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Theoretical analysis of high pressure effects on conformational equilibria

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Abstract

Along with temperature, pressure is the most important physical parameter determining the thermodynamic properties and reactivity of chemical systems. In this work, we discuss the effects of high pressure on conformational properties of organic molecules and propose an approach toward calculation of conformational volume changes based on molecular dynamics simulations. The results agree well with the experimental data. Furthermore, we demonstrate that pressure can be used as an instrument for fine-tuning of molecular conformations and to propel a properly constructed molecular rotor possessing a suitable combination of energy and volume profiles.

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Keywords:

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1. Introduction

The importance of pressure in chemistry can hardly be overstated. Along with temperature, pressure is the most important physical parameter determining the thermodynamic properties and reactivity of chemical systems.¹ Although in the gas phase the role of pressure is merely that of controlling the concentration, in condensed media pressure operates at a much deeper physical level by causing significant deformations of the potential energy surfaces of chemical systems,² which at extreme pressures results in drastic changes in the chemical and physical properties of compressed species.³ In this work we will focus on theoretical analysis of high pressure effects on conformational interconversions.

The pressure dependence of an equilibrium constant K is described by the thermodynamic relationship⁴

$$\left(\frac{\partial \ln K}{\partial P}\right)_T = -\frac{\Delta V}{RT} \quad (1)$$

where T is temperature, R is the gas constant, and ΔV is the so-called reaction volume, defined as the difference

$$\Delta V = V_P - V_R \quad (2)$$

between partial molar volumes of reactants (V_R) and products (V_P). For stable species, the values of V_R and V_P can be directly measured, thus giving ΔV by eq. (2). In the cases involving unstable and short-lived compounds, as in conformational equilibria where individual conformers cannot be isolated, the value of ΔV can be determined by the reversal of eq. (1)

$$\Delta V = -RT \left(\frac{\partial \ln K}{\partial P}\right)_T \quad (3)$$

as the isothermal logarithmic pressure derivative of the equilibrium constant, usually assessed spectroscopically.^{5,6}

Similarly, the pressure dependence of a rate constant k , including that of a conformational interconversion, is expressed by the equation

$$\Delta V^\ddagger = -RT \left(\frac{\partial \ln k}{\partial P} \right)_T \quad (4)$$

in terms of its activation volume $\Delta V^\ddagger$, which within the framework of transition state (TS) theory can be described as the difference in partial molar volumes between the TS and the reactant species:⁷

$$\Delta V^\ddagger = V^\ddagger - V_R \quad (5)$$

Experimental activation volumes are available for a wide range of chemical and biochemical processes.^{1,8}

Activation and reaction volumes are elements of a more general construct describing the volumetric properties of a chemical system – its volume profile⁹

$$\Delta V(x) = V(x) - V_R \quad (6)$$

along reaction coordinate x . Obviously,

$$\Delta V(x^\ddagger) = \Delta V^\ddagger \quad (7)$$

for $x^\ddagger$ describing the TS location on the reaction coordinate. If such location is unknown, eq. (7) offers a simple method of determining $x^\ddagger$ by comparing the theoretically calculated volume profiles $\Delta V(x)$ with experimentally measured activation volumes $\Delta V^\ddagger$.¹⁰

Another important application of volume profiles stems from the fact that, thermodynamically, volume is an isothermal pressure derivative of Gibbs energy, and therefore a pressure-induced change in the Gibbs energy profile $G(x, P)$ can be assessed by integration of the volume profile $\Delta V(x; P)$ over pressure:

$$G(x; P) = G_0(x) + \int_{P_0}^P \Delta V(x; p) dp \quad (8)$$

where $G_0(x) = G(x; P_0)$ is the Gibbs energy profile at a reference pressure P_0 . If the pressure dependence of $\Delta V(x)$ can be neglected, eq.(8) reduces to a much simpler approximate relation^{2b,c}

$$G(x; P) \approx G_0(x) + (P - P_0)\Delta V(x) \quad (9)$$

In this paper, we will use the above to discuss high pressure as an instrument for investigation and control of conformational properties of organic molecules. Direct application of eqs. (2), (5), (6) and (9) to analysis of pressure-dependent conformational interconversions require a reliable technique for generating accurate values of molecular volumes for all relevant stable, meta-stable, and transient conformations, based solely on the structural characteristics of a molecular system in those conformations and specific to a particular choice of a solvent as well as physical parameters (pressure and temperature). Our recently proposed displacement volume method¹¹, utilizing molecular dynamics (MD) simulations of the solvent and solvent-solute systems, serves this purpose well. For convenience, we will start with a brief overview of this method.

