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Classical hybrid Monte-Carlo simulations of the interconversion of hexabromocyclododecane
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Marcus Weber, Roland Becker, Robert Köppen, Vedat Durmaz†

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Abstract

In this paper, we investigate the interconversion processes of the major flame retardant – 1,2,5,6,9,10-hexabromocyclododecane (HBCD) – by the means of statistical thermodynamics based on classical force-fields. Three ideas will be presented. First, the application of classical hybrid Monte-Carlo simulations for quantum mechanical processes will be justified. Second, the problem of insufficient convergence properties of hybrid Monte-Carlo methods for the generation of low temperature canonical ensembles will be solved by an interpolation approach. Furthermore, it will be shown how free energy differences can be used for a rate matrix computation. The results of our numerical simulations will be compared to experimental results.

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Keywords: Markov process, molecular dynamics, rate matrix.

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*Supported by Federal Institute for Materials Research and Testing (BAM), Berlin, Germany.
†Email: weber@zib.de, durmaz@zib.de; address: Zuse-Institute Berlin (ZIB), Takustraße 7, 14195 Berlin. Email: roland.becker@bam.de, robert.koeppen@bam.de; address: Federal Institute for Materials Research and Testing (BAM), Department of Analytical Chemistry, Reference Materials, Richard-Willstätter-Straße 11, 12489 Berlin.
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Introduction

Molecular dynamics simulations based on classical force fields can be used to determine the rate of conformational changes inside the conformational space $\Omega$ of small molecules. However, the classical description of molecular motion fails if molecules also partially change their chirality. This is a quantum mechanical process. The timescale of such an interconversion process is often far away from the step length of quantum mechanical simulations. In this paper, a simple example for such a situation is presented. The corresponding molecule, 1,2,5,6,9,10-hexabromocyclododecane (HBCD), is shown in Figure 1. We will mainly present three ideas in this paper:

1. It will be explained in Section 1, how classical simulation methods can be used to investigate the interconversion processes of HBCD.

2. It will be shown in Section 4, how the trapping problem of low-temperature molecular simulations can be solved by a reweighting approach.

3. In Section 5 it is presented, how free-energy differences and a steady state approximation can be used for a rate matrix computation.

Our goal was to find a classical approach for the estimation of interconversion rates making simulation as simple as possible and, therefore, reproducible. The presented ideas may be the basis for further developments in this field. Our motivation for the use of thermodynamical methods for the investigation of HBCD was the poor prediction results based on single-point quantum chemical calculations. For these calculations, i.e. dipole momentum, polarizability, HOMO and LUMO, we used global minimal potential energy conformations from converging high-temperature simulations (as described below) of the minus enantiomers of each of the three diastereomers in Figure 1. $\alpha$- and $\gamma$-HBCD have the property of $c2$ symmetry which is missing for $\beta$-HBCD. By hint of this property we calculated optimal geometries for each diastereomer, using Gaussian03 with a Becke3LYP/6-31+G* set of basis functions. Unfortunately, there exists no correlation between the predicted water solubility (based on dipol momenta and polarizability and confirmed by similar results of other publications [1, 32]) with experimental results [22]. This observation leads us to the assumption that it is hardly possible to generalize the output from a single-point calculation based on one conformation to a whole ensemble of conformations, as it usually occurs in reality. It is necessary to consider a molecular system as an ensemble of many different states, each holding (slightly) different molecular properties. In this article, transition rates are not estimated using saddle-point energy computations, but they are derived from classical thermodynamics simulations.

1 The isomerism of HBCD and the interconversion mechanism

HBCD is one of the major flame retardant additives to plastics and it is increasingly found in trace amounts in the environment, biota, and humans [6, 7, 8, 28]. Therefore, HBCD is currently one of the emerging environmental analytes of interest. There is evidence for activity of HBCD as endocrine disruptor [33] and
an EU risk assessment is under way. Technical HBCD consists mainly of three diastereomeric pairs of enantiomers (Figure 1). The absolute configurations of enantiomers were only recently correlated with their order of chromatographic elution [27]. In the absence of a chiral environment, the (−)-enantiomers behave in the same way as the (+)-enantiomers. Therefore, in the followings we only investigate the (+)-enantiomers. The results for the (−)-enantiomers (e.g., in Tables 5-7) can be derived by simply changing sign. We are interested in the interconversion of the HBCD stereoisomers shown in Figure 1 because it is important to understand their behavior in technical processes and gas chromatographic analysis. Furthermore, the diastereomeric and enantiomeric composition in biological samples differ from that of technical mixture and the biological induced interconversion of HBCD at ambient temperature is discussed [28]. The chemical mechanism of the transition between these structures is shown in Figure 2: Two vicinal bromine atoms change their positions with two hydrogen atoms under inversion of absolute configurations. This is a quantum mechanical process. The interconversion can only take place, if the bromine
Figure 3: Possible interconversion reactions of the HBCD isomers connected to the three sets of vicinal bromine atoms.

