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# Supplementary Information

## Critical evaluation of anharmonicity and configurational averaging in QM/MM modelling of equilibrium isotope effects

Maite Roca,[a] Catherine M. Upfold[b] and Ian H. Williams*[b]

a. *Departament de Química Física i Analítica; Universitat Jaume I, 12071 Castellón (Spain)*
b. *Department of Chemistry, University of Bath, Bath BA2 7AY (United Kingdom)*

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**Anharmonicity in $C_\alpha H$ stretching and bending modes.**

**Fortran driver program for use with fDynamo library to interface with Gaussian 16 for anharmonic frequency calculations within a field of point charges.**

```
program relax_anharmonic
use dynamo
implicit none
integer                                    :: i, j, follow_mode, isnap
character (len = 10 )                      :: label
logical, allocatable, dimension(:)         :: acs, flg
real(kind=dp), dimension(:),allocatable    :: x
call dynamo_header
call cabinitio_init

! Read force-field parameter file "opls"
call mm_file_process ( "borra", "opls" )

! Read sequence file "Me_start.seq" for solvated methyl cation
call mm_system_construct ( "borra", "Me_start.seq" )

! Read the number "isnap" of the solute/solvent snapshot configuration
read(*,*) isnap
call encode_integer( isnap, label, '(i4)' )

! Read the coordinate file "Me_1ns_isnap.crd" for this structure
call coordinates_read( 'Me_1ns_' // trim( label ) // '.crd' )

! Allocate array
allocate( acs(1:natoms), flg(1:natoms) )

! Define QM region: check subsystem name matches that in ".seq" file
acs = atom_selection( subsystem = (/ "SOLUTE" /) )
call cabinitio_setup( acs )
skip_cabinitio = .false.

! Define the core and environment
call my_sele_qmnb( flg )
flg = flg .and. .not. acs

! Nonbonding interactions
call energy_initialize
call energy_non_bonding_options( &
    list_cutoff  = 15.0_dp, outer_cutoff = 13.5_dp, inner_cutoff = 12.0_dp, &
    minimum_image = .true. )                                  ! periodic boundary conditions

! Freeze positions of atoms in the MM region
call atoms_fix ( .not. acs )
write(*,*) "Flexible atoms",count( acs ),"Frozen Atoms",count ( .not. acs )
skip_cabinitio = .false.

! Energy minimisation for QM region only
call optimize_lbfgsb( print_frequency = 1, step_number = 200, gradient_tolerance = 0.5_dp )
call gradient

! Write coordinates for relaxed QM region
call coordinates_write         ( "bfgs_" // trim( label ) // ".crd" )
call pdb_write                 ("bfgs_" // trim( label ) // ".pdb" )
```

```
! Trick the program into doing G16" freq=anharmonic" jobs for two isotopologues.
! Normally, a subroutine call to "energy" sets up a value for "code == 0" which evaluates the
! energy alone, but here it gets hijacked and the inclusion of "freq_g16.f90" (below), instead
! of the usual "with_g16.f90", calls a bespoke version of "subroutine chrg_server" to set up
! the Gaussian calculations

write(*,*) "Start anharmonic frequency calculations"
call energy
write(*,*) "End anharmonic frequency calculations"
call energy

deallocate( acs, flg )
call cabinitio_exit
call dynamo_footer
end relax_anharmonic
include "notfix.f90"
include "freq_g16.f90"


subroutine my_sele_qmnb( sele )
use atoms, only                                   : natoms
use atom_manipulation, only                       : atom_selection
logical, dimension(1:natoms), intent(inout)       :: sele
sele = .true.
end subroutine my_sele_qmnb


subroutine chrg_server( code, natm, naqm, atmn, cord, ener, qfit, grad, hess )
implicit none
integer, intent( in ) :: code, natm, naqm
real*8, dimension(1:natm), intent( in ) :: atmn
real*8, dimension(1:3*natm), intent( in ) :: cord
real*8, intent( inout ) :: ener
real*8, dimension(1:naqm), intent( inout ) :: qfit
real*8, dimension(1:*), intent( inout ) :: grad
real*8, dimension(1:*), intent( inout ) :: hess
real*8 :: smm
real*8, parameter :: bohr = 0.529177249d0
integer :: i, j, k, l, n3, nh, ierr
character( len=256 ) :: str
character( len=2 ), dimension(1:109), parameter :: smb = (/ &
"H ", "He", "Li", "Be", "B ", "C ", "N ", "O ", "F ", "Ne", "Na", "Mg", &
"Al", "Si", "P ", "S ", "Cl", "Ar", "K ", "Ca", "Sc", "Ti", "V ", "Cr", "Mn", "Fe", &
"Co", "Ni", "Cu", "Zn", "Ga", "Ge", "As", "Se", "Br", "Kr", "Rb", "Sr", "Y ", "Zr", &
"Nb", "Mo", "Tc", "Ru", "Rh", "Pd", "Ag", "Cd", "In", "Sn", "Sb", "Te", "I ", "Xe", &
"Cs", "Ba", "La", "Ce", "Pr", "Nd", "Pm", "Sm", "Eu", "Gd", "Tb", "Dy", "Ho", "Er", &
"Tm", "Yb", "Lu", "Hf", "Ta", "W ", "Re", "Os", "Ir", "Pt", "Au", "Hg", "Tl", "Pb", &
"Bi", "Po", "At", "Rn", "Fr", "Ra", "Ac", "Th", "Pa", "U ", "Np", "Pu", "Am", "Cm", &
"Bk", "Cf", "Es", "Fm", "Md", "No", "Lr", "Rf", "Db", "Sg", "Bh", "Hs", "Mt" /)

! Create Gaussian job file "calc1.gjf"
open( unit=999, file = "calc1.gjf", action = "write", form = "formatted" )

if( code == 1 ) then
```

```
! This sets up a job to evaluate the electrostatic-potential-fitted (ESP) atomic charges
! and the gradient for the QM atoms with the point charges of the MM environment
    write( 999, "(a/a/a/a)" ) "%Chk=calc", "%nprocshared=1", "%mem=3GB", &
    "#B3LYP/6-31+g(d) charge scf=(direct,tight) nosymm int=ultrafine"
    write( 999, "(a/)" ) "force pop=(CHelpG,ReadRadii)"
    write( 999, "(a//2i4)" ) "- light -", 1, 1
    do i = 1, naqm
        j = ( i - 1 ) * 3
        write( 999, "(a8,3f20.10)" ) smb(int(atmn(i))), cord(j+1), cord(j+2), cord(j+3)
    end do
    write( 999, "(a)" ) ""
    smm = 0.0d0
    if( naqm == natm ) then
        write( 999, "(f28.10,2f20.10,f8.3)" ) 999.0d0, 999.0d0, 999.0d0, 0.0d0
    else
        do i = naqm + 1, natm
            j = ( i - 1 ) * 3
            write( 999, "(f28.10,2f20.10,f8.3)" ) cord(j+1), cord(j+2), cord(j+3), atmn(i)
            do k = i + 1, natm
                l = ( k - 1 ) * 3
                smm = smm + atmn(i) * atmn(k) / dsqrt( sum( ( cord(j+1:j+3) - cord(l+1:l+3) ) ** 2 ) ) * bohr
            end do
        end do
    end if
    write( 999, "(a)" ) ""
    write( 999, "(//)" )
    close( 999 )

! Execute Gaussian calculation; convert unformatted checkpoint file to formatted (calc.fchk)
    call system( ". $g16root/g16/bsd/g16.profile; g16 < calc1.gjf > calc.log; formchk calc.chk calc.fchk" )

    ener = 0.0d0
    qfit = 0.0d0
    open( unit = 999, file = "calc.fchk", action = "read", form = "formatted" )
    read( 999, "(a)", end = 999 ) str
    do while( .true. )
        if( str(1:12) == "Total Energy" ) read( str(50:71), "(f22.15)", end = 999 ) ener
        if( str(1:11) == "ESP Charges" ) then
            k = 1
            do i = 1, int( naqm / 5 )
                read( 999, "(a)", end = 999 ) str
                do j = 1, 5
                    read( str((j-1)*16+1:j*16), "(f16.8)" ) qfit(k)
                    k = k + 1
                end do
            end do
            i = mod( naqm, 5 )
            if( i > 0 ) then
                read( 999, "(a)", end = 999 ) str
                do j = 1, i
```

```
                    read( str((j-1)*16+1:j*16), "(f16.8)" ) qfit(k)
                    k = k + 1
                end do
            end if
        end if

        if( str(1:18) == "Cartesian Gradient" .and. ( code == 1 .or. code == 2 ) ) then
            n3 = 3 * naqm
            grad(1:n3) = 0.0d0
            k = 1
            do i = 1, int( n3 / 5 )
                read( 999, "(a)", end = 999 ) str
                do j = 1, 5
                    read( str((j-1)*16+1:j*16), "(f16.8)" ) grad(k)
                    k = k + 1
                end do
            end do
            i = mod( n3, 5 )
            if( i > 0 ) then
                read( 999, "(a)", end = 999 ) str
                do j = 1, i
                    read( str((j-1)*16+1:j*16), "(f16.8)" ) grad(k)
                    k = k + 1
                end do
            end if
        end if
        read( 999, "(a)", end = 999 ) str
    end do
999     continue
    close( 999 )
    ener = ener - smm
    return

else if( code == 0 ) then

! Normally "code == 0" would specify an energy evaluation,
! but in this case it requests two anharmonic frequency calculations

    write( 999, "(a/a/a/a)" ) "%Chk=calc", "%nprocshared=1", "%mem=3GB", &
    "#B3LYP/6-31+g(d) charge scf=(direct,tight) nosymm int=ultrafine"
    write( 999, "(a/)" ) "freq=anharmonic punch=(coord,derivatives)"
    write( 999, "(a//2i4)" ) "- light -", 1, 1
    do i = 1, naqm
        j = ( i - 1 ) * 3
        write( 999, "(a8,3f20.10)" ) smb(int(atmn(i))), cord(j+1), cord(j+2), cord(j+3)
    end do
    write( 999, "(a)" ) ""
    smm = 0.0d0
    if( naqm == natm ) then
        write( 999, "(f28.10,2f20.10,f8.3)" ) 999.0d0, 999.0d0, 999.0d0, 0.0d0
    else
        do i = naqm + 1, natm
```

```
            j = ( i - 1 ) * 3
            write( 999, "(f28.10,2f20.10,f8.3)" ) cord(j+1), cord(j+2), cord(j+3), atmn(i)
            do k = i + 1, natm
                l = ( k - 1 ) * 3
                smm = smm + atmn(i) * atmn(k) / dsqrt( sum( ( cord(j+1:j+3) - cord(l+1:l+3) ) ** 2 ) ) * bohr
            end do
        end do
    end if
    write( 999, "(a)" ) ""
    write( 999, "(//)" )
    close( 999 )

! Execute Gaussian calculation for light isotopologue
    call system( ". $g16root/g16/bsd/g16.profile; g16 < calc1.gjf > calc1.out" )
    write(*,*) "...anharmonic frequencies for isotopologue 1"

! Create Gaussian job file "calc2.gjf" for heavy isotopologue by editing "calc1.gjf"
    call system( " sed 's/light/heavy/; s/H      /H(Iso=2)/; s/punch=(coord,derivatives)//' < calc1.gjf >
calc2.gjf")

! Execute Gaussian calculation for heavy isotopologue
    call system( ". $g16root/g16/bsd/g16.profile; g16 < calc2.gjf > calc2.out" )
    write(*,*) "...anharmonic frequencies for isotopologue 2"

end if
end subroutine chrg_server
```

