Supplementary Information.

Standard error calculation:

We adopted the "Delta Method" to evaluate approximated values of the standard error of a ratio between two independent random variables (whose standard errors are known). For estimators, the delta method is important because while the theoretical standard error of a mean of an SRS is known, there is no general theoretical expression for standard errors of most functions of a mean, such as the inverse of a mean, or the ratio of two means.

Suppose we have random variables K_1, K_2. A Taylor series expansion of $f(K_1, K_2)$ about the values $(\overline{K}_1, \overline{K}_2)$ is given by:

$$f(K_1,K_2) = f(\overline{K}_1,\overline{K}_2) + \left.\frac{\partial f(K_1,K_2)}{\partial K_1}\right|_{(\overline{K}_1,\overline{K}_2)} (K_1 - \overline{K}_1) + \left.\frac{\partial f(K_1,K_2)}{\partial K_2}\right|_{(\overline{K}_1,\overline{K}_2)} (K_2 - \overline{K}_2) + ...$$

If we suppose $f(K_1,K_2) = K_2 / K_1$ then $\frac{\partial f(K_1,K_2)}{\partial K_1} = -\frac{K_2}{K_1}, \frac{\partial f(K_1,K_2)}{\partial K_2} = \frac{1}{K_1}$

$$\Rightarrow f(K_1,K_2) = \frac{K_2}{K_1} \approx \frac{\overline{K}_2}{\overline{K}_1} + \frac{-\overline{K}_2}{\overline{K}_1^{\,2}}(K_1 - \overline{K}_1) + \frac{1}{\overline{K}_1}(K_2 - \overline{K}_2)$$

Hence if we want to evaluate the standard error of the latter ratio:

$$(SD(K_2/K_1) \approx \sqrt{\frac{\overline{K}_2^{\,2}}{\overline{K}_1^{\,4}} SD^2(K_1) + \frac{1}{\overline{K}_1^{\,2}} SD(K_2) - 2\frac{\overline{K}_2}{\overline{K}_1^{\,3}} Cov(K_1K_2)}\ )$$

Since the random variables K_1, K_2 are independent:

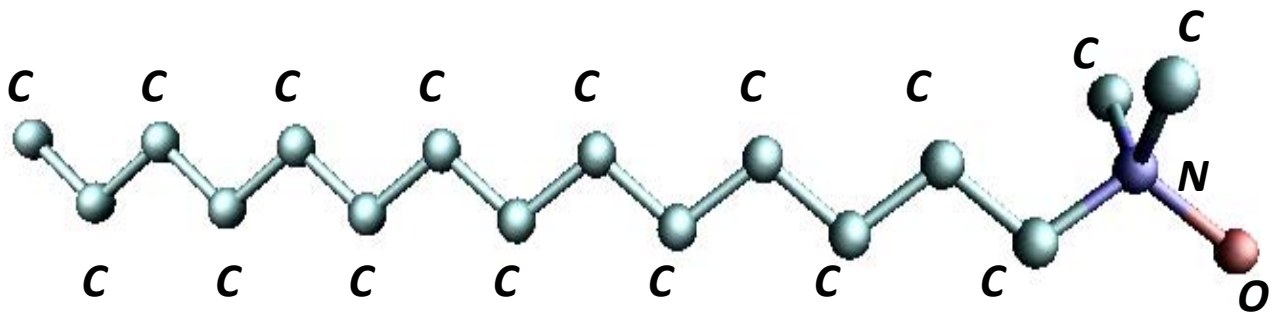
$$SD(K_2/K_1) \approx \sqrt{\frac{\overline{K}_2^{\,2}}{\overline{K}_1^{\,4}} SD^2(K_1) + \frac{1}{\overline{K}_1^{\,2}} SD(K_2)}$$

Furthermore if $SD(K_1) \simeq SD(K_2)$:

$$SD(K_2/K_1) \approx SD(K_1)\sqrt{\frac{\overline{K}_2^{\,2}}{\overline{K}_1^{\,4}} + \frac{1}{\overline{K}_1^{\,2}}} = \frac{SD(K_1)}{\overline{K}_1^{\,2}}\sqrt{\overline{K}_1^{\,2} + \overline{K}_2^{\,2}}$$

which represents the final formula for our calculations.