atoms are in anti-position. Once the bromine atoms are in anti-position, the rate of the interconversion process can be seen as largely independent from the structure of the rests R in Figure 2. Such a reaction has been denoted as cyclic-concerted mechanism and was so far only investigated on variously substituted 1,2-dibromocyclohexane systems [2, 3, 4, 16, 25]. In case of HBCD there are three sets of vicinal bromine atoms each being able to undergo the concerted interconversion and at the same time mutually influencing the conformational alignment of the cyclododecane ring and resulting in diastereomer-specific distribution of conformers. It was shown experimentally [23, 29, 19] that a mixture containing α-, β-, and γ-HBCD in any composition interconverts towards an equilibrium which is dominated by α-HBCD. The reaction pathways are depicted in Figure 3. This leads to the following idea, that classical simulation can be used in order to characterize the interconversion processes qualitatively.

Via computer simulation and for every dihedral angle (C1C2, C5C6, C9C10) in Figure 1, we will determine the part of the configurational space of (+)-α-HBCD, (+)-β-HBCD, and (+)-γ-HBCD for which the dihedral angle is in anti-position compared to the part of the configurational space, where the angle is in gauche-position. These results are presented in terms of free energy differences in Tables 5-7. The more the anti-position is preferred, the faster the conversion at the corresponding dihedral angle will occur. The basis for our simulations will be the Boltzmann distribution (canonical ensemble) of states. This is the most likely distribution of states at constant temperature, constant number of particles and constant volume. Since the interconversion of neat HBCD only takes place above its melting point at about 430 K, this will be the temperature of interest. As an approximation, the simulations in this paper are performed for the vacuum.

2 Experimental results

The experimental set-up is discussed in detail elsewhere [26]. In brief, pure (+)-γ-HBCD is exposed to 160°C for different periods between two and 60 minutes and then the concentrations of all six stereoisomers (Figure 1) are determined for each point in time by liquid chromatography with diode array detection using a chiral column. Since no other compound including different HBCD isomers were detected, the sum concentration of the six HBCD stereoisomers measured at a particular time was set to 100% for each point in time. Then, the molar fraction of each diastereomer was calculated as mol-(%). The Mathematica 4.0 software package from Wolfram Research, Inc. (USA) was used for a parameter estimation of the kinetic constants. For this purpose, the time dependen...
Figure 4: Interconversion experiment starting with 100% $(+)-\gamma$-HBCD.
concentration vector $x \in \mathbb{R}^6$ is modelled as a solution of a rate equation

$$\frac{dx(t)}{dt} = Q^T x(t),$$

where $Q \in \mathbb{R}^{6 \times 6}$ is the corresponding rate matrix and $x$ is the vector of the concentrations of the six species of Figure 1 (in the corresponding order: (+)-$\alpha$, (+)-$\beta$, (+)-$\gamma$, (-)-$\alpha$, (-)-$\beta$, (-)-$\gamma$). The least squares fit of the experimental data corresponds to the following rate matrix result

$$Q^{exp.} = 0.001 \begin{pmatrix}
-0.1608 & 0.0188 & 0.1420 & 0 & 0 & 0 \\
0.1200 & -1.3900 & 0 & 0 & 1.1000 & 0.1700 \\
1.5000 & 0 & -1.6460 & 0 & 0.1460 & 0 \\
0 & 0 & 0 & -0.1608 & 0.0188 & 0.1420 \\
0 & 1.1000 & 0.1700 & 0.1200 & -1.3900 & 0 \\
0 & 0.1460 & 0 & 1.5000 & 0 & -1.6460
\end{pmatrix}.$$

The corresponding time-dependent concentration plots are shown in Figure 4.