## Shell script "Qanh" to extract partition functions and zero-point energies from Gaussian 16 output files for anharmonic frequency calculations and to evaluate isotopic partition-function ratios

```
#!/bin/bash

# Shell script (Qanh) to extract partition functions and zero-point energies
# from Gaussian output files for anharmonic frequency calculations.

# Loop over required number of structures...
# EDIT the arguments after 'seq' as necessary:
#  first  - number of the initial structure... (which may be 0);
#  second - in increments of...;
#  third  - number of final structure...

for i in `seq 0 1 1000`; do
    n=`printf "%01d" $i`
    if [ -d "$i" ]; then
        cd $i
        echo "$n" > NUM
        if [ -f "calc1.out" ]; then
            grep -m 1 -A 6 "Total Bot" calc1.out | grep "Translational" \
            | sed 's/D/E/' | awk '{$2 = sprintf("%f",$2); print $2 > "LQ"}'
            grep -m 1 -A 6 "Total Bot" calc1.out | grep "Rotational" \
            | sed 's/D/E/' | awk '{$2 = sprintf("%f",$2); print $2 >> "LQ"}'
            sed '1{N;s/\n/  /;}' < LQ | awk '{printf("%5.3f\n", $1*$2) > "MMI"}'
            fi
        if [ -f "calc2.out" ]; then
            grep -m 1 -A 6 "Total Bot" calc2.out | grep "Translational" \
            | sed 's/D/E/' | awk '{$2 = sprintf("%f",$2); print $2 > "HQ"}'
            grep -m 1 -A 6 "Total Bot" calc2.out | grep "Rotational" \
            | sed 's/D/E/' | awk '{$2 = sprintf("%f",$2); print $2 >> "HQ"}'
            sed '1{N;s/\n/  /;}' < HQ | awk '{printf("%5.3f\n", $1*$2) >> "MMI"}'
            awk 'BEGIN {a = 1.0}
            {b = $1/a
            a = $1}
            END   {printf("%7.6f\n", b) > "FMMI"}' MMI
        fi
        if [ -f "calc1.out" ]; then
            grep "ZPE(harm)"  calc1.out | sed 's/D/E/g' \
            | awk '{$3 = sprintf("%f",$3); print $3 >  "QZharm"; \
            $6 = sprintf("%f",$6); print $6 >  "QZanh"}'
            grep -m 1 "QZvib" calc1.out | sed 's/D/E/g' \
            | awk '{$2 = sprintf("%f",$2); print $2 >  "QVharm"; \
            $3 = sprintf("%f",$3); print $3 >  "QVanh"}'
        fi
        if [ -f "calc2.out" ]; then
            grep "ZPE(harm)"  calc2.out | sed 's/D/E/g' \
            | awk '{$3 = sprintf("%f",$3); print $3 >> "QZharm"; \
            $6 = sprintf("%f",$6); print $6 >> "QZanh"}'
            grep -m 1 "QZvib" calc2.out | sed 's/D/E/g' \
```

```
            | awk '{$2 = sprintf("%f",$2); print $2 >> "QVharm"; \
            $3 = sprintf("%f",$3); print $3 >> "QVanh"}'
        fi
        sed '1{N;s/\n/  /;}' < QZharm > ZQharm                              ;       rm -f QZharm
        sed '1{N;s/\n/  /;}' < QZanh   > ZQanh                              ;       rm -f QZanh
        sed '1{N;s/\n/  /;}' < QVharm > VQharm                              ;       rm -f QVharm
        sed '1{N;s/\n/  /;}' < QVanh   > VQanh                              ;       rm -f QVanh

        awk '{printf("%f\n", $2/$1) > "FVharm"}' VQharm                     ;       rm -f VQharm
        awk '{printf("%f\n", $2/$1) > "FVanh"}'  VQanh                      ;       rm -f VQanh
        awk '{printf("%f\n", exp(($1-$2)/2.4789568)) > "FZharm"}' ZQharm    ;       rm -f ZQharm
        awk '{printf("%f\n", exp(($1-$2)/2.4789568)) > "FZanh"}'  ZQanh     ;       rm -f ZQanh
        paste NUM FMMI FVharm FZharm FVanh FZanh  >> ../Qanh.out            ;       rm -f LQ HQ MMI
        cd ..
    fi
done
```

## Modified subroutine BMAT (from program CAMVIB) to determine the transformation between Cartesians and internal- and external-coordinates for methyl cation.

