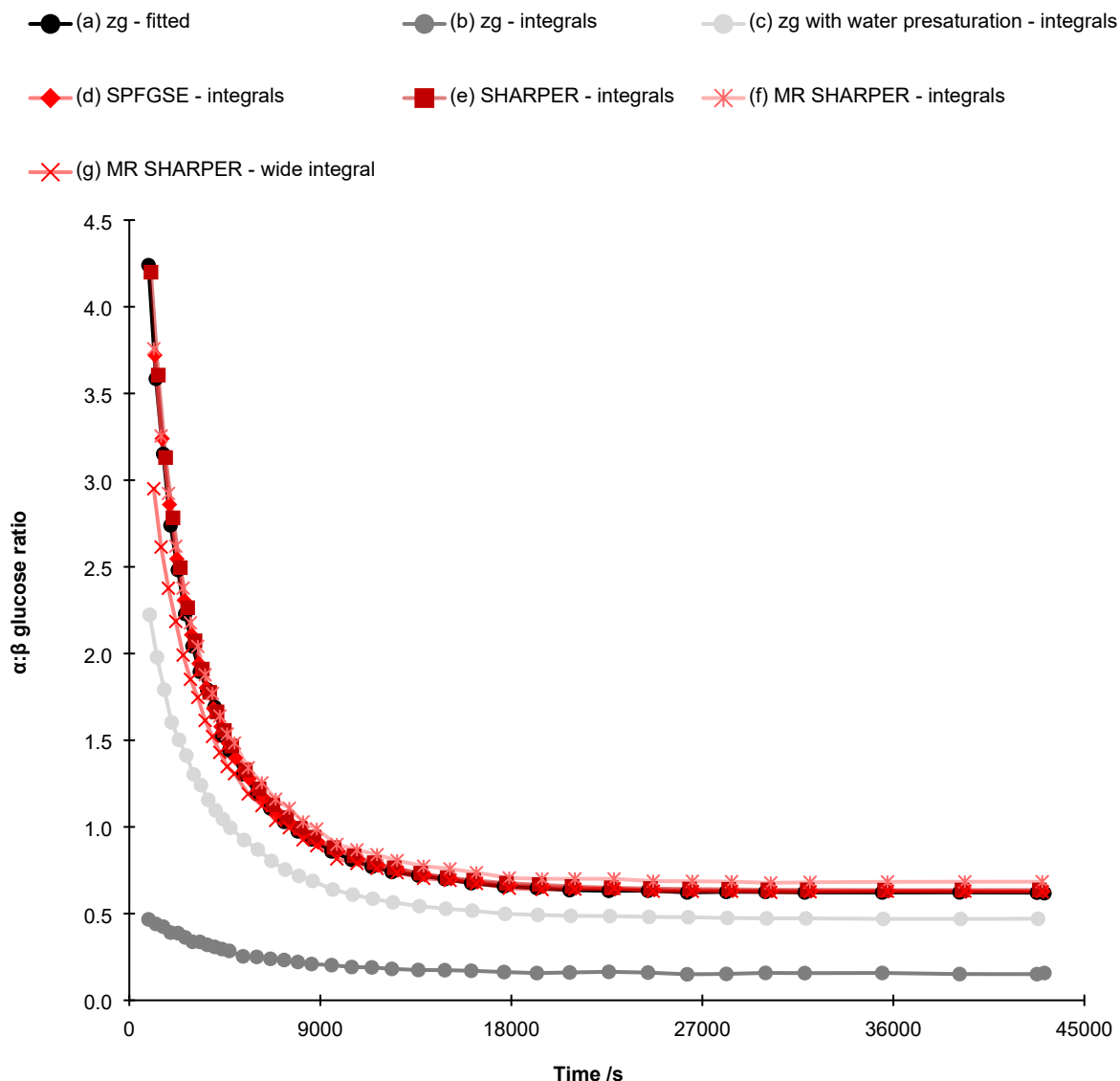


Figure S6: $\alpha:\beta$ ratio for 99% α -D-glucose (a) zg - fitted, analysis of 1D ^1H spectra, where integrals were measured by fitting (lineshape fitting, MRN 14.0.0) to ensure that that a partial overlap of HDO did not affect integration of H1 β integrals. (b) zg – integrals, analysis of 1D ^1H spectra where integrals were measured directly without fitting to show impact of overlap with HDO on H1 β integrals. (c) zg with water presaturation – integrals, analysis of 1D ^1H spectra with water pre-saturation where integrals were measured directly without fitting to show that the HDO overlap with H1 β proton was not fully resolved. (d) SPFGSE – integrals, analysis of 1D ^1H spectra with water pre-saturation where integrals were measured