3 Hybrid Monte-Carlo simulation

In the Boltzmann distribution of states at temperature $T$, the probability $\pi(q)$ for a conformation $q \in \Omega$ of the conformational space $\Omega$ is proportional to

$$\pi(q) \propto \exp(-\beta V_{pot}(q))$$

with the inverse temperature

$$\beta = 1/(T \cdot 0.008314403 \frac{kJ}{mol \cdot K}) \Rightarrow \beta \propto 1/T.$$ 

In (2), $V_{pot} : \Omega \to \mathbb{R}$ is the potential energy of the conformational states. For our classical simulations, this function is given by the Merck Molecular Force Field which has been designed for small molecules like HBCD [17, 18]. In order to generate a set of states (a trajectory of states) distributed according to (2), we applied the hybrid Monte-Carlo method (HMC) [9, 30]. This method is a combination of a Markov Chain Monte-Carlo approach with short time (78 fs using a velocity verlet integrator [12] with a time-step of 1.3 fs) molecular dynamics (MD) simulations. The initial momenta for the MD part of the algorithm are taken from the Boltzmann-distribution of momenta at the given temperature. Unfortunately, the HMC-method rarely overcomes high potential energy barriers [10, 11]. Only if the kinetic energy of the initial momenta is high enough, the HMC-method is able to reach the important parts of the conformational space. For this reason, we have simulated the three molecules at an artificial high temperature $T = 1500$ K with $\beta_0 = 0.08018$ mol/kJ. In a first computer experiment, we compared the results of five different HMC-samplings, each of them consisting of 10,000 steps. The proposed Gelman-Rubin convergence indicator (convergence value = 1.1; observables = sine and cosine of dihedral angles) was not reached after this number of sampling steps [13, 14]. In addition, the symmetry of the $\gamma$-structure was not reflected by the sampling data. Therefore, we performed a HMC-sampling with 100,000 steps. In this case, the convergence indicator was reached and the symmetry of the
α— and the γ—structure could also be found in the sampling data. We also performed samplings with $5 \times 100,000$ steps for each of the (−)-structures and found the same symmetries and results. The bad convergence properties lead us to an academic question: Due to the low convergence rate, we can conclude that there are dynamical metastabilities inside the ring structure. This may be a reason for non-existence of stereoisomer-specific interconversion rates. In order to write down interconversion rates from, e.g., (+)-α-HBCD to another stereoisomer of HBCD, we have to assume, that each isomer can be seen as one kinetic species. But each metastable subset of the conformational space of, e.g., (+)-α-HBCD may have a different dynamical behavior (and may, therefore, be an own species from the kinetic point of view). Only, if the timescale of conformational changes within the conformational space of the HBCD isomers is much shorter than the timescale of interconversion, the postulation of interconversion rates makes sense. From experiments we can conclude that the timescale of interconversion is in the range of seconds. This is the timescale of protein folding. HBCD is much smaller and more flexible than a protein. This means, that the definition of interconversion rates is reasonable. We are interested in the thermodynamics of the molecules at low temperature $T = 430 \text{ K}$ with $\beta_1 = 0.27971 \text{ mol/kJ}$. Thus, in a first step, we derive thermodynamical values from the HMC sampling for $T = 1500 \text{ K}$. In a second step, we reweight these quantities to low temperature. One thermodynamic value is the free energy $A$ of the system. It is given by the partition function

$$A(\beta) = -\frac{1}{\beta} \ln \left( \int_{\Omega} \exp(-\beta V_{pot}(q)) \, dq \right). \quad (4)$$

In equation (4), the kinetic energy part of $A$ is missing. This simplification is possible, because we are only interested in free energy differences. Furthermore, potential and kinetic energy are separable and the kinetic energy part is identical for the observed subsystems. The integral in (4) can not be approximated by numerical methods. But ratios of integrals over certain subsets of $\Omega$ can be approximated, i.e. free energy differences can be computed. For a given dihedral angle $\theta$, we are interested in the portion of states that can be seen as anti compared to the portion of states that are gauche with respect to $\theta$. In the present application, we defined dihedral angles $120^\circ \geq \theta \geq -120^\circ$ as gauche. With this separation of states, we have determined free energy differences from the HMC-sampling by counting the different states $N_{\text{anti}}$ and $N_{\text{gauche}}$ respectively and applying

$$\Delta_{ga} A(\beta) \approx -\frac{1}{\beta} \ln \left( \frac{N_{\text{gauche}}}{N_{\text{anti}}} \right). \quad (5)$$

The results are given in Tables 1-3. The more negative $\Delta_{ga} A$ the more the gauche states are preferred. Another interesting value can be derived from the