### *Notes*

This version is dimensioned specifically for a 4-atom fragment. The sections treating stretching, angle-bending and out-of-plane wagging are essentially as found in the version of program CAMVIB available on GITHUB (I. H. Williams and P. B. Wilson, *SoftwareX*, 2017, **6**, 1-6). The 3 in-plane bond angles of planar $CH_3^+$ are each described by a valence coordinate HCH, but these are combined into local symmetry coordinates for in-plane scissoring and in-plane rocking in another subroutine within CAMVIB; there are 7 internal valence coordinates and 6 internal symmetry coordinates. The section treating the six external coordinates (3 translations + 3 rotations) has not been described elsewhere by ourselves. The method proposed here is not unique. The first-listed CH bond defines the local *x*-axis which together with the second-listed CH determines the local *xy*-plane; the local *z*-axis is normal to this plane, and the local *y*-axis is mutually perpendicular.

```
subroutine BMAT
!     calculates transformation matrix B in the matrix equation R = BX,
!     where R & X are column vectors of internal and cartesian coordinates respectively.
      implicit none
      double precision e1(3),e2(3),e3(3),en(3),er1(3),er2(3),ex(3),ey(3),ez(3)
      double precision c,c1,c2,cosr1,cosr2,s,sp,s1,s2,sinr1,sinr2,sxy,syz,szx,sfac
      double precision bp,bq,br,br1,br2,rp,r1,r2,rr1,rr2,rp,rq,qp,qr,pq
      integer list(4),ntyp(8),I,ic,ii,ip,iq,ir,it,ityp,j,ni,inco,lab1,lab2
      character*4 labs,slab
      character*2 lmnt
      character*1 coord(4),star,type,lab1
      common /bloc2/ u(12,13),b(13,12),ub(12,12),fi(12,12),
      *red(13,12),ired(12),lab2(13),labs(13),lab1(13)
      common /gdata/ x(3,5),wt(5),sf(13),inco(4,13),lmnt(4)
      data coord/'s','b','w','e'/,star/'*'/
      b       = 0.0D0     !         initialize array B
      ntyp    = 0 !   initialize array ntyp
!     NOTE: subroutine DC computes the unit vector between two atoms;
!           function DOT computes the scalar product between two unit-vectors;
!           subroutine CROSS computes the vector product between two unit-vectors.
!    Specify a "type" of coordinate involving the atoms in "list"
!       S      stretch
!       B      bend
!       W      wag (out-of-plane bend)
!       E      external translations + rotations
      ii=0
1     read(5,101) type,(list(i),i=1,4),sfac,slab
      if(type.eq.star) go to 99
      ii=ii+1
      if(sfac.eq.0.0D0) sfac=1.0D0
      sf(ii)=sfac
      do i=1,4
        inco(i,ii)=list(i)
      end do
      do it=1,4
```

```
        if(type.eq.coord(it)) ityp=it
      end do
      ntyp(ityp)=ntyp(ityp) + 1
      lab1(ii)= coord(ityp)
      lab2(ii)=ntyp(ityp)
      labs(ii)=slab
!     branch according to the type of coordinate to compute a row of the B matrix
    go to (10,20,30,40), ityp
!    stretching coordinate for bond p-q specified by: list(1) = p , list(2) = q
10    np=list(1)
      nq=list(2)
      write(6,210) ii,lab1(ii),lab2(ii),lmnt(np),np,lmnt(nq),nq,sf(ii)
      ip=(np-1)*3
      iq=(nq-1)*3
      call dc(np,nq,e1,r1)
      do j=1,3
        b(ii,ip+j) = b(ii,ip+j - e1(j)
        b(ii,iq+j) = b(ii,iq+j) + e1(j)
      end do
      go to 1
!    bending coordinate for angle p-q-r specified by: list(1) = p , list(2) = q , list(3) = r
20    np=list(1)
      nq=list(2)
      nr=list(3)
      write(6,220) ii,lab1(ii),lab2(ii),lmnt(np),np,lmnt(nq),nq,lmnt(nr),nr,sf(ii)
      call dc(nq,np,e1,qp)
      ip=(np-1)*3
      iq=(nq-1)*3
      ir=(nr-1)*3
      call dc(nq,nr,e2,qr)
      c=dot(e1,e2)
      s = dsqrt( 1.0D0 - c*c )
      do j=1,3
        bp = ( c*e1(j) - e2(j) ) / (qp*s)
        br = ( c*e2(j) - e1(j) ) / (qr*s)
        b(ii,ip+j)=b(ii,ip+j)+bp
        b(ii,iq+j)=b(ii,iq+j) -(bp+br)
        b(ii,ir+j)=b(ii,ir+j)+br
      end do
      go to 1
!     out-of-plane bending coordinate for four coplanar atoms, apical atom q bonded to end atom p and
!     anchor atoms r1 and r2, specified by: list(1)=p ,list(2)=r1 ,list(3)=r2 ,list(4)=q
30    np=list(1)
      nr1=list(2)
      nr2=list(3)
      nq=list(4)
      write(6,230) ii,lab1(ii),lab2(ii),lmnt(np),np,lmnt(nq),nq,lmnt(nr1),nr1,lmnt(nq),nq,lmnt(nr2),nr2,sf(ii)
      ip=(np-1)*3
      ir1=(nr1-1)*3
```

```
      ir2=(nr2-1)*3
      iq=(nq-1)*3
      call dc(nq,np,e3,pq)
      call dc(nq,nr1,e1,r1)
      call dc(nq,nr2,e2,r2)
      call cross(e1,e2,en,sp)
      c1=dot(e3,e2)
      c2=dot(e3,e1)
      s1=dsqrt(1.0D0 - c1*c1)
      s2=dsqrt(1.0D0 - c2*c2)
      do j=1,3
        bp = en(j) / pq
        br1= en(j)*s1 / (r1*sp)
        br2= en(j)*s2 / (r2*sp)
        b(ii,ip+j)=b(ii,ip+j)+bp
        b(ii,ir1+j)=b(ii,ir1+j)+br1
        b(ii,ir2+j)=b(ii,ir2+j)+br2
        b(ii,iq+j)=b(ii,iq+j) -(bp+br1+br2)
      end do
      go to 1
40    np=list(1)                  ! translations & rotations
      nr1=list(2)
      nr2=list(3)
      nq=list(4)
      ip=(np-1)*3
      ir1=(nr1-1)*3
      ir2=(nr2-1)*3
      iq=(nq-1)*3
      call dc(nq,np,ex,rp)        ! determine q-p bond vector & define this as the local x-axis
      call dc(nq,nr1,er1,rr1)     ! determine q-r1 …
      call dc(nq,nr2,er2,rr2)     ! … & q-r2 bond vectors
      call cross(ex,er1,ez,sinr1) ! define the local z-axis as normal to r1-q-p plane
      call cross(ez,ex,ey,szx)    ! define the local y-axis as normal to local z- and x- axes
      cosr1= dot(ex,er1)          ! determine cosine of angle for each bond vector …
      cosr2= dot(ex,er2)          ! … with local x-axis
      call cross(ex,er2,en,sinr2) ! determine sine of (reflex) angle for bond vector q-r2 with local x-axis
      if(slab .eq. 'trax') then
        write(6,241) ii,lab1(ii),lab2(ii)
        do j=1,3
          b(ii,ip+j) =b(ii,ip+j) + ex(j)
          b(ii,ir1+j)=b(ii,ir1+j)+ ex(j)
          b(ii,ir2+j)=b(ii,ir2+j)+ ex(j)
           b(ii,iq+j) =b(ii,iq+j) + ex(j)
        end do
      elseif(slab .eq. 'tray') then
        write(6,242) ii,lab1(ii),lab2(ii)
        do j=1,3
          b(ii,ip+j) =b(ii,ip+j) + ey(j)
          b(ii,ir1+j)=b(ii,ir1+j)+ ey(j)
```

```
          b(ii,ir2+j)=b(ii,ir2+j)+ ey(j)
           b(ii,iq+j) =b(ii,iq+j) + ey(j)
        end do
      elseif(slab .eq. 'traz') then
        write(6,243) ii,lab1(ii),lab2(ii)
        do j=1,3
          b(ii,ip+j) =b(ii,ip+j) + ez(j)
          b(ii,ir1+j)=b(ii,ir1+j)+ ez(j)
          b(ii,ir2+j)=b(ii,ir2+j)+ ez(j)
          b(ii,iq+j) =b(ii,iq+j) + ez(j)
        end do
      elseif(slab .eq. 'rotx') then
        write(6,244) ii,lab1(ii),lab2(ii)
        do j=1,3
          b(ii,ir1+j) = b(ii,ir1+j) - ez(j)
          b(ii,ir2+j) = b(ii,ir2+j) + ez(j)
        end do
      elseif(slab .eq. 'roty') then
        write(6,245) ii,lab1(ii),lab2(ii)
        do 450  j=1,3
          b(ii,ip+j)  = b(ii,ip+j)  - ez(j)
          b(ii,ir1+j) = b(ii,ir1+j) + ez(j)*cosr1
          b(ii,ir2+j) = b(ii,ir2+j) + ez(j)*cosr2
        end do
      elseif(slab .eq. 'rotz') then
        write(6,246) ii,lab1(ii),lab2(ii)
        do j=1,3
          bp  = ey(j)
          br1 = - ex(j)*sinr1 + ey(j)*cosr1
          br2 = + ex(j)*sinr2 + ey(j)*cosr2
          b(ii,ip+j)  = b(ii,ip+j)  + bp
          b(ii,ir1+j) = b(ii,ir1+j) + br1
          b(ii,ir2+j) = b(ii,ir2+j) + br2
        end do
      endif
      go to 1
99    ni=ii
      return
101   format(a1,4i3,f10.3,a4)
210   format(1x,i4,2x,a1,i2,2x,'stretch',2x,a2,i2,' - ',a2,i2,39x,f6.3)
220   format(1x,i4,2x,a1,i2,2x,'bend',5x,a2,i2,' - ',a2,i2,' - ',a2,i2,32x,f6.3)
230   format(1x,i4,2x,a1,i2,2x,'wag',6x,a2,i2,' - ',a2,i2,2x,'out of plane',2x,a2,i2,' - ',a2,i2,' - ',a2,i2,5x,f6.3)
241   format(1x,i4,2x,a1,i2,'  translation about x-axis')
242   format(1x,i4,2x,a1,i2,'  translation about y-axis')
243   format(1x,i4,2x,a1,i2,'  translation about z-axis')
244   format(1x,i4,2x,a1,i2,'  rotation about x-axis')
245   format(1x,i4,2x,a1,i2,'  rotation about y-axis')
246   format(1x,i4,2x,a1,i2,'  rotation about z-axis')
      end
```

## QM anharmonic frequency calculations for methyl cation embedded with the point-charge distribution due to the frozen MM aqueous environment.

**Table S1.** Partial list of B3LYP/6-31+G(d) anharmonic and harmonic fundamental frequencies (as wavenumbers/cm$^{-1}$) for relaxed methyl cation within the point-charge representation of its frozen MM solvent environment.

| structure | quasi-degenerate CH stretches | | | | symmetric CH stretch | |
|---|---|---|---|---|---|---|
| | higher | | lower | | | |
| | anh | harm | anh | harm | anh | harm |
| 1 | 3167 | 3309 | 3146 | 3290 | 2989 | 3101 |
| 2 | 3141 | 3286 | 3136 | 3281 | 2975 | 3087 |
| 3 | 3153 | 3296 | 3137 | 3282 | 2980 | 3092 |
| 4 | 3147 | 3292 | 3131 | 3277 | 2975 | 3087 |
| 5 | 3174 | 3315 | 3148 | 3292 | 2992 | 3104 |
| 6 | 3163 | 3306 | 3158 | 3300 | 2994 | 3106 |
| 7 | 3168 | 3312 | 3151 | 3297 | 2993 | 3106 |
| 8 | 3177 | 3320 | 3165 | 3308 | 3004 | 3117 |
| 9 | 3164 | 3308 | 3154 | 3298 | 2992 | 3105 |
| 10 | 3178 | 3321 | 3158 | 3303 | 3001 | 3114 |
| 11 | 3177 | 3318 | 3154 | 3299 | 2997 | 3109 |
| 12 | 3174 | 3317 | 3158 | 3301 | 2998 | 3111 |
| 13 | 3172 | 3314 | 3152 | 3297 | 2994 | 3107 |
| 14 | 3169 | 3312 | 3156 | 3300 | 2997 | 3108 |
| 15 | 3146 | 3290 | 3134 | 3280 | 2977 | 3087 |
| 16 | 3155 | 3297 | 3131 | 3277 | 2978 | 3089 |
| 17 | 3151 | 3295 | 3139 | 3285 | 2981 | 3093 |
| 19 | 3171 | 3314 | 3158 | 3302 | 2997 | 3110 |
| 20 | 3183 | 3325 | 3144 | 3290 | 2994 | 3107 |
| *etc.* | | | | | | |
| count | 928 | 928 | 928 | 928 | 929 | 929 |
| mean | 3176 | 3318 | 3160 | 3304 | 3000 | 3112 |
| stdev | 15 | 14 | 15 | 14 | 13 | 13 |

*Notes*:

1. There is no entry for #18 as this structure did not converge in the BFGS relaxation of the solute within the frozen solvent configuration.
2. The means and standard deviations are over the full number (“count”) of relaxed structures, not only the first few structures.