directly without fitting to show that the HDO overlap with H1 β was fully resolved. (e) SHARPER – integrals, integrals were measured directly without fitting from consecutively measured sel-SHARPER spectra for the α and β anomeric protons. (f) MR-SHARPER – integrals, integrals were measured directly from the main singlet peak without fitting from simultaneously measured α and β anomeric protons from a single MR-sel-SHARPER spectra. (g) MR-SHARPER - wide integrals, from simultaneously measured α and β anomeric protons in a single MR-sel-SHARPER spectrum the integrals were measured directly without fitting from the main singlet peak for the H1 α signal and accounting for the artefacts for the H1 β .

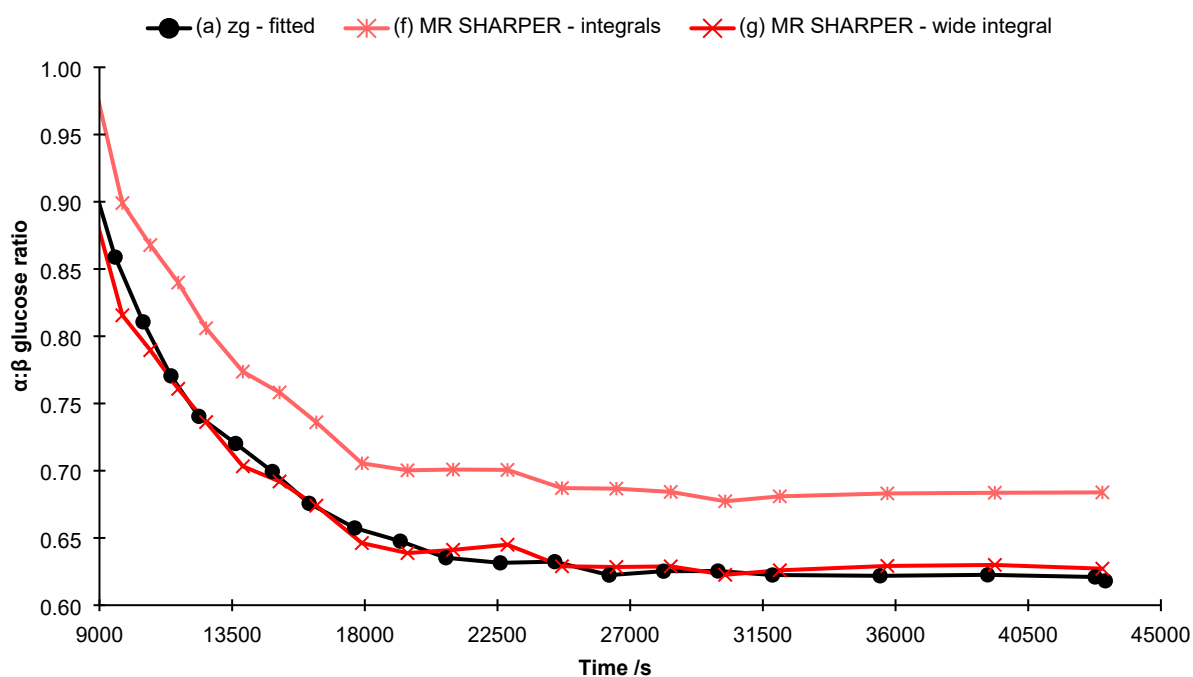
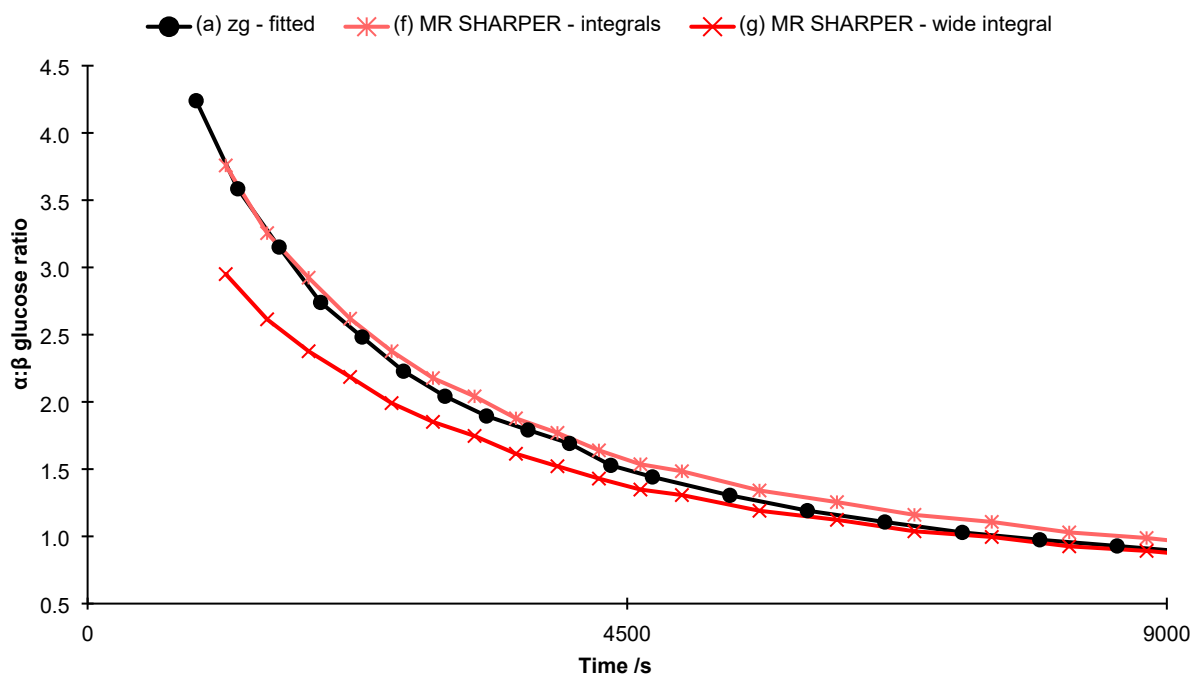