2. Displacement volume method

Thermodynamically, the partial molar volume V_X of solute **X** in solvent **S** is defined as

$$V_X = \left(\frac{\partial V}{\partial n_X} \right)_{P,T} \quad (10)$$

where V is the total volume of the solution and n_X is the number of moles of the solute. For dilute solutions this can be replaced with a finite-difference expression,

$$V_X = \frac{V(n_S, n_X) - V(n_S, 0)}{n_X} \quad (11)$$

and in the limit of infinite dilution represents the change in volume upon addition of a single solute molecule. Using constant-pressure MD we can obtain the volume of a single solute

molecule as an Archimedean displacement volume, i.e. as the volume difference between a pure solvent (N particles: $N\cdot\mathbf{S}$) and a system containing, in addition, one solute molecule ($N+1$ particles: $\mathbf{X} + N\cdot\mathbf{S}$):

$$V(\mathbf{X}) = V(\mathbf{X} + N\mathbf{S}) - V(N\mathbf{S}) \quad (12)$$

This concept is illustrated by Fig. 1 for the case of *anti-gauche* isomerization of 1,2-dichloroethane. When a conformer is inserted in pure solvent, it displaces the latter. This displacement, combined with the solute-induced restructuring of the solvent, leads to a change in the overall volume of the solvent-solute system relative to the volume previously occupied by the pure solvent. The resulting incremental volume change represents the partial molar volume of the conformer and can be used as a measure of its volume in a given solvent. Molecular volume, so defined, is sensitive to temperature, pressure, the nature and strength of solvent-solute interactions, and most importantly, the geometrical configuration (in this case, a conformation) of the solute.

Insert Figure 1 here

3. Computational details

MD simulations were performed using the GROMACS software package¹² for the solvent-solute systems maintained at constant pressure and temperature conditions using Berendsen temperature and pressure coupling¹³ with $\tau_T = 0.1$ ps and $\tau_P = 1.0$ ps. The MD trajectories were obtained via leap-frog integration¹⁴ with a time step of 1 fs in a cubic box with periodic boundary conditions and an interaction cutoff of 1.0 nm for Lennard-Jones interactions. In calculations of sections 4-6, where a higher accuracy was required, the long-range electrostatic interactions were

calculated using the particle mesh Ewald method¹⁵ with a real-space cut off of 1.0 nm. In calculations of sections 8 and 10, due to their exploratory nature, computationally less expensive direct summation was used for electrostatic interactions. The lengths of the trajectories were determined by the convergency of the calculated quantities. The OPLS force field¹⁶ was used for organic molecules in all cases. Cavity images shown in Figs. 1, 17 and 18 were produced using the VMD package¹⁷ as graphic renderings of MD trajectories. Quantum mechanical (QM) calculations were performed with the Gaussian 09 suite.¹⁸ The images of molecular structures shown in Figs. 11 and 15 were generated using GaussView.¹⁹

4. Direct calculation of conformational volume changes

Conformational volume changes were calculated directly from eq. (2) using our displacement volume method¹¹ for selected neat halogenated hydrocarbons, undergoing conformational transformations described by eqs. (13)-(17):

The calculated and experimental values of the conformational volume changes are compared in Table 1.

Insert Table 1 here

As stated earlier, the volume changes due to conformational equilibria are usually determined experimentally from eq. (3) as the isothermal logarithmic pressure derivatives of the spectroscopically measured equilibrium constants. The errors of such determinations, typically based on a linear approximation for $K(P)$, can be relatively high in comparison with the values of ΔV , as illustrated in Table 2 by the case of *anti-gauche* isomerization of 1,2-dichloroethane.⁵ This situation seems to be quite typical for the observed conformational volume changes, the reported values of which are usually small.^{5,6} Consequently, to obtain these small values theoretically using eq. (2), the volumes of conformers must be calculated with an extreme accuracy, preferably within a fraction of 1 cm³/mol. As can be seen from the convergency plots of Fig. 2, this stringent accuracy requirement was met by our calculations.

