Supporting information for:
Searching for Hydrodynamic Orienting Effects in the Association of Tri-N-acetylglucosamine with Hen Egg-White Lysozyme

Beata Wielgus-Kutrowska, Urszula Marcisz, and Jan M. Antosiewicz*

*Biophysics Division, Institute of Experimental Physics, Faculty of Physics, University of Warsaw, Pasteura 5 St., 02-093 Warsaw, Poland

E-mail: jantosi@fuw.edu.pl
Phone: +48 22 55 32 340
This file includes Supporting Figure S1, Supporting Tables S1 to S6, comments to the data presented in these Tables, and examples of the UHBD program inputs.

Figure S1: Comparison of the ionic strength dependencies of the binding anisotropy $\kappa$ defined by Equation 2, for the most restrictive reaction criterion, obtained from Brownian dynamics simulations for two different solvent viscosities (1.002 cP black, 1.150 cP red), with (upper part) and without (bottom part) hydrodynamic interactions included. See text for details.
Table S1: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 1, for the “wild type” receptor model, $k^{WT}$, and the mutated receptor model, $k^{MT}$, with hydrodynamic interactions included during simulations. See text for details.

| Ionic Strength [mM] | viscosity [cP] | $k^{WT}$ [μM$^{-1}$s$^{-1}$] | StdErr | $k^{MT}$ [μM$^{-1}$s$^{-1}$] | StdErr |
|---------------------|----------------|-----------------------------|--------|-----------------------------|--------|
| 0.                  | 1.002          | 415                         | 21     | 75.5                        | 4.3    |
|                     | 1.150          | 165                         | 9      | 55.5                        | 3.1    |
| 25.                 | 1.002          | 299                         | 15     | 75.3                        | 4.3    |
|                     | 1.150          | 126                         | 7      | 53.1                        | 2.9    |
| 50.                 | 1.002          | 245                         | 12     | 79.9                        | 4.4    |
|                     | 1.150          | 119                         | 6      | 55.3                        | 3.1    |
| 100.                | 1.002          | 181                         | 9      | 77.1                        | 4.3    |
|                     | 1.150          | 133                         | 7      | 51.9                        | 2.9    |
| 150.                | 1.002          | 216                         | 11     | 76.4                        | 4.4    |
|                     | 1.150          | 118                         | 6      | 55.3                        | 3.1    |
| 200.                | 1.002          | 146                         | 8      | 81.8                        | 4.6    |
|                     | 1.150          | 92.9                        | 4.8    | 50.7                        | 3.0    |
| 300.                | 1.002          | 167                         | 9      | 92.2                        | 5.5    |
|                     | 1.150          | 83.1                        | 4.4    | 48.7                        | 2.9    |
| 400.                | 1.002          | 137                         | 8      | 87.3                        |        |
|                     | 1.150          | 70.3                        | 3.7    | 46.8                        | 2.8    |
| 500.                | 1.002          | 119                         | 7      | 72.6                        | 4.5    |
|                     | 1.150          | 90.2                        | 4.9    | 45.1                        | 2.8    |
Table S2: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 2, for the “wild type” receptor model, $k_{a}^{WT}$, and the mutated receptor model, $k_{a}^{MT}$, with hydrodynamic interactions included during simulations. See text for details.