<table>
<thead>
<tr>
<th>(+)-α-HBCD</th>
<th>$\langle V_{pot} \rangle = 921$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>$\Delta_{ga} A = -17$</td>
</tr>
<tr>
<td>C5C6</td>
<td>$\Delta_{ga} A = -40$</td>
</tr>
<tr>
<td>C9C10</td>
<td>$\Delta_{ga} A = -40$</td>
</tr>
</tbody>
</table>

Table 1: Free energy differences $\Delta_{ga} A$, mean potential energy $\langle V_{pot} \rangle$ and mean potential energy differences $\Delta_{ga} \langle V_{pot} \rangle$ of (+)-α-HBCD at $T=1500 \text{ K}$ in kJ/mol.
Table 2: Free energy differences $\Delta_{ga} A$, mean potential energy $\langle V_{pot} \rangle$ and mean potential energy differences $\Delta_{ga} \langle V_{pot} \rangle$ of (+)-$\beta$-HBCD at T=1500 K in [kJ/mol].

<table>
<thead>
<tr>
<th>(+)-$\beta$-HBCD</th>
<th>$\langle V_{pot} \rangle$ = 931</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>$\Delta_{ga} A = -14$</td>
</tr>
<tr>
<td>C5C6</td>
<td>$\Delta_{ga} A = -36$</td>
</tr>
<tr>
<td>C9C10</td>
<td>$\Delta_{ga} A = -34$</td>
</tr>
</tbody>
</table>

Table 3: Free energy differences $\Delta_{ga} A$, mean potential energy $\langle V_{pot} \rangle$ and mean potential energy differences $\Delta_{ga} \langle V_{pot} \rangle$ of (+)-$\gamma$-HBCD at T=1500 K in [kJ/mol].

<table>
<thead>
<tr>
<th>(+)-$\gamma$-HBCD</th>
<th>$\langle V_{pot} \rangle$ = 926</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>$\Delta_{ga} A = -10$</td>
</tr>
<tr>
<td>C5C6</td>
<td>$\Delta_{ga} A = -41$</td>
</tr>
<tr>
<td>C9C10</td>
<td>$\Delta_{ga} A = -41$</td>
</tr>
</tbody>
</table>

simulations: The mean potential energy value

$$\langle V_{pot} \rangle(\beta) = \int_\Omega V_{pot}(q) \frac{\exp(-\beta V_{pot}(q))}{\int_\Omega \exp(-\beta V_{pot}(q))} dq.$$  \hspace{1cm} (6)

The inner energy $\langle V_{tot} \rangle$ of the system is the sum

$$\langle V_{tot} \rangle = \langle V_{pot} \rangle + \langle V_{kin} \rangle$$ \hspace{1cm} (7)

of the mean potential and the mean kinetic energy. Numerically, $\langle V_{pot} \rangle$ can be approximated by the mean of the potential energy values of the HMC-sampling. Mean potential energy differences can also be computed if we split the set of states into anti- and gauche-conformations. The corresponding results are also presented in the Tables 1-3.

4 Reweighting formula

In a second step, we have to reweight the sampling data from the high-temperature sampling with $T = 1500 \, K$ to $T = 430 \, K$. The term “reweighting” is mostly used for the following method: A statistical weight is assigned to every generated data-point from the high-temperature sampling. One tries to adjust these weights in order to approximate the low-temperature distribution of energies. This procedure often fails: In a high temperature sampling the potential energy values are distributed in a broader range with a higher mean value compared to a low-temperature sampling, see Figure 5. Most of the sampling points have a high potential energy value. If we aim at a reweighting of the sampling points in order to get the low-temperature distribution, the low-energy points of the high-temperature sampling are weighted up statistically. Therefore, point-wise reweighting schemes only make use of the sampling points located in the small overlap region of the high-temperature and the low-temperature distribution. The occupation of this region depends on the input parameters of the algorithms very sensitively. The common opinion is that reweighting is only possible for sufficiently overlapping distributions. This opinion led to many sophisticated (but not simple) sampling methods in the past. The most famous one is replica simulations.
exchange [31]. Other examples can be found in modern textbooks [5]. In our case, we will see that it is not important to approximate the complete distribution of states at the lower temperature. It is sufficient to know, how the mean value in Figure 5 depends on the temperature. Instead of a point-wise reweighting scheme, we present a thermodynamical approach in this work. For the purpose of simplicity we set \( U := \langle V_{\text{pot}} \rangle \) for the mean potential energy in the followings. As an approximation, we assume that the mean potential energy \( U \) depends linearly on the temperature \( T \) of the system. In this case \( \Delta U(\beta) \) goes with \( 1/\beta \) due to (3), i.e

\[
\Delta U(\beta) = \frac{(\Delta U(\beta_0) - \Delta U(\infty))}{\beta} + \Delta U(\infty).
\]