**Table S2.** Partial output from program Qanh for B3LYP/6-31+G(d) $^{2}H_3$ Isotopic partition-function ratios (*f*) at 298.15 K (*cf*. "QM relaxation and anharmonic frequencies" in Fig. 1) for relaxed methyl cation within the point-charge representation of its frozen MM solvent environment.

| structure number | translation +rotation | harmonic | | anharmonic | |
|---|---|---|---|---|---|
| | $f_{\mathrm{MMI}}$ | $f_{\mathrm{vib}}$ | $f_{\mathrm{zpe}}$ | $f_{\mathrm{vib}}$ | $f_{\mathrm{zpe}}$ |
| **NUM** | **FMMI** | **FVharm** | **FZharm** | **FVanh** | **FZanh** |
| 0 | 3.718150 | 1.014754 | 6470.846122 | 1.015944 | 5191.657120 |
| 1 | 3.718149 | 1.014952 | 6731.780259 | 1.016142 | 5422.839929 |
| 2 | 3.718134 | 1.015052 | 6531.162634 | 1.016140 | 5250.629693 |
| 3 | 3.718148 | 1.014854 | 6685.773503 | 1.015943 | 5372.758985 |
| 4 | 3.718159 | 1.015052 | 6541.709708 | 1.016140 | 5252.748201 |
| 5 | 3.718120 | 1.015250 | 6677.687364 | 1.016338 | 5381.435370 |
| 6 | 3.718113 | 1.015250 | 6683.077036 | 1.016338 | 5390.125766 |
| 7 | 3.718133 | 1.015349 | 6707.384442 | 1.016438 | 5390.125766 |
| 8 | 3.718115 | 1.015250 | 6805.501388 | 1.016338 | 5480.015520 |
| 9 | 3.718093 | 1.015250 | 6683.077036 | 1.016338 | 5377.095427 |
| 10 | 3.718106 | 1.015250 | 6835.766882 | 1.016439 | 5502.166304 |
| 11 | 3.718136 | 1.015150 | 6794.529009 | 1.016340 | 5475.596076 |
| 12 | 3.718093 | 1.015447 | 6666.921057 | 1.016635 | 5361.933172 |
| 13 | 3.718121 | 1.015250 | 6734.496376 | 1.016439 | 5422.839929 |
| 14 | 3.718142 | 1.015052 | 6819.241784 | 1.016140 | 5497.728996 |
| 15 | 3.718131 | 1.014854 | 6648.121770 | 1.015944 | 5351.129173 |
| 16 | 3.718113 | 1.014952 | 6560.208086 | 1.016142 | 5273.980346 |
| 17 | 3.718143 | 1.014952 | 6629.375494 | 1.016142 | 5323.140548 |
| 19 | 3.718123 | 1.015449 | 6745.371810 | 1.016537 | 5427.216793 |
| 20 | 3.718108 | 1.015251 | 6816.491487 | 1.016240 | 5488.865113 |
| *etc.* | | | | | |

*Note*: there is no entry for #18 as this structure did not converge in the BFGS relaxation of the solute within the frozen solvent configuration.

$f_{\mathrm{internal}} = f_{\mathrm{vib}} \times f_{\mathrm{zpe}}$

$f_{\mathrm{external}} = f_{\mathrm{MMI}}$

$f_{\mathrm{total}} = f_{\mathrm{internal}} \times f_{\mathrm{external}}$

**Table S3.** Partial list of B3LYP/6-31+G(d) symmetry force constants (/aJ Å$^{-2}$) for relaxed methyl cation within the point-charge representation of its frozen MM solvent environment.

| structure | 3 × CH stretches | | | 2 × IP bends | | OP bend |
|---|---|---|---|---|---|---|
| 1 | 5.684 | 5.781 | 5.753 | 0.428 | 0.433 | 0.371 |
| 2 | 5.715 | 5.684 | 5.659 | 0.435 | 0.427 | 0.362 |
| 3 | 5.701 | 5.674 | 5.746 | 0.439 | 0.432 | 0.362 |
| 4 | 5.729 | 5.649 | 5.687 | 0.430 | 0.429 | 0.372 |
| 5 | 5.754 | 5.813 | 5.679 | 0.427 | 0.426 | 0.380 |
| 6 | 5.747 | 5.748 | 5.755 | 0.427 | 0.429 | 0.367 |
| 7 | 5.731 | 5.735 | 5.805 | 0.426 | 0.425 | 0.378 |
| 8 | 5.770 | 5.829 | 5.756 | 0.422 | 0.428 | 0.378 |
| 9 | 5.700 | 5.801 | 5.748 | 0.424 | 0.429 | 0.379 |
| 10 | 5.775 | 5.749 | 5.830 | 0.422 | 0.428 | 0.364 |
| 11 | 5.726 | 5.838 | 5.746 | 0.433 | 0.423 | 0.368 |
| 12 | 5.799 | 5.708 | 5.793 | 0.425 | 0.422 | 0.365 |
| 13 | 5.710 | 5.770 | 5.799 | 0.427 | 0.426 | 0.364 |
| 14 | 5.806 | 5.748 | 5.742 | 0.429 | 0.426 | 0.368 |
| 15 | 5.740 | 5.672 | 5.673 | 0.436 | 0.429 | 0.361 |
| 16 | 5.682 | 5.749 | 5.655 | 0.423 | 0.433 | 0.389 |
| 17 | 5.719 | 5.737 | 5.671 | 0.426 | 0.431 | 0.374 |
| 19 | 5.755 | 5.759 | 5.797 | 0.431 | 0.425 | 0.355 |
| 20 | 5.684 | 5.863 | 5.754 | 0.429 | 0.428 | 0.359 |
| *etc.* | | | | | | |
| mean | 5.770 | 5.781 | 5.778 | 0.427 | 0.427 | 0.369 |
| stdev | 0.063 | 0.064 | 0.064 | 0.004 | 0.004 | 0.009 |
| average | | 5.776 | | 0.4269 | | 0.3687 |
| stderr | | 0.006 | | 0.0004 | | 0.0008 |

*Notes*:

1. There is no entry for #18 as this structure did not converge in the BFGS relaxation of the solute within the frozen solvent configuration.
2. The means and standard deviations are taken over the first 122 relaxed structures.
3. The order of the three columns of CH-stretching and of the two columns of in-plane bending force constants is arbitrary.

**Fig. S1.** B3LYP/6-31+G(d)/TIP3P potential energy for QM methyl cation relaxed within the "frozen" environment of 1032 MM water molecules (black dots) and moving average (mean of the preceding 25 values, red dots) for structures extracted from a 1 ns MD trajectory (298 K).

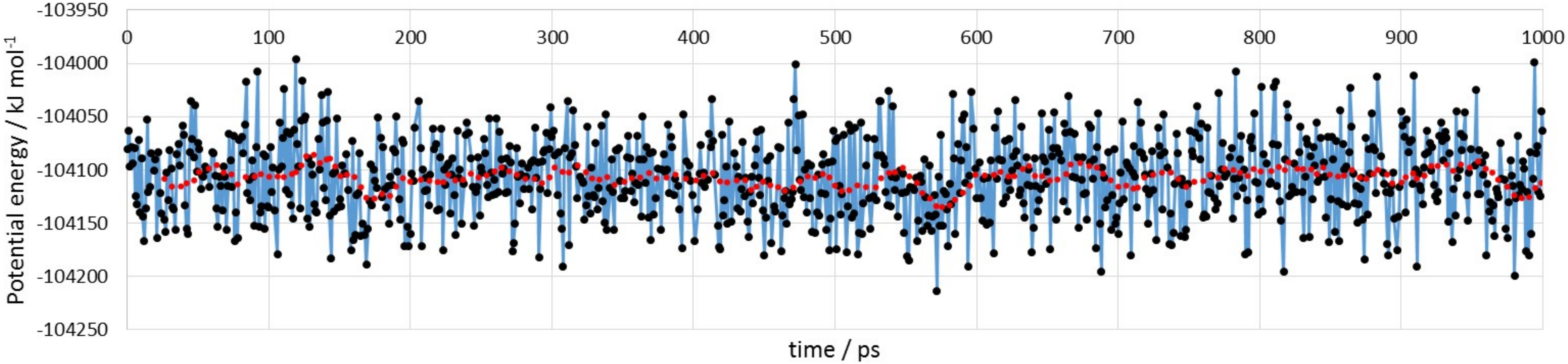
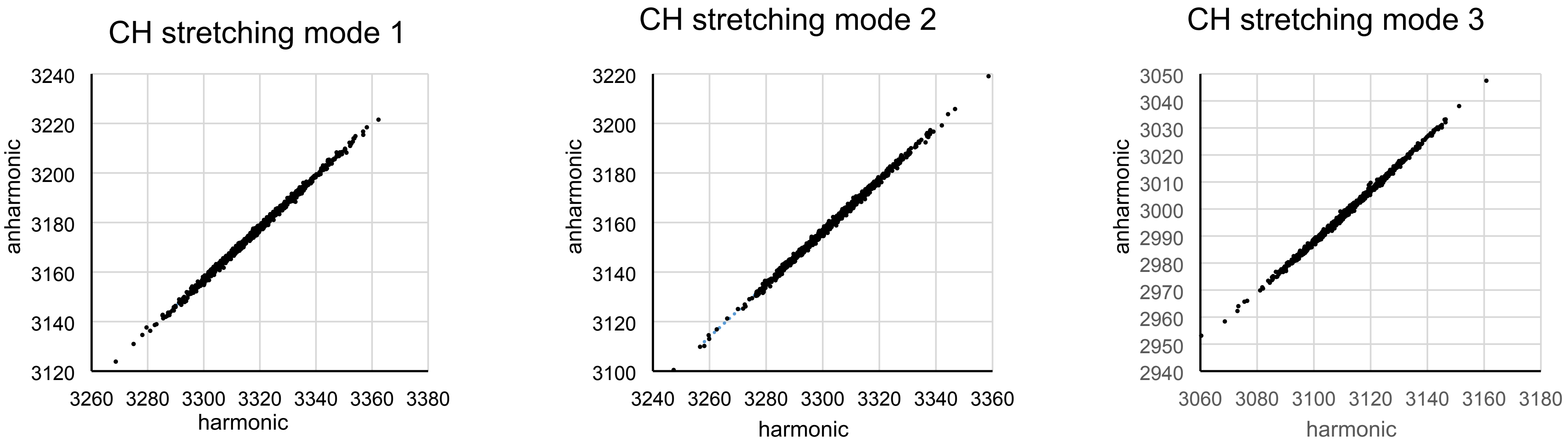
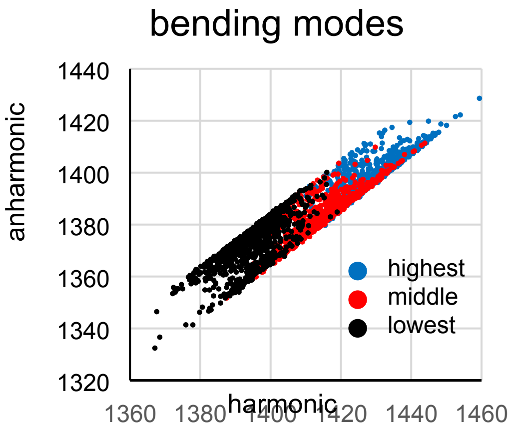