| Ionic Strength [mM] | viscosity [cP] | $k_{a}^{WT}$ [$\mu$M$^{-1}$s$^{-1}$] | StdErr | $k_{a}^{MT}$ [$\mu$M$^{-1}$s$^{-1}$] | StdErr |
|---------------------|----------------|-------------------------------------|--------|-------------------------------------|--------|
| 0.                  | 1.002          | 239                                 | 16     | 6.83                                | 1.29   |
|                     | 1.150          | 95.2                                | 6.3    | 6.13                                | 1.02   |
| 25.                 | 1.002          | 168                                 | 12     | 10.4                                | 1.6    |
|                     | 1.150          | 72.3                                | 4.8    | 7.21                                | 1.08   |
| 50.                 | 1.002          | 136                                 | 10     | 11.6                                | 1.7    |
|                     | 1.150          | 65.1                                | 4.5    | 9.25                                | 1.24   |
| 100.                | 1.002          | 115                                 | 8      | 15.1                                | 2.0    |
|                     | 1.150          | 60.4                                | 4.3    | 10.5                                | 1.4    |
| 150.                | 1.002          | 115                                 | 8      | 15.1                                | 2.0    |
|                     | 1.150          | 60.4                                | 4.3    | 10.5                                | 1.4    |
| 200.                | 1.002          | 77.5                                | 5.5    | 17.4                                | 2.1    |
|                     | 1.150          | 48.3                                | 3.5    | 10.8                                | 1.4    |
| 300.                | 1.002          | 82.5                                | 6.1    | 21.7                                | 2.7    |
|                     | 1.150          | 43.3                                | 3.2    | 11.1                                | 1.4    |
| 400.                | 1.002          | 65.3                                | 5.3    | 20.6                                | 2.7    |
|                     | 1.150          | 34.3                                | 2.6    | 10.8                                | 1.4    |
| 500.                | 1.002          | 56.7                                | 4.5    | 17.0                                | 2.2    |
|                     | 1.150          | 45.8                                | 3.5    | 11.0                                | 1.4    |
Table S3: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 3 (the most restrictive one), for ‘the “wild type” receptor model, $k^\text{WT}_a$, and the mutated receptor model, $k^\text{MT}_a$, with hydrodynamic interactions included during simulations. See text for details.

| Ionic Strength [mM] | viscosity [cP] | $k^\text{WT}_a$ [µM$^{-1}$s$^{-1}$] | StdErr | $k^\text{MT}_a$ [µM$^{-1}$s$^{-1}$] | StdErr |
|---------------------|----------------|-------------------------------------|--------|-------------------------------------|--------|
| 0.                  | 1.002          | 71.7                                | 8.6    | 0.355                               | 0.292  |
|                     | 1.150          | 30.0                                | 3.6    | 0.190                               | 0.181  |
| 25.                 | 1.002          | 44.2                                | 5.8    | 0.177                               | 0.206  |
|                     | 1.150          | 20.0                                | 2.5    | 0.120                               | 0.140  |
| 50.                 | 1.002          | 34.9                                | 4.7    | 0.266                               | 0.253  |
|                     | 1.150          | 17.7                                | 2.5    | 0.304                               | 0.224  |
| 100.                | 1.002          | 27.0                                | 3.6    | 0.356                               | 0.293  |
|                     | 1.150          | 19.1                                | 2.6    | 0.181                               | 0.172  |
| 150.                | 1.002          | 28.1                                | 4.0    | 0.824                               | 0.452  |
|                     | 1.150          | 14.2                                | 2.1    | 0.434                               | 0.270  |
| 200.                | 1.002          | 18.3                                | 2.7    | 1.22                                | 0.56   |
|                     | 1.150          | 10.4                                | 1.6    | 0.505                               | 0.294  |
| 300.                | 1.002          | 16.5                                | 2.8    | 1.20                                | 0.63   |
|                     | 1.150          | 8.49                                | 1.39   | 0.548                               | 0.301  |
| 400.                | 1.002          | 16.2                                | 2.6    | 0.905                               | 0.527  |
|                     | 1.150          | 6.83                                | 1.16   | 0.545                               | 0.300  |
| 500.                | 1.002          | 11.5                                | 2.0    | 1.20                                | 0.57   |
|                     | 1.150          | 10.1                                | 1.7    | 0.677                               | 0.337  |
Table S4: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 1, for ‘the “wild type” receptor model, $k_{a}^{WT}$, and the mutated receptor model, $k_{a}^{MT}$, with hydrodynamic interactions not included during simulations. See text for details.