(8)

Since the mean kinetic energy \( \langle V_{\text{kin}} \rangle \) in (7) depends linearly on the temperature, the assumption (8) is equivalent to a linear model for the inner energy \( \langle V_{\text{tot}} \rangle \) of the system. Furthermore, assuming a linear model for the inner energy in reality would mean that the heat capacity \( C_V \) is a temperature-independent constant. This assumption is not true, but mostly according to quantum effects which are not part of the classical model used in this work. From the classical viewpoint, (8) is exact, if the potential energy \( V_{\text{pot}} \) is a quadratic function. It is a good approximation, if the conformation space \( \Omega \) can be decomposed, such that each part of this decomposition has a Gaussian-like Boltzmann distribution. This is a widely used assumption in many applications. More details can be found in Appendix A. In order to apply (8), we have to compute the limit \( \Delta U(\infty) \). With increasing \( \beta \), the Boltzmann-distribution more and more focuses on the global optimum of the system. In our case, we have split our system into two parts: the anti- and the gauche-states. The limit of \( \Delta U \) for increasing \( \beta \) is equivalent to the difference \( \Delta_{\text{ga}} V_{\text{pot}}^0 \) of the lowest potential energy values of the two subsystems, i.e. \( \Delta_{\text{ga}} V_{\text{pot}}^0 = \Delta U(\infty) \). The entries in Table 4 are the results of local minimizations (using the conjugate gradient method [21]) applied to each point of the trajectories of the given high-temperature HMC-samplings. The gauche-position of the bromine atoms is always preferred. This also corresponds to the experiment: All known crystal structures of HBCD stereoisomers display all-gauche configuration of all vicinal bromine atoms [27, 19, 20]. The mean
potential energy values \( \langle V_{pot} \rangle \) according to a linear model (8) are presented in the Tables 5-7. In order to interpret reaction rates, we are not interested in the mean potential energy values but in free energy differences \( \Delta_{ga}A(\beta) \). The \( \beta \)-dependency of \( A \) can be calculated by differentiating (4) and inserting (6):

\[
\frac{d}{d\beta} \Delta_{ga} A(\beta) = -\frac{1}{\beta} \Delta_{ga} A(\beta) + \frac{1}{\beta} \Delta_{ga} \langle V_{pot} \rangle(\beta).
\]  

(9)

Using the linear model (8) for \( U \) provides

\[
\frac{d}{d\beta} \Delta_{ga} A(\beta) = -\frac{1}{\beta} \Delta_{ga} A(\beta) + \frac{(\Delta U(\beta_0) - \Delta U(\infty)) \beta_0}{\beta^2} + \frac{\Delta U(\infty)}{\beta}.
\]  

(10)

The ordinary differential equation (10) can be solved analytically, such that

\[
\Delta_{ga} A(\beta) = \frac{1}{\beta} ((\beta - \beta_0) \Delta U(\infty) + \ln \left( \frac{\beta}{\beta_0} \right)) \beta_0 \left( \Delta U(\beta_0) - \Delta U(\infty) \right) + \beta_0 \Delta_{ga} A(\beta_0)
\]

(11)

for an initial value \( \Delta_{ga} A(\beta_0) \) which can be found in Tables 1-3. Via formula (11) and the corresponding values for \( \Delta U(\beta_0) \), \( \Delta U(\infty) \), and \( \Delta_{ga} A(\beta_0) \) the free energy differences can be computed for 430 K. The results are given in the Tables 5-7. In contrast to a point-wise reweighting scheme, formula (11) is robust against small perturbations of the input data.

### 5 Rate matrix computation

In Tables 5-7, the results of the reweighting formula are presented. The most important questions are: How do these simulation results fit to the experimental results? Do they reflect the qualitative behavior of the HBCD-system? In order to answer these questions, the meaning of the simulation results for the qualitative behavior of the HBCD-system will be visualized in the followings.