Insert Table 2 and Figure 2 here

Comparison of the experimental and MD calculated ΔV values listed in Table 1 shows a [reasonable](#) match in most cases, with the exception of 2-bromobutane and 1-chloro-2-

methylpropane for which the reported experimental ΔV are positive. We believe that these discrepancies are due to inaccuracy in the experimental values. As can be seen in Table 3, ΔV values reported for the same transformations in hexane solvent are all negative and closely match our values calculated for neat solution. Since such solvent-dependent switch in the sign of the volume changes is not observed for the similar cases of 2-chlorobutane and 1-bromo-2-methylpropane, it seems likely that the positive experimental ΔV values for 2-bromobutane and 1-chloro-2-methylpropane are erroneous.

Insert Table 3 here

5. Conformational volume changes obtained from equilibrium constants

Due to the small size of the halogenated hydrocarbons discussed in the previous section, direct MD simulations of their conformational equilibria was feasible and was performed for temperature and pressures matching the experimental conditions. These calculations were limited to the subset of the systems and processes listed in Table 1, for which the experimental $K(P)$ values were available. The simulated equilibrium constants were obtained as the ratios of the resident times spent by the systems in the targeted conformations. The convergency trends are shown in Fig. 3. The calculated equilibrium constants plotted in Fig. 4 match the experimental constants within the error limits.

Insert Figures 3 and 4 here

In all cases the pressure dependences of the equilibrium constants, both experimental and simulated, look roughly linear and the idea of using linear regression for obtaining ΔV from $K(P)$ might seem reasonable. However, there is ample evidence in the literature that linear (and often

quadratic) regression is inadequate for this purpose for data spread over a wide pressure range.^{20,21} In fact, a variety of more elaborate empirical fitting functions has been proposed for that purpose, the most reliable of which are listed below starting with the quadratic eq. (18):²⁰

$$\ln K / K_0 = a_1 P + a_2 P^2 \quad (18)$$

$$\ln K / K_0 = a_3 P / (1 + a_4 P) \quad (19)$$

$$\ln K / K_0 = a_1 P + a_3 P / (1 + a_4 P) \quad (20)$$

$$\ln K / K_0 = a_2 \ln(1 + a_4 P) \quad (21)$$

$$\ln K / K_0 = a_1 P + a_2 \ln(1 + a_4 P) \quad (22)$$

The ΔV values obtained from equations (18)-(22) fitted to the experimental and simulated $K(P)$ data of Fig. 4 are listed in Table 4.

Insert Table 4 here

There was a notable difference in the case of 1,2-dichloroethane between ΔV values obtained using eqs. (18)-(22) and those assessed by linear regression, both for the volume changes derived from the experimental and simulated $K(P)$ data, with the simulated values matching very closely the average of the values obtained from two of the available experimental sources.^{5b,e} In the case of monohalogenated hydrocarbons, this difference was no longer substantial, which should likely be attributed to the smaller absolute values of ΔV resulting in a much lesser pressure dependence of K . In a few instances eqs. (20) and (22) failed to produce a reasonable fit and generated obviously wrong values for the conformational volume changes. This is consistent with our analysis^{20b} of the performance of various fitting functions, including eqs. (18)-(22), which indicates that tri-parametric eq. (20) and (22), although usually robust and

more accurate, tend to display an instability of the fit when the level of errors in $K(P)$ data is relatively high.

6. Activation volumes and three-point volume profiles for conformational interconversions

Pressure dependent MD trajectories of conformational interconversions used, as previously described, to generate equilibrium constants $K(P)$ can also be utilized to assess the rate constants $k(P)$ for these processes. The latter can be estimated as the inverse of the resident times for staying in a “reactant” conformation multiplied by the frequency of exit into a “product” conformation. The rate constants thus obtained are plotted as functions of pressure in Fig. 5 for 1,2-dichloroethane, 1-bromobutane, and 1-bromohexane. To calculate activation volumes according to eq. (4) as the pressure derivatives of $\ln k(P)$, the latter were fitted by eq. (18)-(22). Simultaneously, the volumes of activation were calculated directly from eq. (5) using the displacement volume model. In the cases of 1-bromobutane and 1-bromohexane, the pressure dependences of $\ln k$ were practically linear and all fitting equations gave a consistent prediction of the $\Delta V^\ddagger$ values. For 1,2-dichloroethane, $\ln k(P)$ displayed a significant nonlinearity, and only two of the fitting equations – (19) and (21) – offered a reasonable approximation for the kinetic data, with the $\Delta V^\ddagger$ values of 2.0 and 3.2 cm³/mol, respectively. The $\Delta V^\ddagger$ predicted by these equations for 1-bromobutane and 1-bromohexane were, correspondingly, 0.7 and 1.3 cm³/mol. The results are summarized in Fig. 6 in the form of three-point volume profiles for conformational interconversions. A notable difference in the signs of the activation volumes obtained by two different techniques, observed in all cases, should probably be attributed to the dynamic effects of solvent discussed in the next section.