**Fig. S2.** Correlation of anharmonic *vs*. harmonic fundamental frequencies (as wavenumbers/cm$^{-1}$) for relaxed methyl cation (B3LYP/6-31+G(d)) within the "frozen" TIP3P aqueous environment.





*N.B.* The Gaussian output for anharmonic frequency calculations does not assign frequencies to specific vibrational modes, but simply presents them in descending order of magnitude. Although the three stretching frequencies are clearly distinguishable and occur in the same order, this is not so for the three bending modes (in-plane scissoring and rocking, and out-of-plane wagging), which unfortunately are not in the same order for all structures. The scatter plot for the bending modes displays overlapping bands that cannot easily be deconvoluted into individual correlations.

**Fig. S3.** Residual r.m.s. gradient (/kJ mol$^{-1}$ Å$^{-1}$) for relaxed methyl cation (B3LYP/6-31+G(d)) within the "frozen" TIP3P aqueous environment.

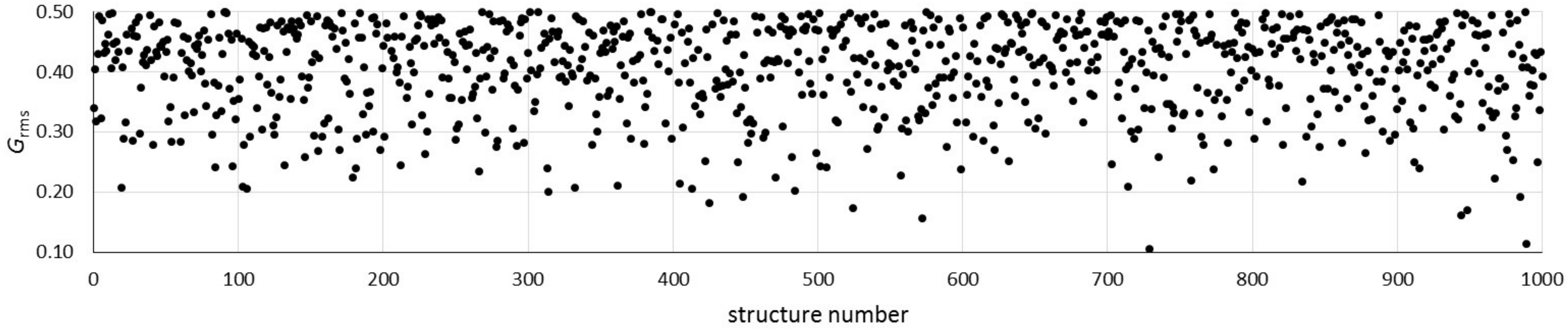
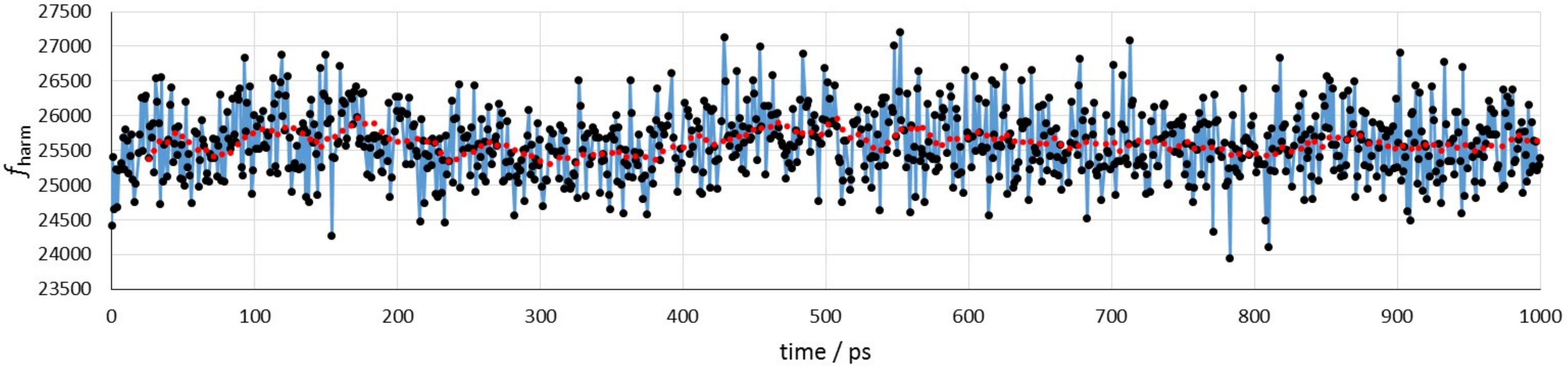


**Fig. S4.** Harmonic isotopic partition-function ratio ($^2H_3$, 298.15 K) for B3LYP/6-31+G(d) methyl cation in TIP3P water (black dots) and moving average (mean of the preceding 25 values, red dots) for structures extracted from a 1 ns MD trajectory.



$f_{\mathrm{harm}}$
27500
27000
26500
26000
25500
25000
24500
24000
23500
0
100
200
300
400
500
600
700
800
900
1000
time / ps

**Fig. S5.** Correlation of anharmonic *vs*. harmonic B3LYP/6-31+G(d) IPFR values ($^2H_3$, 298.15 K) for 6 internal degrees of freedom for 930 configurations of methyl cation in water.

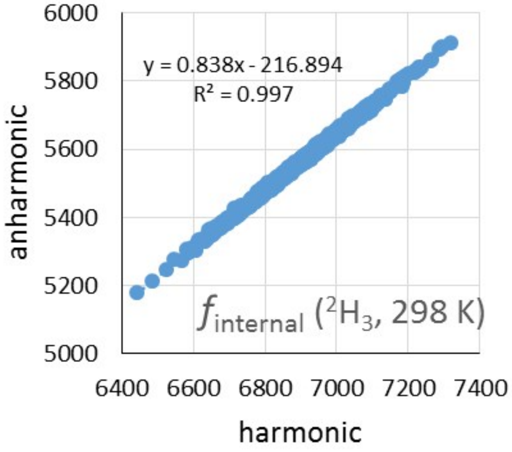


**Fig. S6.** (Lack of) correlation between harmonic isotopic partition-function ratio ($^2H_3$, 298.15 K) for methyl cation in water and the B3LYP/6-31+G(d)/TIP3P potential energy.

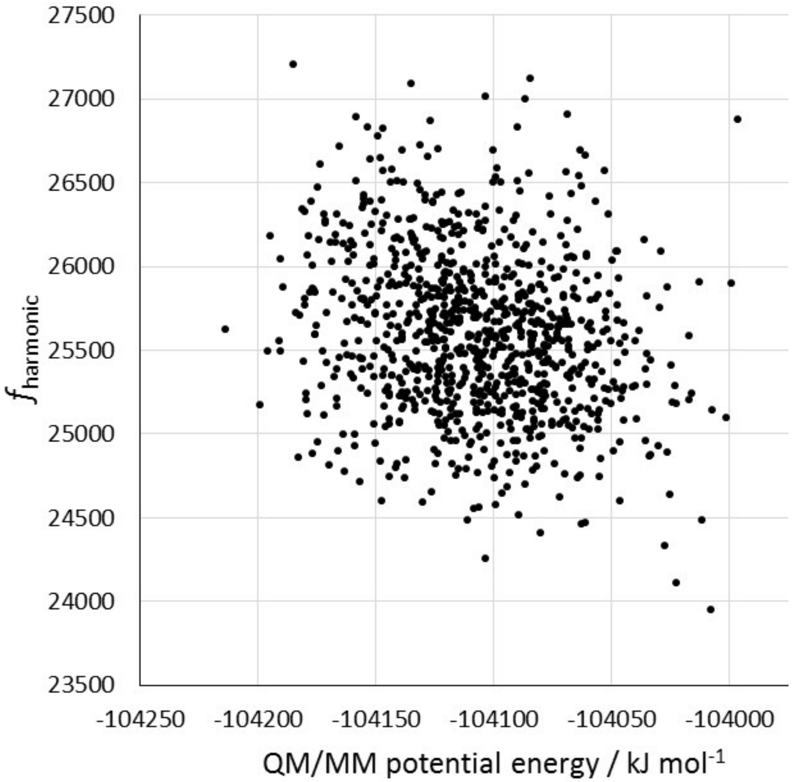


**Fig. S7.** Variation in average B3LYP/6-31+G(d) IPFR values ($^{2}H_{3}$, 298.15 K) for 100 ps intervals over the course of a 1 ns classical molecular dynamics simulation for flexible TIP3P water around a frozen methyl cation with ESP/ B3LYP/6-31+G(d) atomic charges.