From a mathematical point of view, we will apply the Arrhenius equation [15]:

\[
k \propto \exp(-\beta \Delta_{ag}A).
\]  

(12)
Table 5: Free energy differences $\Delta_{ga}A$ and mean potential energy $\langle V_{pot} \rangle$ of $(+)-\alpha$-HBCD at $T=430$ K.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta_{ga}A$ (kJ/mol)</th>
<th>$\langle V_{pot} \rangle$ (kJ/mol)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>-13</td>
<td>435</td>
<td>interconv. to ...</td>
</tr>
<tr>
<td>C5C6</td>
<td>-33</td>
<td>-</td>
<td>$(+)-\gamma$-HBCD</td>
</tr>
<tr>
<td>C9C10</td>
<td>-32</td>
<td>-</td>
<td>$(+)-\beta$-HBCD</td>
</tr>
</tbody>
</table>

Table 6: Free energy differences $\Delta_{ga}A$ and mean potential energy $\langle V_{pot} \rangle$ of $(+)-\beta$-HBCD at $T=430$ K.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta_{ga}A$ (kJ/mol)</th>
<th>$\langle V_{pot} \rangle$ (kJ/mol)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>-9</td>
<td>445</td>
<td>interconv. to ...</td>
</tr>
<tr>
<td>C5C6</td>
<td>-30</td>
<td>-</td>
<td>$(−)-\alpha$-HBCD</td>
</tr>
<tr>
<td>C9C10</td>
<td>-25</td>
<td>-</td>
<td>$(−)-\gamma$-HBCD</td>
</tr>
</tbody>
</table>

In this approach, the reaction rate $k$ of an interconversion is proportional to the Boltzmann expression of the activation energy. With $\Delta_{ag}A = -\Delta_{ga}A$, the free energy differences in Tables 5-7 can be used to estimate these activation energies. On the basis of these considerations, a rate matrix $Q \in \mathbb{R}^{6 \times 6}$ will be constructed for the six species of Figure 1 (in the corresponding order: $(+)-\alpha$, $(+)-\beta$, $(+)-\gamma$, $(−)-\alpha$, $(−)-\beta$, $(−)-\gamma$). The model is based on the rate equation (1) with the concentration vector $x \in \mathbb{R}^6$. It is known from theory [24], that the rate matrix $Q$ of this Markov process can be written in the form

$$Q = R(K - id), \quad (13)$$

where $id$ is the six-dimensional unit matrix, $K \in \mathbb{R}^{6 \times 6}$ is the embedded Markov chain and $R \in \mathbb{R}^{6 \times 6}$ is a diagonal matrix of rate factors. On the basis of the free energy differences and (12), the embedded Markov chain can be computed by inserting the values of the Arrhenius equation into a matrix and rescaling the rows, such that the row sums are 1. For HBCD, it has to be taken into account that there are sometimes two different ways for an interconversion from one stereoisomer to another (multiplication of $k$ with factor 2):

$$K = \begin{pmatrix}
0 & 0.0074 & 0.9926 & 0 & 0 & 0 \\
0.0112 & 0 & 0 & 0 & 0.9860 & 0.0028 \\
0.9990 & 0 & 0 & 0 & 0.0010 & 0 \\
0 & 0 & 0 & 0 & 0.0074 & 0.9926 \\
0 & 0.9860 & 0.0028 & 0.0112 & 0 & 0 \\
0 & 0.0010 & 0 & 0.9990 & 0 & 0
\end{pmatrix}.$$

For the computation of the rate factors, it can be used that the equilibrium concentration of the six species is a steady state of equation (1). We will not use experimental data in order to determine the steady state vector $\pi \in \mathbb{R}^6$. The equilibrium concentrations can be estimated by the mean potential energy values in Tables 5-7 and the Boltzmann expression (2) instead (replace $V_{pot}$ by $\langle V_{pot} \rangle$). The result is

$$\pi^T = (0.4626, 0.0282, 0.0092, 0.4626, 0.0282, 0.0092).$$

12
Table 7: Free energy differences $\Delta_{ga}A$ and mean potential energy $\langle V_{pot} \rangle$ of
(+)-\(\gamma\)-HBCD at T=430 K.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta_{ga}A$</th>
<th>$\langle V_{pot} \rangle$</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1C2</td>
<td>-6.1 kJ/mol</td>
<td>449 kJ/mol</td>
<td>interconv. to ...</td>
</tr>
<tr>
<td>C5C6</td>
<td>-28 kJ/mol</td>
<td>(+)(-\alpha)-HBCD</td>
<td></td>
</tr>
<tr>
<td>C9C10</td>
<td>-28 kJ/mol</td>
<td>(-)(-\beta)-HBCD</td>
<td></td>
</tr>
</tbody>
</table>