Insert Figures 5 and 6 here

7. Solvent interference: the dynamic effects of solvent

Solvent viscosity can have a profound effect on reaction kinetics in condensed media,²² resulting in reaction rates considerably lower than those predicted by TS theory (TST). The cause of the effect lies in the fact that viscous solvents are too slow to properly adjust to a changing configuration of the solute undergoing a reaction transformation and thus start interfering with the solute's reaction dynamics. Experimentally, this effect has been observed in various high pressure reactions,²³ where solvent viscosity exponentially increases with pressure.²⁴ Due to the fact that conformational interconversions occur on a very fast time scale, the dynamic effects of solvent become noticeable even at relatively low viscosities.²⁵ Since TST is no longer applicable in this case, eq. (4) needs to be modified to include the viscosity-dependent dynamic effects of solvent. For butane *anti-gauche* isomerization, the viscosity-dependent rate constant k can be related to the TST rate constant k_{TST} by an approximate equation²⁶

$$\ln k \approx \ln k_{TST} - \alpha \ln D^{-1} + \beta \quad (22)$$

with constant parameters α and β , and solvent viscosity expressed in the form of the reciprocal solvent diffusion coefficient D^{-1} . Differentiation of eq. (22) with respect to pressure gives

$$-RT \left(\frac{\partial \ln k}{\partial P} \right)_T \approx \Delta V^\ddagger - \alpha RT \left(\frac{\partial \ln D}{\partial P} \right)_T \quad (23)$$

Fig. 7 displays a linear plot of the logarithm of the calculated diffusion coefficient for 1,2-dichloroethane as a function of pressure, with a slope of approximately $-4.9 \times 10^{-4} \text{ bar}^{-1}$. The value of parameter α for *anti-gauche* isomerization of butane just outside the TST-valid region is *ca*

0.4.²⁶ If we assume that the value of this coefficient for *anti-gauche* isomerization of 1,2-dichloroethane is approximately the same, the contribution of nonequilibrium solvation (*i.e.* the solvent dynamics interference) to the pressure dependence of the rate constant can be roughly estimated as $ca + 5 \text{ cm}^3/\text{mol}$, which can account for the difference between the activation volume values of -1.2 and $+(2.0-3.2) \text{ cm}^3/\text{mol}$ on the volume profiles of Fig. 6 for 1,2-dichloroethane.

Insert Figure 7 here

8. Continuous volume profiles: pressure controlled conformational tuning

If the locations of the minima of the ambient pressure Gibbs energy profile $G_0(x)$ and the volume profile $V(x)$ are different then, according to eq. (9), the location of the minima of the high pressure Gibbs energy profile, determined by the competition of G_0 and PV terms, will become a function of pressure. This can be used to achieve a desired conformation by applying high pressures if the stable ambient conformation possesses a greater volume. As an example, we will consider here the pressure tuning of the conformations of 3-methyl-2,2'-bithiophene **1**. The behaviour of **1** is of interest as it provides a low-molecular-weight model for the conformational properties of polythiophenes, conducting polymers that attract close attention of polymer researchers and materials scientists due to their electronic and optical properties as conjugated polymers.²⁷ Obviously, such properties are greatly affected by the conformation-dependent extent of conjugation in these molecules. The conformation of 3-methyl-2,2'-bithiophene **1** is described by the S-C-C-S torsion angle φ , as shown in Fig. 8.