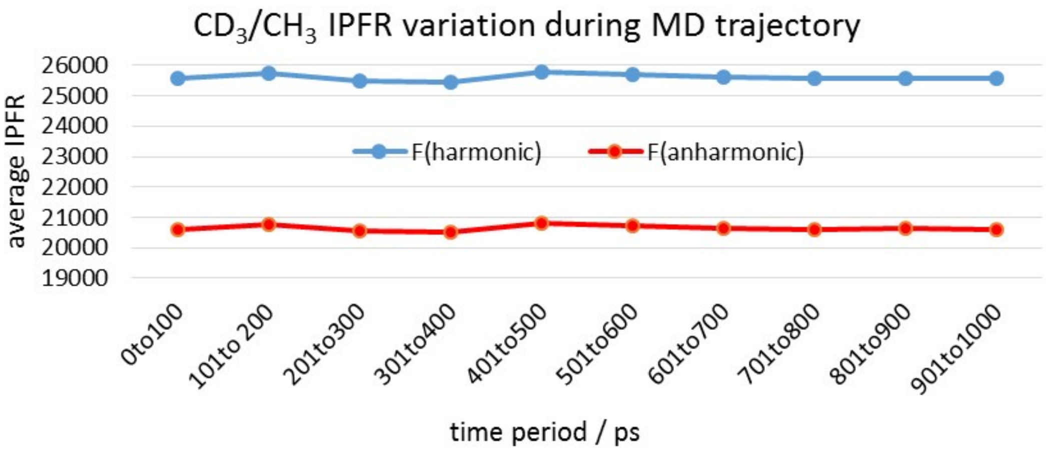


**Table S4.** Block-averaged harmonic B3LYP/6-31+G(d) IPFR values ($^2H_3$, 298.15 K) for methyl cation in water for structures obtained from a 1 ns MD trajectory at 1 ps intervals.

| | blocksize ($L_b$) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 24 | 32 | 40 | 48 | 64 |
| $N_b$ | 930 | 465 | 310 | 232 | 155 | 116 | 77 | 58 | 38 | 29 | 23 | 19 | 14 |
| $A_\beta$ | 25603 | 25603 | 25604 | 25603 | 25604 | 25605 | 25604 | 25604 | 25605 | 25604 | 25605 | 25605 | 25603 |
| stdev | 487 | 366 | 487 | 110 | 409 | 221 | 185 | 164 | 142 | 125 | 124 | 115 | 119 |
| BSE | 15.97 | 16.97 | 17.99 | 18.91 | 19.63 | 20.58 | 21.19 | 21.67 | 23.40 | 23.70 | 26.38 | 27.00 | 33.07 |

**Table S5.** Block-averaged anharmonic B3LYP/6-31+G(d) IPFR values ($^2H_3$, 298.15 K) for methyl cation in water for structures obtained from a 1 ns MD trajectory at 1 ps intervals.

| | blocksize ($L_b$) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 24 | 32 | 40 | 48 | 64 |
| $N_\mathrm{b}$ | 930 | 465 | 310 | 232 | 155 | 116 | 77 | 58 | 38 | 29 | 23 | 19 | 14 |
| $A_\beta$ | 20642 | 20642 | 20642 | 20642 | 20642 | 20643 | 20643 | 20642 | 20644 | 20642 | 20643 | 20644 | 20642 |
| stdev | 409 | 307 | 266 | 241 | 204 | 185 | 155 | 137 | 120 | 105 | 105 | 96 | 101 |
| BSE | 15.97 | 14.23 | 15.11 | 15.83 | 16.46 | 17.25 | 17.79 | 18.16 | 19.68 | 19.91 | 22.29 | 22.73 | 27.88 |

**Fig. S8.** Block standard error as a function of blocksize for harmonic IPFRs.

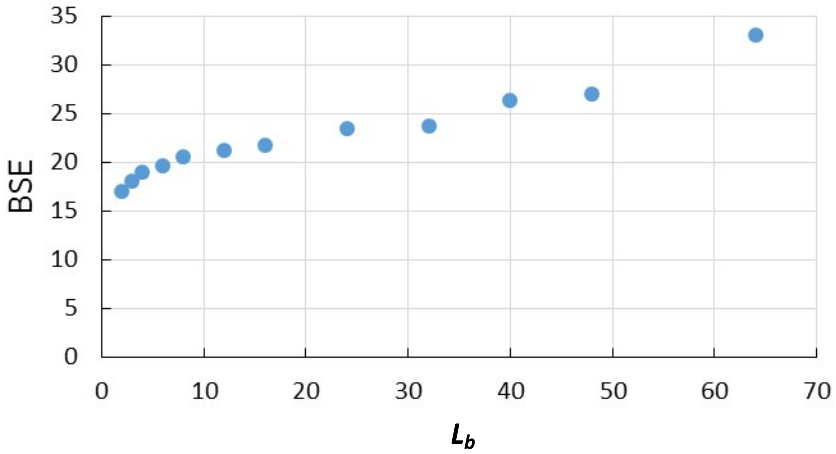


**Fig. S9.** Block standard error as a function of blocksize for anharmonic IPFRs.

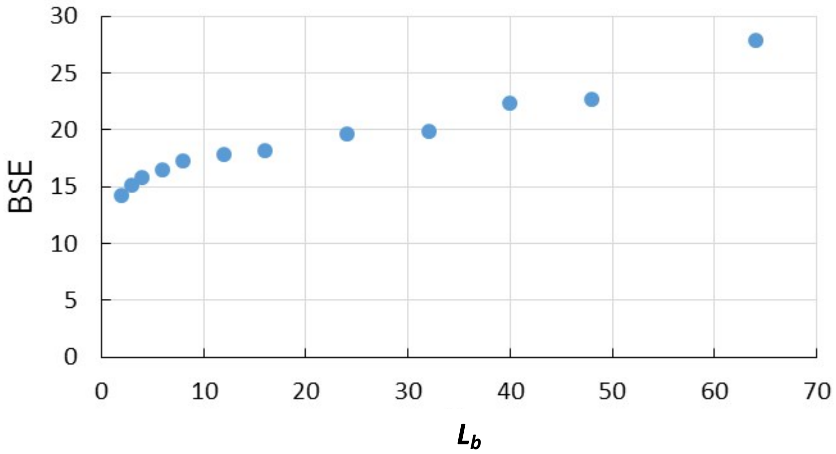
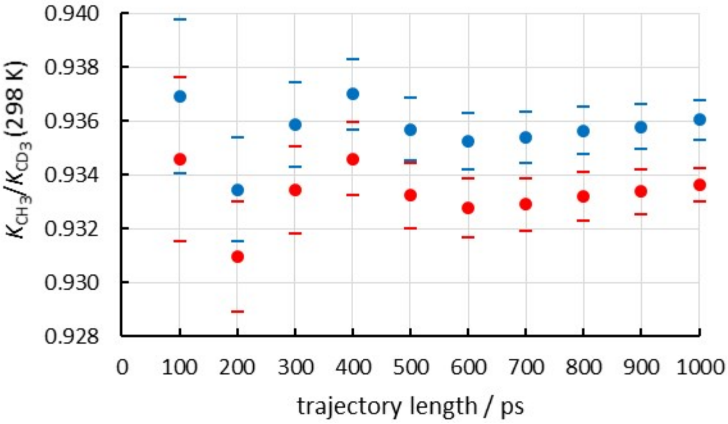


**Table S6.** B3LYP/6-31+G(d) equilibrium isotope effect ($^2H_3$, 298.15 K) for transfer of methyl cation from vacuum to water for snapshot structures obtained from a 1 ns MD trajectory at 8 ps intervals.

| | | harmonic | | anharmonic | |
|---|---|---|---|---|---|
| *t* / ps | snapshots | EIE | SE | EIE | SE |
| 100 | 12 | 0.9369 | 0.0029 | 0.9346 | 0.0030 |
| 200 | 24 | 0.9335 | 0.0019 | 0.9310 | 0.0020 |
| 300 | 36 | 0.9359 | 0.0016 | 0.9334 | 0.0016 |
| 400 | 47 | 0.9370 | 0.0013 | 0.9346 | 0.0014 |
| 500 | 58 | 0.9357 | 0.0012 | 0.9332 | 0.0012 |
| 600 | 70 | 0.9353 | 0.0011 | 0.9328 | 0.0011 |
| 700 | 82 | 0.9354 | 0.0009 | 0.9329 | 0.0010 |
| 800 | 93 | 0.9357 | 0.0009 | 0.9332 | 0.0009 |
| 900 | 104 | 0.9358 | 0.0008 | 0.9334 | 0.0009 |
| 1000 | 116 | 0.9360 | 0.0008 | 0.9336 | 0.0006 |

**Fig. S10.** Harmonic (blue) and anharmonic (red) B3LYP/6-31+G(d) EIEs ($^2H_3$, 298.15 K) for transfer of methyl cation from vacuum to water. Bounds of the standard error are shown by the short lines above and below each solid circle. Individual EIEs evaluated for snapshot solvent configurations at 1 ps intervals were averaged over 8 ps blocks. The points plotted in the graph represents cumulative averages of these block averages over intervals up to the total length of the 1 ns MD trajectory.



## QM/MM harmonic frequency calculations for methyl cation embedded with the full TIP3P potential due to the frozen MM aqueous environment.