Figure S7: Expansions of Figure S6 for $\alpha:\beta$ ratio for 99% α -D-glucose (a) zg - fitted, analysis of 1D ^1H spectra, where integrals were measured by fitting (lineshape fitting, MRN 14.0.0) to ensure that that a partial overlap of HDO did not affect integration of H1 β integrals. (f) MR-SHARPER – integrals, integrals were measured directly from the main singlet peak without fitting from simultaneously measured α and β anomeric protons from a single MR-sel-SHARPER spectra. (g) MR-SHARPER - wide integrals, from simultaneously measured α and β anomeric protons in a single MR-sel-SHARPER spectrum the integrals were measured directly without fitting from the main singlet peak for the H1 α signal and accounting for the artefacts for the H1 β .

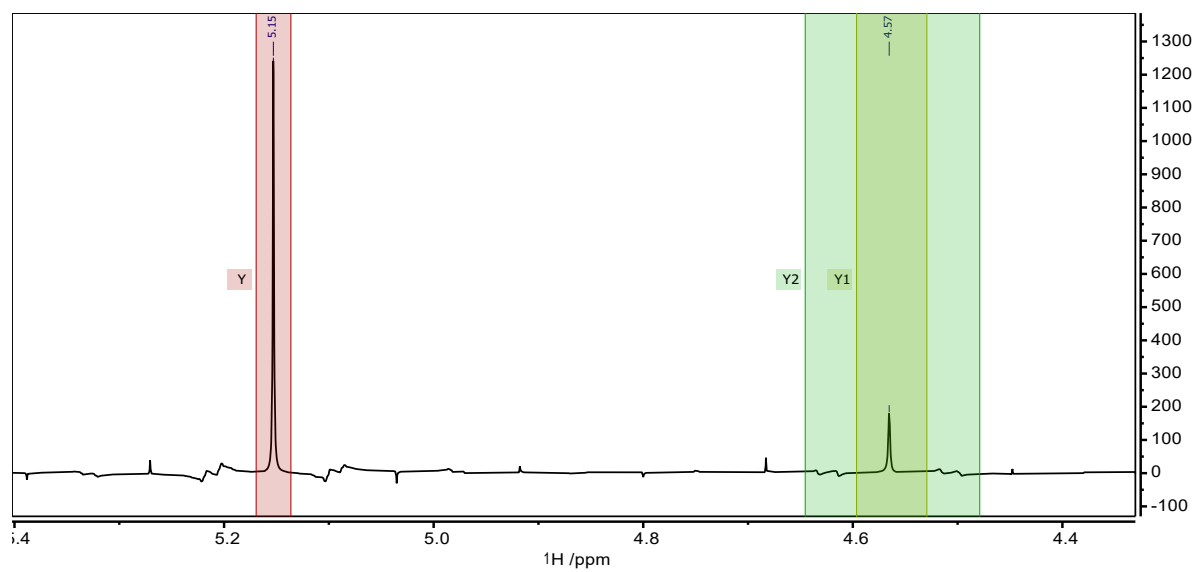


Figure S8: Integral regions for α and β anomeric protons, Y and Y1 indicating integration of the “main peak” and Y2 the “wide” integral region for the off-resonance peak.

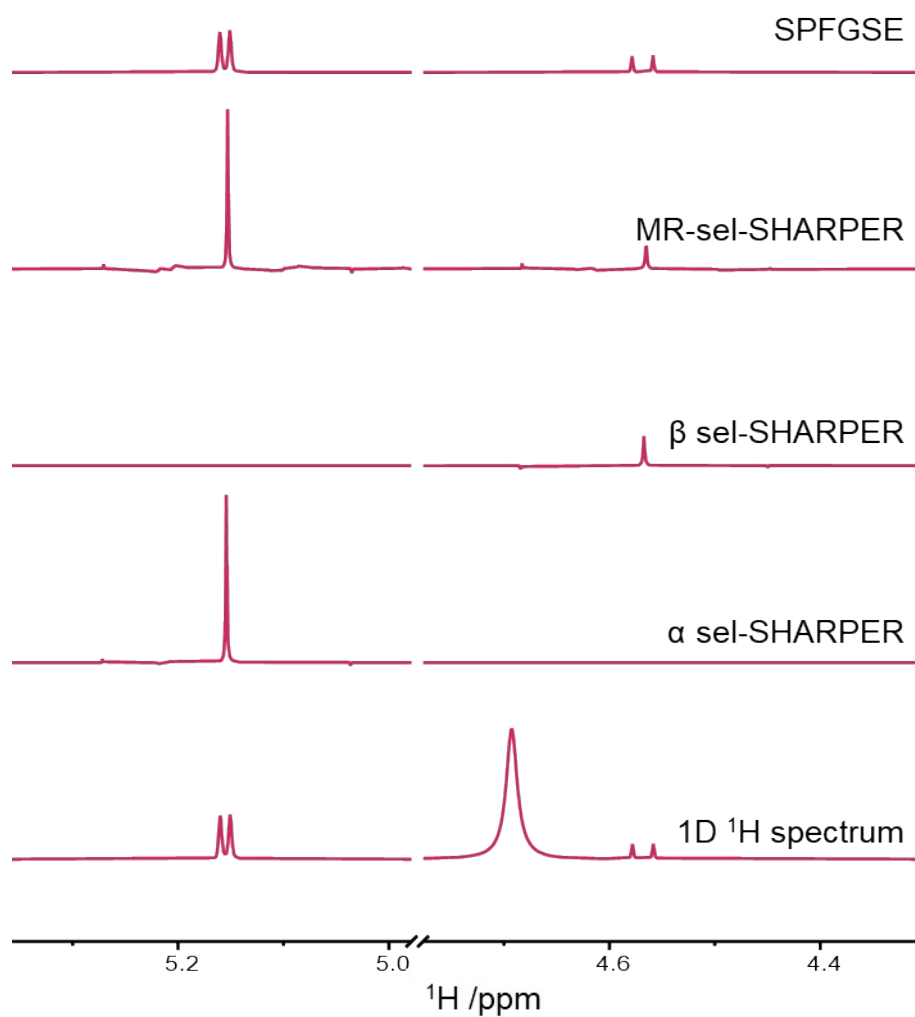


Figure S9: Overlay of NMR spectra recorded used to generate Figure 8. 1D ^1H spectrum, 1D ^1H SPFGSE spectrum, MR-sel-SHARPER spectra and sel-SHARPER spectrum. All spectra are plotted on the same vertical scale.