Insert Structures 1 and 2 and Fig. 8 here

Conformational properties of oligothiophenes have previously been discussed.²⁸ It was noted that even unsubstituted 2,2'-bithiophene **2** is slightly twisted out of the planar conformations (*cis* or *trans*) thus reducing the degree of π -electron conjugation between monomeric units, and that a substituent in the 3-position amplifies the effect. The B3LYP/6-31++G(d,p) gas phase torsion profile $U_0(\varphi)$ for 3-methyl-2,2'-bithiophene **1**, shown in Fig. 9, illustrates this point. In solution, the gas phase profile $U_0(\varphi)$ needs to be augmented by solvation Gibbs energy $G_{\text{solv}}(\varphi)$ to produce the ambient Gibbs energy profile $G_0(\varphi) = U_0(\varphi) + G_{\text{solv}}(\varphi)$. This solvation Gibbs energy was obtained for toluene solvent using thermodynamic integration,^{15b} and is shown in Fig. 10 together with the resulting Gibbs energy profile $G_0(\varphi)$. It appears that solvation further shifts the *trans* minimum away from 180°.

Insert Figures 9-12 here

The volume profile $\Delta V(\varphi)$ for 3-methyl-2,2'-bithiophene **1**, shown in Fig. 11, was generated using the displacement volume method¹¹ with a step of 10° and approximated by a quadratic polynomial to smooth out computational errors. It was then used, together with the ambient Gibbs energy profile $G_0(\varphi)$, to produce a series of pressure dependent Gibbs energy profiles $G(\varphi, P)$ in accordance with eq. (9). These profiles, shown in Fig. 12, display a trend of increasing planarity of the *trans* conformation at elevated pressures. The HOMO-LUMO gap was observed to decrease by 53 kJ/mol as the system became planar (compared to 29 kJ/mol decrease for butadiene in a similar conformational change). Thus the increasing pressure, favoring more planar conformations, enhances the level of π -electron conjugation and significantly modifies the electronic properties of the thiophene dimer.

9. Pressure-driven molecular rotor

Crowned with the 2016 Nobel Prize,³⁰ the studies of molecular machines and, in particular, molecular rotors have been a subject of interest of experimental and theoretical research for quite some time now.³¹ The unidirectional rotation in the latter is typically achieved by means of a specially designed sequence of chemical or photochemical modifications of a molecular system causing the desired progression of its conformational changes, adding up into a full rotation.³² Through its ability to continuously tune molecular conformations, as illustrated in the previous section, pressure seems to offer an alternative mechanism of sustaining perpetual unidirectional motion in a molecular rotor system. As an example, we will consider a hypothetical prototype system, shown in Fig. 13, with a four-fold ambient Gibbs energy torsional profile $G_0(\varphi)$ and a two-fold volume profile $\Delta V(\varphi)$, slightly shifted with respect to each other. The system is designed so that it is the most compact when it is flat, thus giving $\Delta V(\varphi)$ minima near φ of 0° (**A**), 180° (**E**), and 360° (**I**). Due to steric repulsion between the static (blue) and moving (red) parts of the rotor, the $G_0(\varphi)$ function has maxima near those points. Its additional maxima at 90° (**C**), and 270° (**G**) are due to a different type of interaction – say, π -electron conjugation or specific chemical interactions of properly positioned functional groups – favoring planar conformations. As a result, the minimum energy conformations (**B**, **D**, **F**, **H**) are somewhat twisted, as in the case of the stable ambient conformations of bithiophene **1**.

Insert Figures 13-15 here

A periodic pressure pulse sequence designed to propel this molecular rotor system in the clockwise direction is shown in Fig. 14. The general schematic explaining the mechanism of the propelling effect is presented in Fig. 15, where the red-filled circles label the current configuration of the system at a given time. Initially ($t=0$, $P=0$), the system is assumed to be in

its leftmost minimum **B**, separated from the next minimum **D** by maximum **C** at $\varphi=90^\circ$. The first (negative) pressure pulse pushes the system over this barrier. Since $\Delta V(\varphi)$ has a maximum right behind **C** the increasingly negative $P\Delta V(\varphi)$ term biases $G(\varphi, P) = G_0(\varphi) + P\Delta V(\varphi)$ to the right, eventually eliminating barrier **C** and leaving **D** the only minimum between 0° and 180° (Fig. 15a). The system is now in minimum **D** and the remaining (upward) part of the negative pressure pulse just restores the ambient pressure without any further significant conformational changes (Fig. 15b). The subsequent (positive) pressure pulse pushes the system from **D** to **F** by eliminating barrier **E** (Fig. 15c). Again, the downward part of the positive pressure pulse just restores the ambient pressure without any further significant conformational changes (Fig. 15d). In the end of this two-pulse pressure cycle, the system ends up shifted continuously and clockwise from minimum **B** to minimum **F** periodically related to it. Further two pulses of the pressure cycle will rotate the system full 360° .