| Ionic Strength [mM] | viscosity [cP] | $k_{a}^{WT}$ [µM$^{-1}$s$^{-1}$] | StdErr | $k_{a}^{MT}$ [µM$^{-1}$s$^{-1}$] | StdErr |
|---------------------|---------------|-------------------------------|--------|-------------------------------|--------|
| 0.0                 | 1.002         | 4130                          | 36     | 7150                          | 44     |
|                     | 1.150         | 2750                          | 24     | 4780                          | 29     |
| 25.0                | 1.002         | 3900                          | 35     | 6670                          | 43     |
|                     | 1.150         | 2600                          | 24     | 4470                          | 28     |
| 50.0                | 1.002         | 3670                          | 34     | 6440                          | 42     |
|                     | 1.150         | 2470                          | 23     | 4250                          | 28     |
| 100.0               | 1.002         | 3410                          | 33     | 5860                          | 41     |
|                     | 1.150         | 2290                          | 22     | 3950                          | 27     |
| 150.0               | 1.002         | 3180                          | 32     | 5470                          | 40     |
|                     | 1.150         | 2120                          | 22     | 3670                          | 26     |
| 200.0               | 1.002         | 3030                          | 32     | 5220                          | 39     |
|                     | 1.150         | 2020                          | 21     | 3430                          | 26     |
| 300.0               | 1.002         | 2760                          | 30     | 4710                          | 37     |
|                     | 1.150         | 1860                          | 20     | 3120                          | 25     |
| 400.0               | 1.002         | 2580                          | 30     | 4340                          | 36     |
|                     | 1.150         | 1710                          | 20     | 2870                          | 25     |
| 500.0               | 1.002         | 2400                          | 29     | 4030                          | 35     |
|                     | 1.150         | 1600                          | 19     | 2710                          | 24     |
Table S5: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 2, for ‘the “wild type” receptor model, $k_{a}^{WT}$, and the mutated receptor model, $k_{a}^{MT}$, with hydrodynamic interactions not included during simulations. See text for details.

| Ionic Strength [mM] | Viscosity [cP] | $k_{a}^{WT}$ [µM$^{-1}$s$^{-1}$] | StdErr | $k_{a}^{MT}$ [µM$^{-1}$s$^{-1}$] | StdErr |
|---------------------|----------------|-------------------------------|--------|-------------------------------|--------|
| 0.                  | 1.002          | 3860                          | 36     | 6324                          | 42     |
|                     | 1.150          | 2580                          | 23     | 4250                          | 28     |
| 25.                 | 1.002          | 3620                          | 34     | 5830                          | 41     |
|                     | 1.150          | 2420                          | 23     | 3920                          | 27     |
| 50.                 | 1.002          | 3400                          | 33     | 5610                          | 40     |
|                     | 1.150          | 2290                          | 22     | 3690                          | 26     |
| 100.                | 1.002          | 3110                          | 32     | 4980                          | 38     |
|                     | 1.150          | 2090                          | 21     | 3370                          | 26     |
| 150.                | 1.002          | 2860                          | 31     | 4570                          | 37     |
|                     | 1.150          | 1910                          | 20     | 3080                          | 25     |
| 200.                | 1.002          | 2700                          | 30     | 4310                          | 36     |
|                     | 1.150          | 1810                          | 20     | 2820                          | 24     |
| 300.                | 1.002          | 2420                          | 29     | 3790                          | 34     |
|                     | 1.150          | 1630                          | 19     | 2500                          | 23     |
| 400.                | 1.002          | 2220                          | 28     | 3400                          | 33     |
|                     | 1.150          | 1470                          | 18     | 2250                          | 22     |
| 500.                | 1.002          | 2050                          | 26     | 3070                          | 32     |
|                     | 1.150          | 1360                          | 18     | 2080                          | 22     |
Table S6: Diffusional encounter rate constants, obtained from Brownian dynamics simulations, and their standard errors, obtained for the reaction criterion 3 (the most restrictive one), for ‘the “wild type” receptor model, \( k_{a}^{WT} \), and the mutated receptor model, \( k_{a}^{MT} \), with hydrodynamic interactions not included during simulations. See text for details.