Protodeboronation of **1**

Rate equations

As described in reference 16 first-order decay was assumed. The rate constant was extracted as the gradient from linear regression using the following equation:

$$\ln [1]_t = \ln [1]_0 - k_{obs}t$$

[16]

Where $[1]_0$ is the initial concentration of 2,6-Difluoro-4-methoxyphenylboronic acid (**1**), $[1]_t$ is the concentration of **1** at time, t and k_{obs} is the observed rate constant.

Determination of rate constant, k_{obs}

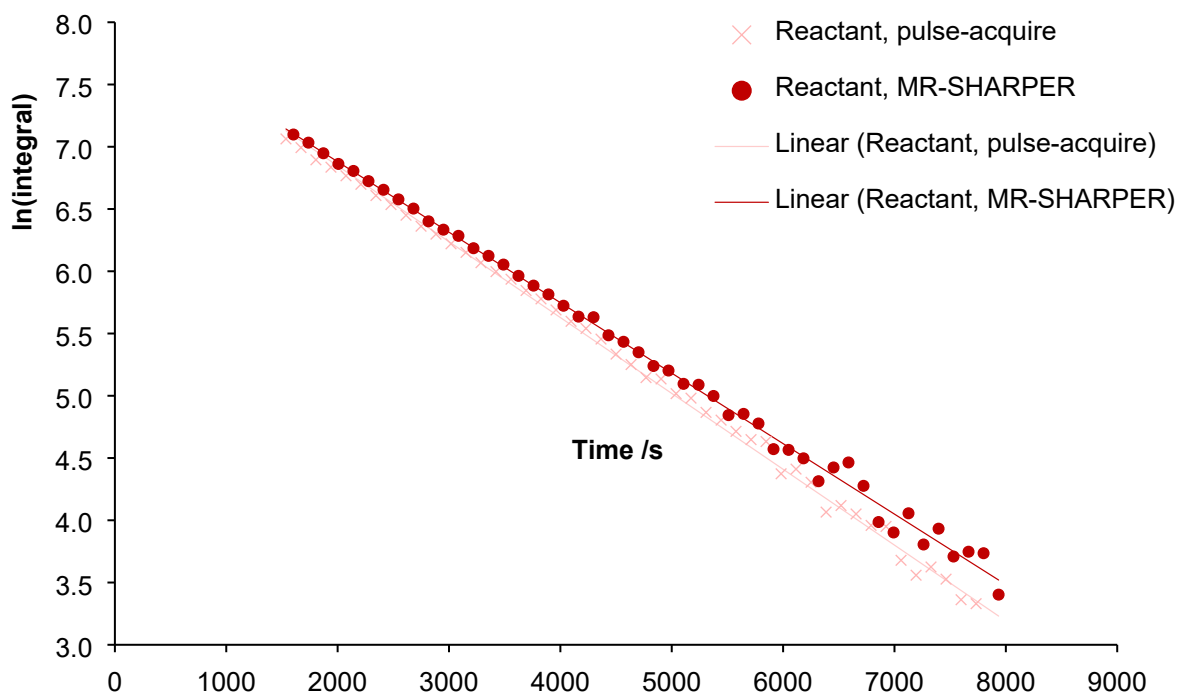


Figure S10: Extraction of k_{obs} from the gradient of the natural logarithm of the measured reactant (**1**) integrals over time. Red indicates pulse-acquire results, and light red MR-SHARPER results.

MR SHARPER Python 2.7 Scripts

Description of operation

The methodology described in the paper relies on precisely set Δ values, Δ being the data chunk durations within the sequence. Whilst delays can be trivially set with a high degree of precision, setting precise acquisition timings proves more challenging.

The duration of each data chunk is determined by the number of data points per chunk (which must be an integer) and the dwell time (which can only take a discrete series of values with less than 12.5 ns precision). Thus, setting data chunk durations for a MR-SHARPER experiment requires finding a combination of dwell time and spectral width which fits most closely to the required data chunk duration (as dictated by the frequency of resonances within the spectrum) whilst also considering total data chunk duration and spectral width. This problem was solved by means of a Python 2.7 script, the operation of which is summarised in Figure S11. The same script is used both for cases where the transmitter offset is placed on one of the two resonances and when it is placed directly between them.