TDDNO monomer Gromacs topology:

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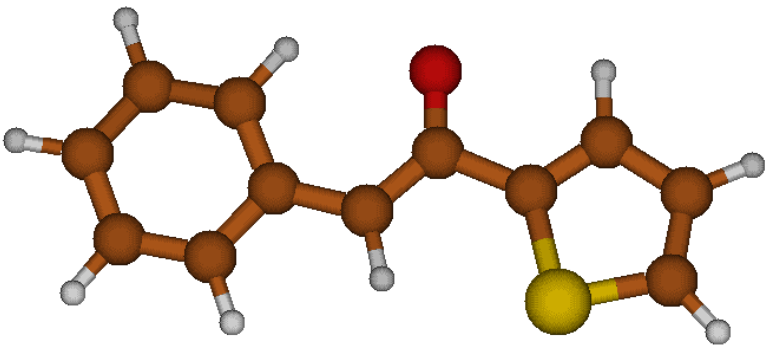
[ moleculetype ]
; Name            nrexcl
tddno               3

[ atoms ]
;   nr       type  resnr residue  atom   cgnr     charge       mass  typeB    chargeB
massB

     1        CH3      1    TDD      C      1          0.     15.035   ; qtot 0.129
     2        CH2      1    TDD      C      2          0.     14.027   ; qtot 0.377
     3        CH2      1    TDD      C      3          0.     14.027   ; qtot 0.625
     4        CH2      1    TDD      C      4          0.     14.027   ; qtot 0.873
     5        CH2      1    TDD      C      5          0.     14.027   ; qtot 1
     6        CH2      1    TDD      C      6          0.     14.027   ; qtot 1
     7        CH2      1    TDD      C      7          0.     14.027   ; qtot 1
     8        CH2      1    TDD      C      8          0.     14.027   ; qtot 1
     9        CH2      1    TDD      C      9          0.     14.027   ; qtot -0.8
    10        CH2      1    TDD      C     10          0.     14.027   ; qtot 1
    11        CH2      1    TDD      C     11          0.     14.027   ;
    12        CH2      1    TDD      C     12          0.     14.027   ; qtot=-1
    13        CH2      1    TDD      C     13          0.     14.027   ;
    14        CH2      1    TDD      C     14     0.0268     14.027   ;
    15          N      1    TDD      N     14     0.6164    14.0067   ;
    16        CH3      1    TDD      C     14     0.0316     15.035   ;
    17        CH3      1    TDD      C     14     0.0314     15.035   ;
    18          O      1    TDD      O     14    -0.7062    15.9994   ;
```

Enolate topology:



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[ moleculetype ]
; Name            nrexcl
Protein_A           3

[ atoms ]
;   nr       type  resnr residue  atom   cgnr     charge       mass  typeB    chargeB
massB
     1          S      1    FNT      S      1     -0.1     32.065    ; qtot -0.83
     2        CR1      1    FNT      C      1     -0.2       12.011   ; qtot -0.415
     3        CR1      1    FNT      C      1     -0.2       12.011   ; qtot -0.415
     4        CR1      1    FNT      C      1      -0.1      12.011   ; qtot -0.415
     5        CR1      1    FNT      C      1      -0.1      12.011   ; qtot -0.415
     6         HC      1    FNT      H      1       0.2       1.008   ; qtot 0
     7         HC      1    FNT      H      1       0.1       1.008   ; qtot -0.28
     8         HC      1    FNT      H      1       0.1       1.008   ; qtot 0
     9          C      1    FNT      C      1      0.7       12.011   ; qtot 0
    10          O      1    FNT      O      1      -0.8     15.9994   ; qtot 0.38
    11          C      1    FNT      C      1      -1.0      12.011   ; qtot -0.28
    12          H      1    FNT      H      1       0.2       1.008   ; qtot 0
    13        CR1      1    FNT      C      1      0.8       12.011   ; qtot 0
    14        CR1      1    FNT      C      1     -0.3       12.011   ; qtot 0
    15        CR1      1    FNT      C      1      0.00      12.011   ; qtot 0
    16        CR1      1    FNT      C      1     -0.3       12.011   ; qtot 0
    17        CR1      1    FNT      C      1     -0.1       12.011   ; qtot 0
    18        CR1      1    FNT      C      1     -0.4       12.011   ; qtot -0.83
    19         HC      1    FNT      H      1       0.1      1.008   ; qtot -0.415
    20         HC      1    FNT      H      1       0.1      1.008   ; qtot 0
    21         HC      1    FNT      H      1       0.1      1.008   ; qtot 0.38
    22         HC      1    FNT      H      1       0.1      1.008
    23         HC      1    FNT      H      1       0.1      1.008
```