| Ionic Strength [mM] | viscosity [cP] | \( k_{a}^{WT} \) [\( \mu \text{M}^{-1}\text{s}^{-1} \)] | StdErr | \( k_{a}^{MT} \) [\( \mu \text{M}^{-1}\text{s}^{-1} \)] | StdErr |
|---------------------|---------------|-----------------|--------|-----------------|--------|
| 0.0                 | 1.002         | 3580            | 34     | 1100            | 20     |
|                     | 1.150         | 2390            | 22     | 755             | 13     |
| 25.0                | 1.002         | 3320            | 33     | 1010            | 19     |
|                     | 1.150         | 2120            | 22     | 689             | 13     |
| 50.0                | 1.002         | 3070            | 32     | 983             | 19     |
|                     | 1.150         | 2080            | 21     | 661             | 12     |
| 100.0               | 1.002         | 2760            | 30     | 894             | 18     |
|                     | 1.150         | 1870            | 20     | 607             | 12     |
| 150.0               | 1.002         | 2510            | 29     | 836             | 17     |
|                     | 1.150         | 1680            | 19     | 558             | 12     |
| 200.0               | 1.002         | 2350            | 28     | 782             | 17     |
|                     | 1.150         | 1570            | 19     | 529             | 11     |
| 300.0               | 1.002         | 2030            | 26     | 718             | 16     |
|                     | 1.150         | 1370            | 18     | 474             | 11     |
| 400.0               | 1.002         | 1820            | 25     | 644             | 15     |
|                     | 1.150         | 1210            | 17     | 444             | 10     |
| 500.0               | 1.002         | 1630            | 24     | 603             | 15     |
|                     | 1.150         | 1090            | 16     | 416             | 10     |
Comments to data presented in Tables S1 to S6

At first glance, the differences between rate constants computed with hydrodynamic interactions included (Tables S1–S3) and neglected (Tables S4–S6), respectively, may seem much too large. Most of the previous studies reported a substantially smaller decrease in the association rate constants caused by the inclusion of HI between two spherical particles or a spherical target and dumbbell dimer. In these studies, spherical elements used to model molecules were considered uniformly reactive over their surfaces, and a single distance criterion was used to define association reactions. On the other hand, Shushin analyzed the effect of hydrodynamic interaction on diffusion-controlled reaction rate of molecules with highly anisotropic reactivity, modeled by small reactive hemispheres around the reactive centers on the surfaces of spherical molecules. He showed that the hydrodynamic interaction effect can lead to about 3-5 times and larger reduction of the rate. In the case of our simulations, we obtain such reductions as 50 (ionic strength 0) and 108 (ionic strength 500 mM) for the most restrictive reaction criterion, and as 10 (ionic strength 0) and 18 (ionic strength 500 mM) for the least restrictive reaction criterion. The increase in the ratio with going from the least to the most restrictive reaction criterion is in qualitative agreement with the results of Shushin. We believe that more complex molecular shapes and requirement to satisfy simultaneously four distance criteria instead of just one are responsible for the higher values in our case.

Finally, in a recent publication on encounter rates between xanthone and 2-naphtoic acid, we also obtained substantial decrease of the association rate with hydrodynamic interactions included in comparison to hydrodynamic interaction neglected, i.e. 10250/723=14. In this case we deal with molecular models composed of several spherical elements, but the reaction criteria used a single distance. It is worthy to note that the rate constant obtained for simulations neglecting receptor-ligand hydrodynamic interactions, 10250 μM⁻¹s⁻¹, for
xanthone and 2-naphthoic acid was shown to be in excellent agreement with the result of the analytical equation of Smoluchowsky, \(11146 \, \mu M^{-1}s^{-1}\).

It may be also noted that that the decrease of the encounter rates with increased solvent viscosity is somewhat larger than predicted by the analytical Smoluchowsky equation for spherical particles, as according to this equation the association rate constant is proportional to the inverse of viscosity of the solvent. However, it should be also noted that no-HI simulation means that there is no hydrodynamic interactions between beads of the receptor model with the beads of the ligand model. The receptor is at rest in the center of the coordinate system, with its hydrodynamic radius of equivalent spere computed assuming hydrodynamic interactions between constituting beads. On the other hand, the ligand diffusion is simulated with hydrodynamic interactions between its constituting beads included. Moreover, it is probably also important that four distances are used in definition of the reaction criteria instead of just one. Thus simple recalculation referring to association of single spheres may be misleading.
Examples of the UHBD program inputs