**Table S7.** Partial list of B3LYP/6-31+G(d)/TIP3P harmonic fundamental frequencies (as wavenumbers/cm$^{-1}$) for relaxed methyl cation within its frozen MM solvent environment.

| | **quasi-degenerate CH stretches** | | | | | | **symmetric CH stretch** | | |
|---|---|---|---|---|---|---|---|---|---|
| | higher | | | lower | | | | | |
| | QM 6 | QM/MM 6 | QM/MM 12 | QM 6 | QM/MM 6 | QM/MM 12 | QM 6 | QM/MM 6 | QM/MM 12 |
| 1 | 3309 | 3317 | 3318 | 3290 | 3305 | 3310 | 3101 | 3119 | 3119 |
| 2 | 3286 | 3287 | 3287 | 3281 | 3280 | 3278 | 3087 | 3087 | 3087 |
| 4 | 3292 | 3300 | 3305 | 3277 | 3291 | 3292 | 3087 | 3104 | 3104 |
| 5 | 3315 | 3330 | 3328 | 3292 | 3305 | 3301 | 3104 | 3116 | 3116 |
| 6 | 3306 | 3315 | 3311 | 3300 | 3307 | 3306 | 3106 | 3112 | 3112 |
| 7 | 3312 | 3327 | 3330 | 3297 | 3311 | 3311 | 3106 | 3125 | 3124 |
| 8 | 3320 | 3337 | 3349 | 3308 | 3317 | 3319 | 3117 | 3137 | 3137 |
| 9 | 3308 | 3337 | 3339 | 3298 | 3304 | 3308 | 3105 | 3125 | 3124 |
| 10 | 3321 | 3341 | 3342 | 3303 | 3318 | 3329 | 3114 | 3143 | 3143 |
| 11 | 3318 | 3329 | 3334 | 3299 | 3312 | 3315 | 3109 | 3128 | 3128 |
| 12 | 3317 | 3331 | 3334 | 3301 | 3310 | 3308 | 3111 | 3124 | 3123 |
| 13 | 3314 | 3333 | 3330 | 3297 | 3308 | 3310 | 3107 | 3124 | 3124 |
| 14 | 3312 | 3332 | 3339 | 3300 | 3317 | 3329 | 3108 | 3142 | 3142 |
| 15 | 3290 | 3305 | 3313 | 3280 | 3298 | 3303 | 3087 | 3115 | 3115 |
| 16 | 3297 | 3304 | 3305 | 3277 | 3294 | 3295 | 3089 | 3105 | 3105 |
| 17 | 3295 | 3307 | 3319 | 3285 | 3300 | 3303 | 3093 | 3118 | 3117 |
| 19 | 3314 | 3326 | 3325 | 3302 | 3308 | 3306 | 3110 | 3118 | 3118 |
| 20 | 3325 | 3342 | 3346 | 3290 | 3310 | 3318 | 3107 | 3135 | 3135 |
| *etc.* | | | | | | | | | |

| | internal bending modes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | highest | | | middle | | | lowest | | |
| | QM 6 | QM/MM 6 | QM/MM 12 | QM 6 | QM/MM 6 | QM/MM 12 | QM 6 | QM/MM 6 | QM/MM 12 |
| 1 | 1432 | 1451 | 1442 | 1426 | 1440 | 1440 | 1400 | 1439 | 1435 |
| 2 | 1435 | 1465 | 1452 | 1415 | 1440 | 1434 | 1406 | 1435 | 1422 |
| 4 | 1428 | 1446 | 1445 | 1421 | 1437 | 1434 | 1409 | 1435 | 1430 |
| 5 | 1425 | 1463 | 1462 | 1419 | 1454 | 1454 | 1396 | 1448 | 1443 |
| 6 | 1422 | 1471 | 1471 | 1419 | 1448 | 1441 | 1399 | 1441 | 1437 |
| 7 | 1422 | 1493 | 1472 | 1412 | 1465 | 1459 | 1406 | 1444 | 1445 |
| 8 | 1427 | 1461 | 1479 | 1410 | 1449 | 1463 | 1400 | 1443 | 1443 |
| 9 | 1427 | 1458 | 1466 | 1409 | 1441 | 1443 | 1404 | 1437 | 1436 |
| 10 | 1431 | 1491 | 1523 | 1409 | 1451 | 1456 | 1404 | 1449 | 1439 |
| 11 | 1435 | 1461 | 1469 | 1408 | 1446 | 1439 | 1402 | 1438 | 1430 |
| 12 | 1417 | 1462 | 1463 | 1411 | 1437 | 1442 | 1397 | 1433 | 1432 |
| 13 | 1420 | 1485 | 1523 | 1418 | 1440 | 1435 | 1405 | 1430 | 1431 |
| 14 | 1431 | 1476 | 1481 | 1423 | 1453 | 1443 | 1401 | 1434 | 1430 |
| 15 | 1442 | 1450 | 1453 | 1426 | 1443 | 1443 | 1408 | 1438 | 1433 |
| 16 | 1437 | 1464 | 1457 | 1425 | 1449 | 1453 | 1398 | 1439 | 1438 |
| 17 | 1431 | 1466 | 1454 | 1420 | 1447 | 1443 | 1411 | 1437 | 1435 |
| 19 | 1422 | 1469 | 1458 | 1411 | 1451 | 1445 | 1401 | 1440 | 1420 |
| 20 | 1444 | 1513 | 1492 | 1415 | 1467 | 1447 | 1391 | 1437 | 1427*etc.* |

**Table S8.** Partial list of harmonic B3LYP/6-31+G(d) $^2H_3$ isotopic partition-function ratios ($f$) at 298.15 K (*cf*. "QM/MM relaxation and harmonic frequencies" in Fig. 1).

| structure | $f_{vib}$ | $f_{zpe}$ | $f_{total}$ | $f_{external}$ | $f_{internal}$ |
|---|---|---|---|---|---|
| 0 | 2.210 | 13850 | 30616 | 4.111 | 7447 |
| 1 | 2.290 | 13287 | 30429 | 4.112 | 7400 |
| 2 | 2.500 | 10815 | 27034 | 3.966 | 6817 |
| 4 | 2.500 | 11231 | 28079 | 3.940 | 7126 |
| 5 | 2.097 | 15440 | 32382 | 4.249 | 7620 |
| 6 | 2.150 | 14825 | 31867 | 4.267 | 7468 |
| 7 | 2.022 | 16731 | 33832 | 4.336 | 7803 |
| 8 | 2.024 | 17906 | 36235 | 4.391 | 8252 |
| 9 | 2.283 | 13805 | 31514 | 4.075 | 7733 |
| 10 | 2.089 | 17614 | 36801 | 4.339 | 8482 |
| 11 | 2.275 | 13765 | 31317 | 4.067 | 7699 |
| 12 | 2.328 | 13203 | 30733 | 4.028 | 7629 |
| 13 | 2.154 | 15544 | 33485 | 4.194 | 7984 |
| 14 | 2.284 | 14585 | 33309 | 4.157 | 8012 |
| 15 | 2.338 | 12854 | 30050 | 4.045 | 7429 |
| 16 | 2.216 | 13854 | 30706 | 4.165 | 7372 |
| 17 | 2.348 | 12836 | 30144 | 4.042 | 7458 |
| 19 | 2.337 | 12750 | 29791 | 4.047 | 7361 |
| 20 | 2.048 | 17280 | 35388 | 4.462 | 7931 |
| *etc.* | | | | | |
| mean(928) | 2.255 | 14284 | 31922 | 4.158 | 7668 |
| stdev | 0.151 | 2034 | 2447 | 0.149 | 349 |
| stderr | 0.005 | 67 | 80 | 0.005 | 11 |

*Note*: there is no entry for #18 as this structure did not converge in the BFGS relaxation of the solute within the frozen solvent configuration.

$f_{total}$ = $f_{vib} \times f_{zpe}$ (both factors are functions of frequencies for 12 modes)
= $f_{int} \times f_{ext}$ (each factor is a function of frequencies for 6 modes)

## Fortran driver program for use with fDynamo library to perform rigid QM/MM potential -energy scans along normal modes

This program performs QM/MM energy scans backwards and forwards along each of the three normal modes obtained for a single H atom following the cutujiso1 procedure. As input, this program takes output from univib.f, which is generated 'in situ' by execution of the go_uniscan script. Output is an fDynamo log file, from which values of energy can be extracted by means of the go_scan_results script and then transferred into an Excel spreadsheet for graph-plotting.

```
program energy_scan
use dynamo
implicit none
integer                               :: i,j,k,ip,mode,point,nh,m
character (len = 10 )                 :: si                  ! To select the configurations of the trajectory file
character (len = 4  )                 :: junk
logical, dimension(:), allocatable    :: qmr
real                                  :: Hcrd(3),disp(3),f
real, parameter                       :: scale = 0.02
call dynamo_header
call mm_file_process    ( "borra", "opls"       )          ! read the force-field parameters and sequence
call mm_system_construct( "borra", "THFyl_Cyhex.seq" )
read (*,*) I                                                          ! read the number of the structure
call encode_integer( i, si, "(i4)" )
call coordinates_read( 'THFyl_Cyhex_' // trim( si ) // '.crd' )     ! read the coordinates file * EDIT AS NEEDED *
call energy_non_bonding_options( list_cutoff   = 15.5_dp, outer_cutoff  = 14.0_dp, &
          inner_cutoff  = 12.5_dp, minimum_image = .true. )                     ! Nonbonding interactions
call energy_initialize
allocate( qmr(1:natoms) )                                                          ! Allocating the array
qmr = atom_selection( subsystem = (/ "SOLUTE" /) )                              ! Defining the QM region
call mopac_setup( method = "AM1", charge = 1, selection = qmr )
write(*,*) "Number of quantum atoms", count (qmr)
nh = ATOM_NUMBER ( "H2", 1, "SOLUTE" )
write(*,*) "nh = ", nh
Hcrd(1:3) = ATMCRD (1:3, nh )                                  ! Store original coordinates for H atom
write(*,"('   coords:',3F12.6)") (Hcrd(j),j=1,3)
point = 0                                                     ! Calculate energy for original structure
write(*,*) "Energy for point", point
call energy
read(*,*) junk
do mode = 1,3                                                        ! Loop over normal modes (1 to 3)
      write(*,*) "Mode",mode
      read(*,*) m,f,(disp(k),k=1,3)
      write(*,"('  disp:',3F12.6)") (disp(k),k=1,3)
      do ip = 1,20                                                  ! Perform scan in forward direction
      write(*,*) "Forward point",ip
            do j=1,3                                                    ! Modify H-atom coordinates
            ATMCRD (j,nh) = ATMCRD (j,nh) + scale*disp(j)
            write(*,*) scale*disp(j)
            end do
      call energy
      end do                                                                          ! forward scan
      ATMCRD (1:3, nh ) = Hcrd(1:3)                                          ! Reset H-atom coordinates
      do ip = 1,20                                                ! Perform scan in backward direction
```