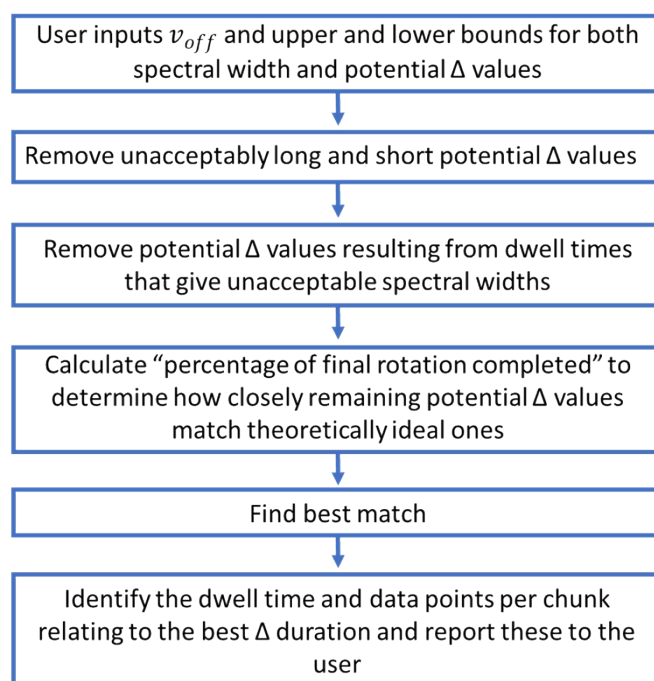


Figure S11: The operation of the MR-SHARPER scripts

The MR-SHARPER scripts require three different arrays of different size, consisting of (i) an array of possible data chunk durations, (ii) an array of dwell times and (iii) numbers of data points – which is simply an array of integers. Note that (i) is simply the product of arrays (ii) and (iii). Values in array (ii) were experimentally determined using Topspin 3.6.1.

Initially, the user defines the frequency of the off-resonance signal(s), frequency of the nucleus on that spectrometer and minimum and maximum values for both spectral width and total data chunk duration. These are used to remove any values from array (i) and (ii), as well as values from corresponding indices in all three arrays.

A modulo operation is then performed on array (i), based on the off-resonance frequency. The result of this is further divided by the off-resonance frequency and multiplied by 100 to yield a value between 0 and 100. Values of 0/50/100 will correspond to data chunk durations.

MR-SHARPER timing script

Script and full arrays available at <https://github.com/matthewdavy/MR-SHARPER>

```
#!/usr/bin/python
#For calculating timings required in multiple resonance SHARPER experiments with two signals
#Suitable for two off-resonance peaks with different |Frequency|
#Calculates a timing for a spectral width and refocussing period within user given bound
#Bounds set to provide nice spectra with adequate decoupling and T2* -> T2
#Wider bounds will improve average spectral quality
#N.B. FutureWarnings are harmless, but may render this way of performing the calculations obsolete in the future

##N.B. This script calculates the value of "Delta" for multiple resonance SHARPER which is the half chunk duration, not the
full chunk duration

import math
import numpy as np
import warnings
from scipy import special
warnings.filterwarnings("ignore", category=FutureWarning) #This ignores a depreciation warning that is currently
irrelevant

#####Start of parameters the user should change#####

#Frequency of NMR signal (Hz)
f1 = 907.9690
#Spectrometer operating Frequency (for the nucleus of interest!)
Spectrometer_Frequency = 369.0 #This is in MHz, for the nucleus of interest
#Allowable Spectral Width
ppm_upper = 375.0
ppm_lower = 330.0 #Around 60ppm spectral width seems to be the limit with 19F at 400MHz proton