Up to an unknown scaling factor $\mu > 0$, there is a unique solution for $R$, for which $\pi$ is the steady state of $Q$ on the basis of $K$ and (13). This solution $r \in \mathbb{R}^6$ is given by the linear equation

$$r^\top D(K - id) = 0,$$

where $K$ is given by the Arrhenius approximation, $D$ is the diagonal matrix $D = \text{diag}(\pi)$ of the given steady state solution, and $r$ is the unknown vector of rate factors, with $R = \text{diag}(r)$. In our case, this means

$$Q^{\text{theo.}} = \mu \cdot \begin{pmatrix} -0.0200 & 0.0001 & 0.0199 & 0 & 0 & 0 \\ 0.0022 & -0.1978 & 0 & 0 & 0.1950 & 0.0005 \\ 0.9990 & 0 & -1.0000 & 0 & 0.0010 & 0 \\ 0 & 0 & 0 & -0.0200 & 0.0001 & 0.0199 \\ 0 & 0.1950 & 0.0005 & 0.0022 & -0.1978 & 0 \\ 0 & 0.0010 & 0 & 0.9990 & 0 & -1.0000 \end{pmatrix}.$$  

For more details about the determination of $Q$, see also [35]. For this matrix $Q$, a kinetic simulation of (1) is shown in Figure 6. $\mu = 0.001$ has been fixed “by eye”. $\mu$ is not available via classical methods because of the unknown interconversion rate (see Figure 2). The kinetic simulation has been performed for the initial condition of the kinetic experiment (Figure 4). Although there have been so many sources of error (classical approach, vacuum, Boltzmann distribution, reweighting to 430K, Arrhenius equation, . . . , see Appendix B), the correct qualitative behavior of the system can be seen in the plots: The different increase of the (+)-\(-\beta\)-HBCD and the (-)-\(-\beta\)-HBCD concentration. The initial increase of the (+)-\(-\alpha\)-HBCD concentration far above its equilibrium value. The low initial concentrations of (-)-\(-\alpha\)-HBCD and (-)-\(-\gamma\)-HBCD. Thus, we can conclude that the numerical simulations reflect qualitatively the behavior of the HBCD-system. A detailed comparison of $K$ and $Q^{\text{theo.}}$ with the experimental results ($Q^{\text{exp.}}$ on page 7) provides the following analogies:

1. $\alpha$-HBCD converts faster into $\gamma$-HBCD (and much slower into $\beta$-HBCD),
2. (+)-\(-\beta\)-HBCD converts faster into (-)-\(-\beta\)-HBCD, and vice versa,
3. $\gamma$-HBCD converts faster into $\alpha$-HBCD,
4. the dominating reaction is the interconversion from $\gamma$-HBCD to $\alpha$-HBCD.

Conclusion

We have investigated the interconversion processes of HBCD. These are quantum mechanical processes which take place on a timescale of seconds. Due to
Figure 6: Qualitative behavior of interconversion based on free energy computations
very different timescales, quantum mechanical molecular simulation algorithms are not applicable for an analysis of these processes. But, whenever the quantum mechanical mechanism is identical for all interconversion processes, it is only important to know which part of the conformational space initializes the process. Then, based on classical simulations, one can compute the portion of the conformational space which can be seen as activated. This portion is a measure for the corresponding transition rate. In our example, even the classical simulation algorithm has to tackle very different timescales and only high temperature HMC-samplings are able to provide correct thermodynamical ensembles. We have presented a simple reweighting formula which can be used to interpolate the important thermodynamical values at lower temperature. With all these simplifications, the HMC-samplings for each of the HBCD-stereoisomers needed 30 million force field evaluations (CPU-time on our simple PC: 6 hours).

Outlook. The presented ideas use the fact that the unknown rate of the interconversion mechanism in Figure 2 is identical for each transition in Figure 3. In this case, the time scale factor \( \mu \) is the only unknown value in the rate matrix computation. If the interconversion mechanism is different for each of the interconversion processes, the above scheme for the rate matrix computation is also valid. In this case, we have to estimate the activation energy of the corresponding interconversion mechanism in Figure 2, e.g., by the means of quantum-based transition state computations. This additional activation energy has to be inserted into the Arrhenius equation (12), too. This means a combination of insufficient single-point quantum chemistry calculations with results of classical thermodynamics simulations.