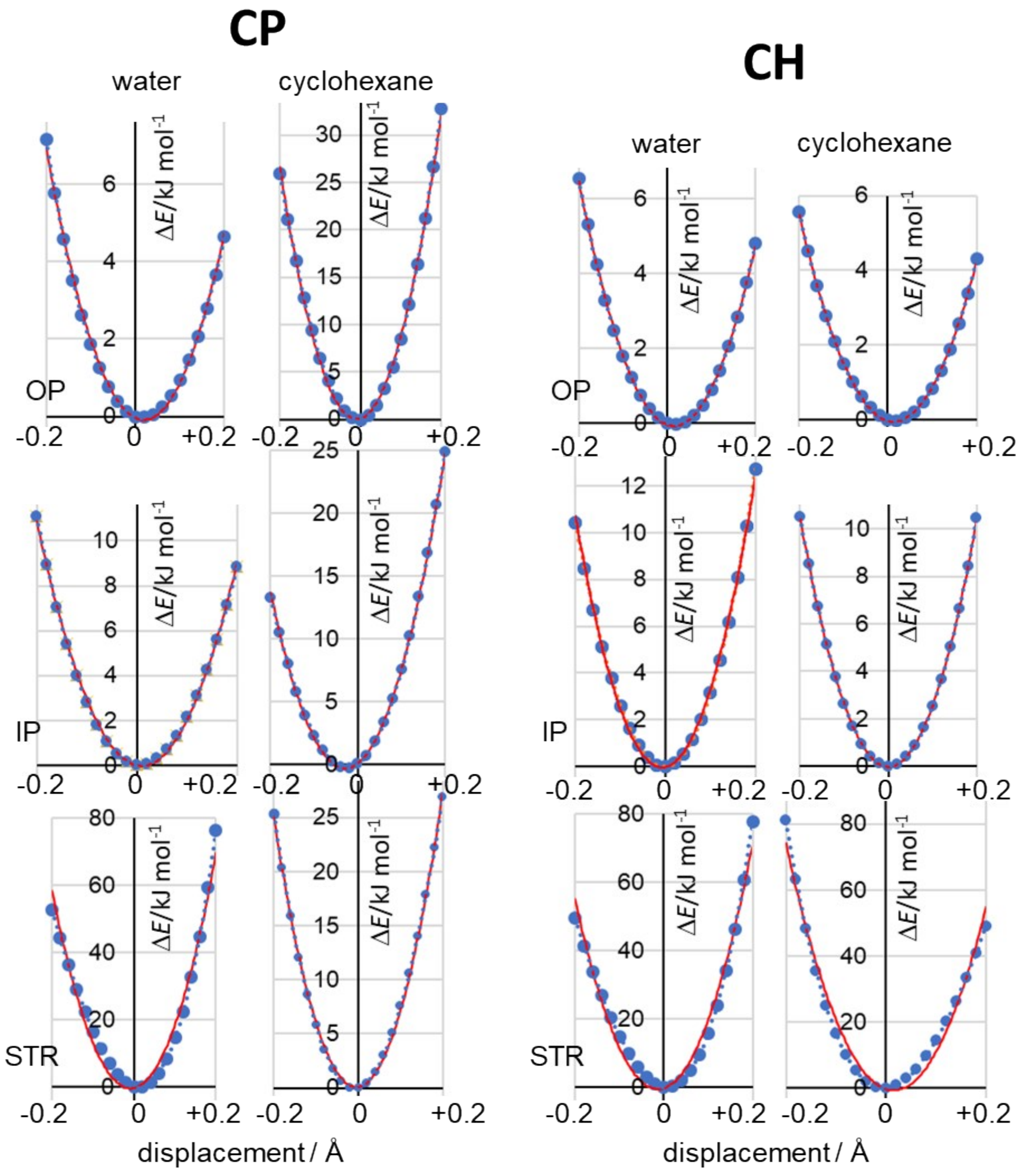
```
          write(*,*) "Backward point",ip
                    do j=1,3                                                      ! Modify H-atom coordinates
                     ATMCRD (j,nh) = ATMCRD (j,nh) - scale*disp(j)
                     end do
          call energy
          end do                                                                          ! backward scan
          ATMCRD (1:3, nh ) =  Hcrd(1:3)                          ! Restore original coordinates for H atom
end do                                                                                ! loop over normal modes
deallocate(qmr)
call dynamo_footer
end program energy_scan
```

### Anharmonicity in C$_\alpha$H stretching and bending modes

**Table S9.** Anharmonic (quartic) and harmonic (quadratic) fits to relative QM/MM energies (kJ mol$^{-1}$) for displacement (Å) along H$_\alpha$ normal modes

| mode | solvent | cation | coefficient of $x^n$ for quartic fit | | | | | | coefficient of $x^n$ for quadratic fit | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $n = 4$ | $n = 3$ | $n = 2$ | $n = 1$ | $n = 0$ | $R^2$ | $n = 2$ | $n = 1$ | $n = 0$ | $R^2$ |
| OP | water | CP | 217 | -56 | 138 | -4.1 | -0.0003 | 1.0000 | 147 | -55.5 | -0.04 | 0.9983 |
| | | THF | 167 | -112 | 145 | 23.5 | -0.0004 | 1.0000 | 151 | 20.6 | -0.03 | 0.9976 |
| | | CH | 261 | 5 | 132 | -4.5 | -0.0003 | 1.0000 | 141 | -4.4 | -0.04 | 0.9996 |
| | | THP | -7 | 194 | 197 | 14.4 | 0.0040 | 1.0000 | 197 | 19.5 | 0.00 | 0.9942 |
| | cyclohexane | CP | -516 | 234 | 754 | 7.9 | 0.0000 | 1.0000 | 735 | 14.1 | 0.08 | 0.9988 |
| | | THF | 55 | 158 | 194 | 22.6 | -0.0001 | 1.0000 | 196 | 26.8 | -0.01 | 0.9972 |
| | | CH | 221 | 4 | 115 | -3.3 | -0.0005 | 1.0000 | 123 | -3.2 | -0.04 | 0.9996 |
| | | THP | -423 | -133 | 453 | -3.7 | 0.0007 | 1.0000 | 438 | -7.2 | 0.07 | 0.9989 |
| IP | water | CP | 97 | -79 | 245 | -2.5 | -0.0002 | 1.0000 | 249 | -4.6 | -0.02 | 0.9989 |
| | | THF | 108 | -99 | 295 | -10.8 | -0.0003 | 1.0000 | 299 | -13.4 | -0.02 | 0.9990 |
| | | CH | 39 | 100 | 288 | 1.8 | -0.0001 | 1.0000 | 290 | 4.4 | -0.01 | 0.9987 |
| | | THP | 83 | -21 | 277 | 7.8 | -0.0004 | 1.0000 | 280 | 7.2 | -0.01 | 0.9999 |
| | cyclohexane | CP | -484 | 95 | 497 | 25.3 | 0.0007 | 1.0000 | 479 | 27.8 | 0.08 | 0.9996 |
| | | THF | -82 | -134 | 325 | 10.9 | 0.0001 | 1.0000 | 322 | 7.3 | 0.01 | 0.9981 |
| | | CH | 120 | 7 | 257 | -0.5 | -0.0004 | 1.0000 | 262 | -0.3 | -0.02 | 1.0000 |
| | | THP | -423 | -133 | 453 | -3.7 | 0.0007 | 1.0000 | 438 | -7.2 | 0.06 | 0.9989 |
| STR | water | CP | 1865 | 2306 | 1538 | -32.9 | -0.0008 | 1.0000 | 1607 | 27.8 | -0.30 | 0.9780 |
| | | THF | 1896 | 2255 | 1561 | -36.4 | -0.0011 | 1.0000 | 1631 | 23.0 | -0.31 | 0.9794 |
| | | CH | 1791 | 2197 | 1520 | -17.1 | -0.0008 | 1.0000 | 1587 | 40.8 | -0.29 | 0.9801 |
| | | THP | 1529 | 2088 | 1461 | -15.4 | -0.0015 | 1.0000 | 1518 | 39.6 | -0.25 | 0.9804 |
| | cyclohexane | CP | -524 | -166 | 674 | 10.5 | 0.0003 | 1.0000 | 655 | 6.1 | 0.09 | 0.9992 |
| | | THF | 1271 | 1945 | 1408 | -13.7 | -0.0016 | 1.0000 | 1455 | 37.4 | -0.21 | 0.9815 |
| | | CH | 1972 | -2326 | 1543 | 13.0 | -0.0006 | 1.0000 | 1617 | -48.2 | -0.32 | 0.9789 |
| | | THP | 228 | 965 | 1134 | -29.8 | -0.0012 | 1.0000 | 1142 | -4.4 | -0.04 | 0.9921 |

**Fig. S11.** AM1/OPLS rigid potential-energy scans for displacements along $H_\alpha$ normal modes from atomic Hessian analysis for cyclopentyl (CP), cyclohexyl (CH), tetrahydrofuranyl (THF) and tetrahydropyranyl (THP) cations in explicit water and cyclohexane: OP = out-of-plane bending, IP = in-plane bending, STR = stretching. Blue dotted line: quartic fit; red solid line: quadratic fit.



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