Simulations with receptor-ligand hydrodynamic interactions included

read mol1 file "./enzym-10bead-model.pdb" pdb end ! read in receptor
read mol2 file "./ligand-3bead-model.pdb" pdb end ! read in ligand
set charge radii file "./qrdata.dat" ! set charges and ra
     para par end ! using data in file
     ! qrdata.dat
read phi grid file "enzyme-par.pot" binary end
elec setup same grid ! no electrostatic calcul
    nsph 280
    sdie 78.0 ! solvent dielectric = 78
    pdie 4.0 ! protein dielectric = 4
    temp 293.0
    ionstr 0.0
    nmap 1.4
end

edit suni iflx 1
    numsub 10 atnum 1 1 2 2 3 3 4 4 5 5 6 6 7 7 8 8 9 9 10 10
    cent atnum 1 2 3 4 5 6 7 8 9 10
    fix 4 atnum 1 5 6 10
    prts
end

edit suni iflx 2
    numsub 3 atnum 11 11 12 12 13 13

S11
cent atnum 11 12 13
fix 0
prts
end

edit funi iflx 1
oldb
loccor dfcnsr 10
1 2 3.00
2 3 3.00
3 4 3.00
  4 5 3.00
  6 7 3.00
  7 8 3.00
  8 9 3.00
  9 10 3.00
1 6 12.00
  5 10 12.00
toler 0.10
mdoseen stick hrient 2.00
hi 15
  2 3
  2 4
  2 7
  2 8
  2 9
  3 4

S12
nbon
nexv
nang
nsol
nonnnb
prts
prin
end

edit funi iflx 2

oldb
loccor dfcnsr 3
11 13 6.000
11 12 3.000
12 13 3.000
toler 0.10
mdoseen stick hrient 2.00
hi 3
  11 12
  11 13
  12 13

nbon
nexv
nang
nsol
nonnnb
prts
prin
end

edit fiun
  num 3  0 1 mdoseen stick nexv nsol end
  0 2 mdoseen stick nexv nsol end
  1 2 mdoseen stick end
prnt
end

bd calc nruns 1 ntraj 3000 ! 1 run of bd, 1000 traj
srad 2.0 ! effective substrate excl
! radius
rad1 7.83 ! hydrodynamic radius of targ
dfcr 100 ! tries to estimate relati
! diffusion coefficient
temp 293.0
svis 1.002

psurf 30.0
bsurf 55.0
qsurf 110.0

delt 0.010
vtim 4 30.0 2.0 45.0 5.0 50.0 10.0 60.0 20.0

ijsd1 10710
klsd1 11800
ijsd2 9301
klsd2 16640

mrxn defrxn 3 4 2 11 9.0
7 11 9.0
4 13 9.0
9 13 9.0
4 2 11 8.0
7 11 8.0
4 13 8.0
9 13 8.0
4 2 11 7.0
7 11 7.0
4 13 7.0
9 13 7.0
Simulations with receptor-ligand hydrodynamic interactions neglected

read mol1 file "./enzym-10bead-model.pdb" pdb end ! read in receptor
read mol2 file "./ligand-3bead-model.pdb" pdb end ! read in ligand
set charge radii file "./qrdata.dat" ! set charges and ra
     para par end ! using data in file
      ! qrdata.dat

read phi grid file "enzyme-par.pot" binary end

elec setup same grid ! no electrostatic calcul
      nsph 280
      sdie 78.0 ! solvent dielectric = 78
      pdie 4.0 ! protein dielectric = 4
      temp 293.0
      ionstr 0.0
      nmap 1.4
end

edit suni iflx 1
     numsub 3 atnum 11 11 12 12 13 13
     cent atnum 11 12 13
     fix 0
     prts
end
edit funi iflx 1

oldb

loccor dfcnsr 3
1 3 6.000
1 2 3.000
2 3 3.000
toler 0.10

mdoseen stick hrident 2.00

hi 3
1 2
1 3
2 3

nbon
nexv
nang
nsol
nonnnb
pnts
prin

end

bd calc nrns 1 ntraj 3000 ! 1 run of bd, 1000 traj

srad 2.0 ! effective substrate excl
! radius

rad1 7.83 ! hydrodynamic radius of targ
dfcr 100 ! tries to estimate relati
! diffusion coefficient
temp 293.0
svis 1.002

psurf 30.0
bsurf 55.0
qsurf 110.0

delt 0.010
vtim 4 30.0 2.0 45.0 5.0 50.0 10.0 60.0 20.0

ijsd1 9073
klsd1 30031
ijsd2 4636
klsd2 21612

mrxn defrxn 3 4 2 1 9.0
          7 1  9.0
          4 3  9.0
          9 3  9.0
          4 2  1  8.0
          7 1  8.0
          4 3  8.0
          9 3  8.0
          4 2  1  7.0
          7 1  7.0
          4 3  7.0
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