#Allowable chunk timings in milliseconds (enter as a decimal, needs to be a float)
longest_timing = 100.0
shortest_timing = 0.000005

#####End of parameters the user should change#####

#Calculate the period of the NMR signal
p1 = 1.0/f1
#Convert to Hz limits
hz_upper=(ppm_upper*Spectrometer_Frequency)
hz_lower=(ppm_lower*Spectrometer_Frequency)

#Calculate the lowest allowed dwell time
dwell_lower=(1e6*(0.5/hz_upper))
#Calculate the maximum allowed dwell time
dwell_upper=(1e6*(0.5/hz_lower))

#Fetch Array Files
t_ar = np.genfromtxt("TimingArray",delimiter=",")
dwell_ar = np.genfromtxt("Dwellarray",delimiter=",")
cp_ar = np.genfromtxt("ChunkPointarray",delimiter=",")

#Produces a boolean mask for suitable dwell times
b = ((dwell_upper>dwell_ar)&(dwell_ar>dwell_lower))

#Produce arrays modified by first boolean mask with only suitable dwell times
dwell_arb = dwell_ar[b]
cp_arb = cp_ar[b]
t_arb = t_ar[b]

#Produce a second boolean mask based on timings
c = (((shortest_timing/1000)<t_arb)&(t_arb<(longest_timing/1000)))
```

```

#Produce arrays modified by second boolean mask with only suitable dwell times
dwell_arbc = dwell_arb[c]
cp_arbc = cp_arb[c]
t_arbc = t_arb[c]

#runs a modulo operation on the timing array with boolean mask applied
mod_arf1 = np.mod(t_arbc, p1)

#turn into a spectral quality array
mod_sqp1 = np.divide(mod_arf1, p1/100)

#Modify arrays to allow incomplete rotations
sub50ind = [(50.00<mod_sqp1)*(mod_sqp1<75.00)]
mod_sqp1[sub50ind] -= 50.0

subfrom50ind = [(25.00<mod_sqp1)*(mod_sqp1<50.00)]
mod_sqp1[subfrom50ind] -= 50.0

subfrom100ind = [(75.00<mod_sqp1)*(mod_sqp1<100.00)]
mod_sqp1[subfrom100ind] -= 100.0

mod_sqp1 = np.absolute(mod_sqp1)

#Troubleshooting line to print arrays
#np.savetxt('fname.txt',mod_sqp1)

#Find minimum element in modulo array
minElement = np.amin(mod_sqp1)
index = np.where(mod_sqp1 == np.amin(mod_sqp1))

#N.B. In the case multiple experimental viable timings are equally close to theoretically valid timings it will report them all

#Fetch the corresponding Chunkpoints and dwell time
print "OptimalDwellTime =", dwell_arbc[index]
print "ChunkpointsMultiple =", cp_arbc[index]
#print index

sq1 = mod_sqp1[index]

#Spectral Quality Prediction - Percentage of final rotation completed
#If this number is not close to 0 or 100 the spectra can be expected to be of poor quality (S/A ratio)
Spectral_Quality_f1 = (sq1)
print 'Percentage of final rotation completed =', Spectral_Quality_f1,'%'
```