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A Temperature dependence of the mean potential energy

In order to justify the linear model for the mean potential energy in (8), it will be shown that this behavior is valid for quadratic potentials \( V_{pot} : \mathbb{R}^d \rightarrow \mathbb{R} \). This also justifies the application of a linear model for multivariate Boltzmann distributions which are locally Gaussian (approximately locally quadratic potential energy functions). Without loss of generality (and via principle axis transformation), the \( d \)-dimensional quadratic potential energy function can be written in separable form:

\[
V_{pot}(q) = \sum_{i=1}^{d} (a_i q_i^2 + b_i q_i + c_i) := \sum_{i=1}^{d} V_i(q_i) \tag{15}
\]

with corresponding constants \( a_i, b_i, c_i \in \mathbb{R} \) and \( a_i > 0 \). A short calculation on the basis of (6) and (15) yields

\[
\langle V_{pot} \rangle = \sum_{i=1}^{d} \int_{-\infty}^{\infty} V_i(q_i) \frac{\exp(-\beta V_i(q_i))}{\int_{-\infty}^{\infty} \exp(-\beta V_i(q_i)) \, dq_i} \, dq_i. \tag{16}
\]
Equation (16) shows that the linear dependency of the mean potential energy can be justified by solving the integral in (6) for the 1-dimensional case. The result is

\[
\langle V_{\text{pot}} \rangle = \sum_{i=1}^{d} \frac{1}{2\beta} - \frac{b_{i}^{2}}{4\alpha_{i}} + c_{i}
\]

which is exactly the claimed $1/\beta$-behavior of $\langle V_{\text{pot}} \rangle$. With $b_{i} = 0$ and $c_{i} = 0$, equation (17) is the well-known $1/2kT$-contribution per degree of freedom to the inner energy of an ideal gas. For a numerical justification of the linear temperature dependence, we performed two HMC samplings of $\text{(+)-}\alpha$-HBCD at $T = 430\, K$. One sampling started in the low energy region of the optimal conformation of $\text{(+)-}\alpha$-HBCD and one sampling started in an high-energy region. After $5 \times 10,000$ steps the samplings did not converge (as expected). The mean potential energy values were 420 $kJ/mol$ and 455 $kJ/mol$, respectively. They are lower and upper bounds for the true value. From the mean potential energy $\langle V_{\text{pot}} \rangle = 921$ $kJ/mol$ at high temperature and an optimal value $V_{0\text{pot}} = 239$ $kJ/mol$ of the potential energy, the linear model (8) predicts a mean energy of 435 $kJ/mol$ at a temperature of 430 $K$ in accordance with the simulated bounds. For a better verification of the reweighting formula, we performed an extensive simulation with the inhouse software \textsc{ZIBgridfree} [34] and a point-wise density estimation strategy [36]. The simulated mean potential energy 434 $kJ/mol$ is very close to the calculated value 435 $kJ/mol$ of the reweighting formula. For all these reasons, we think that the reweighting formula is applicable.

B Medium temperature results

Quantitatively, the simulation results of Section 5 do not predict the experimental results. In fact, a lot of approximations have been used. The severest one may be the vacuum-approximation. Liquid HBCD has a dielectric constant which is different from the vacuum. Also the interactions between the HBCD molecules in a liquid phase can not be neglected. Briefly, the energy barriers and the energy differences are overestimated by the classical model in Section 5. From a statistical point of view, a simple downscaling of the potential energy function is equivalent to increasing the temperature. And, in fact, for a temperature of $T = 670\, K$, we get the steady state estimation:

\[
\pi^{T} = (0.3912, 0.0650, 0.0438, 0.3912, 0.0650, 0.0438),
\]

which perfectly fits to experimental results [1, 29] (78% $\alpha$-HBCD, 14% $\beta$-HBCD, and 8% $\gamma$-HBCD). Furthermore, for this medium temperature, the main interconversion rates ($\alpha \leftrightarrow \gamma$ and $\beta \leftrightarrow \beta$) with $\mu = 0.0015$ also perfectly fit to the experiment:

\[
Q^{\text{theo.}} = 0.001\cdot\begin{pmatrix}
-0.1730 & 0.0084 & \textbf{0.1646} & 0 & 0 & 0 \\
0.0405 & -0.9764 & 0 & 0 & \textbf{0.9152} & 0.0208 \\
\textbf{1.4843} & 0 & -1.5000 & 0 & 0.0157 & 0 \\
0 & 0 & 0 & -0.1730 & 0.0084 & \textbf{0.1646} \\
0 & \textbf{0.9152} & 0.0208 & 0.0405 & -0.9764 & 0 \\
0 & 0.0157 & 0 & \textbf{1.4843} & 0 & -1.5000
\end{pmatrix}
\]
References