Possible dwell times (μs) in increasing order for Bruker Avance III or Avance III HD

0.05	5	10.4	16.2	22.5	28.4	33.6	39.1	44.4	49.8
0.1	5.067	10.5	16.4	22.533	28.5	33.8	39.2	44.5	49.867
0.15	5.1	10.667	16.5	22.667	28.6	34	39.333	44.667	50
0.2	5.2	10.8	16.533	22.8	28.667	34.1	39.467	44.8	50.133
0.25	5.333	11	16.667	23	28.7	34.133	39.5	45	50.267
0.3	5.4	11.2	16.8	23.1	28.8	34.2	39.6	45.067	50.4
0.35	5.5	11.333	16.9	23.2	28.9	34.3	39.667	45.1	50.5
0.4	5.6	11.4	17	23.333	28.933	34.4	40	45.2	50.6
0.5	5.7	11.6	17.067	23.4	29	34.5	40.133	45.333	50.7
0.533	5.867	11.7	17.1	23.5	29.2	34.533	40.2	45.6	50.8
0.6	6	11.733	17.2	23.6	29.4	34.667	40.3	45.733	51
0.7	6.133	11.9	17.333	23.8	29.467	34.8	40.4	45.867	51.1
0.8	6.3	12	17.733	24	29.5	35	40.5	45.9	51.2
1	6.4	12.1	18	24.2	29.6	35.1	40.533	46	51.3
1.067	6.5	12.133	18.2	24.3	29.7	35.2	40.6	46.2	51.333
1.2	6.533	12.267	18.4	24.4	29.9	35.4	40.667	46.4	51.5
1.33	6.6	12.4	18.5	24.5	30	35.467	40.7	46.5	51.6
1.4	6.667	12.5	18.6	24.6	30.1	35.5	40.8	46.667	51.7
1.5	6.8	12.6	18.7	24.7	30.4	35.6	41	46.8	51.8
1.6	6.9	12.667	18.8	24.8	30.5	35.7	41.133	46.9	52
1.8	7	12.8	18.9	25	30.6	35.733	41.333	46.933	52.2
1.867	7	13	19	25.067	30.667	36	41.4	47	52.267
2	7.2	13.067	19.067	25.2	30.8	36.1	41.5	47.2	52.4
2.1	7.333	13.2	19.2	25.3	30.933	36.267	41.6	47.3	52.5
2.133	7.467	13.3	19.33	25.333	31	36.3	41.8	47.333	52.7
2.2	7.5	13.333	19.5	25.5	31.2	36.4	42	47.4	52.8
2.4	7.6	13.5	19.6	25.6	31.333	36.5	42.3	47.467	52.9
2.5	7.7	13.6	19.733	25.8	31.467	36.6	42.4	47.5	53
2.6	7.8	13.8	19.8	25.9	31.5	36.667	42.5	47.6	53.1
2.667	8	13.867	20	26	31.6	36.8	42.533	47.7	53.2
2.7	8.1	14	20.267	26.1	31.733	36.9	42.6	48	53.3
2.8	8.4	14.3	20.3	26.133	31.8	36.9	42.667	48.1	53.4
2.933	8.5	14.4	20.4	26.4	31.9	37	42.7	48.133	53.5
3	8.533	14.5	20.5	26.5	32	37.1	42.8	48.3	53.6
3.2	8.667	14.667	20.533	26.6	32.2	37.2	42.9	48.4	53.733
3.3	8.8	14.7	20.667	26.667	32.267	37.4	42.933	48.5	53.9
3.4	9	14.8	20.7	26.8	32.3	37.5	43	48.533	54
3.5	9.067	14.933	20.8	27	32.4	37.6	43.067	48.6	54.133
3.6	9.1	15	20.9	27.067	32.5	37.8	43.2	48.667	54.267
3.8	9.2	15.2	21	27.2	32.533	37.867	43.333	48.8	54.4
3.9	9.333	15.3	21.2	27.3	32.667	38	43.4	49	54.5
4	9.5	15.333	21.333	27.333	32.8	38.133	43.5	49.067	54.6
4.2	9.6	15.4	21.5	27.5	32.9	38.267	43.6	49.2	54.667
4.267	9.7	15.467	21.6	27.6	32.933	38.4	43.7	49.3	54.8
4.4	9.8	15.5	21.7	27.733	33	38.5	43.8	49.333	54.9
4.5	9.9	15.6	21.867	27.867	33.067	38.533	43.867	49.4	55
4.6	10	15.867	22	27.9	33.2	38.7	44	49.467	55.1
4.667	10.133	16	22.1	28	33.3	38.8	44.1	49.5	55.2
4.8	10.2	16.1	22.2	28.2	33.333	38.933	44.2	49.6	55.3

60.9	66.3	71.1	76.5
61	66.4	71.2	76.533
61.1	66.5	71.3	76.7
61.2	66.6	71.333	76.8
61.333	66.667	71.4	77
61.5	66.7	71.467	77.067
61.6	66.8	71.5	77.2
61.8	67	71.6	77.4
61.867	67.1	71.867	77.5
62	67.2	72	77.6
62.1	67.333	72.2	77.7
62.3	67.467	72.4	77.733
62.4	67.5	72.5	77.867
62.5	67.6	72.533	77.9
62.533	67.733	72.6	78
62.667	67.8	72.667	78.1
62.7	67.9	72.8	78.2
62.8	68	72.9	78.3
62.9	68.133	73	78.4
63	68.2	73.067	78.5
63.067	68.267	73.1	78.6
63.2	68.4	73.2	78.667
63.333	68.5	73.333	78.8
63.5	68.6	73.467	78.933
63.6	68.667	73.5	79
63.7	68.8	73.6	79.1
63.8	68.9	73.7	79.2
63.9	68.933	73.733	79.3
64	69	73.8	79.333
64.133	69.067	74	79.467
64.2	69.2	74.1	79.5
64.4	69.3	74.133	79.6
64.5	69.333	74.2	79.733
64.6	69.5	74.4	79.8
64.667	69.6	74.5	79.9
64.8	69.7	74.533	80
64.9	69.867	74.7	
65	70	74.8	
65.067	70.2	74.9	
65.1	70.267	75	
65.2	70.3	75.2	
65.4	70.4	75.4	
65.5	70.5	75.5	
65.6	70.533	75.6	
65.7	70.667	75.733	
65.733	70.7	75.9	
65.8	70.8	76	
65.867	70.933	76.2	
66	71	76.3	
66.133	71.067	76.4	