10. Concluding remarks

The displacement volume method¹¹ was used to obtain theoretical values of conformational volume changes and produced a **reasonable** match between the experimental and calculated ΔV values for reactions (13)-(17), which recommends this method as a useful tool for analysis of high pressure conformational equilibria, even when the required accuracy of volume calculations is measured by fractions of $1 \text{ cm}^3/\text{mol}$.

The effect of pressure on molecular systems spreads unevenly over their different degrees of freedom, affecting softer modes to a greater degree.^{2b,c} Not surprisingly, torsion angles are affected by pressure much more strongly than other structural parameters, which allows pressure to be used not only to control conformational preferences but, more importantly, as a precise tool

to fine-tune the location of the stable conformation on the Gibbs energy surface of a flexible system, as we showed for a case of bithiophene **1**. As a result, a sequence of positive and negative pressure pulses can be designed to continuously propel a properly constructed molecular system through a series of conformational changes adding up to a full rotation.

Two possible molecular prototypes of such rotors possessing the proper energy profiles are shown in Fig. 16. In both cases, a benzene ring clamped within a pericondensed strap comprises the moving part. Since these molecules are nonpolar, their ambient Gibbs energy profiles are likely to be close to their energy profiles shown in Fig. 17. The energy maxima at the flat conformations are due to steric repulsion; and the additional maxima at the orthogonal positions of the benzene ring are due to the loss of its π -electron conjugation with the strap. The detailed volume profiles for **3** and **4** shown in Fig. 18 were obtained using the displacement volume method in a solvent consisting of 1000 Lennard Jones particles with standard parameters of $\epsilon = 2.0$ kJ/mol and $\sigma = 0.35$ nm or 0.25 nm. In all cases, the flat conformations ($\varphi = 0^\circ$) are more compact than the orthogonal conformations ($\varphi = 90^\circ$). Somewhat unexpectedly, the volume profiles display a more complex behavior in the vicinity of the orthogonal conformation, notably departing from the “ideal” dome shape of the volume profile of Fig. 13, although a notable improvement is achieved with a reduction in the size of the solvent particles. The cavity images of Figures 19-21 hint that this may be related to the different ability of solvent particles to penetrate the “hole” in the pericondensed strap that opens as the benzene ring rotates from the flat to the orthogonal conformation. Further investigations are still necessary to construct a rotor with the proper combination of Gibbs energy and volume profiles.

Insert Figures 16-21 here

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References

1. (a) Hamann, S. D. *Physico-Chemical Effects of Pressure*; Academic Press: New York, 1957.
(b) Gonikberg, M.G. *Chemical Equilibria and Reaction Rates at High Pressures*; National Science Foundation: Washington, DC, 1963. (c) Isaacs, N. S. *Liquid Phase High Pressure Chemistry*; Wiley: New York, 1981. (d) le Noble, W. J. In *Progress in Physical Organic Chemistry*; Streitwieser, A., Taft, R. W., Eds.; John Wiley & Sons: Hoboken, NJ, 1967; Vol. 5, p 207. doi:10.1002/9780470171844.ch3. (d) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, 78, 407. doi:10.1021/cr60314a004. (e) van Eldik, R.; Asano, T.; le Noble, W. J. *Chem. Rev.* **1989**, 89, 549. doi:10.1021/cr00093a005. (f) Drljaca, A.; Hubbard, C. D.; van Eldik, R.; Asano, T.; Basilevsky, M. V.; le Noble, W. J. *Chem. Rev.* **1998**, 98, 2167. doi:10.1021/cr970461b.
2. (a) Basilevsky, M.V.; Weinberg, N. N.; Zhulin, V.M. *J. Chem. Soc., Faraday Trans. 1* **1985**, 81, 875. doi:10.1039/f19858100875. (b) Spooner, J.; Yanciw, B.; Wiebe, B.; Weinberg N. J. *Phys. Chem. A* **2014**, 118, 765. doi:10.1021/jp410496t. (c) Spooner, J.; Smith, B.; Weinberg N. *Can. J. Chem.* **2016**, 94, 1057. doi:10.1139/cjc-2016-0295.
3. (a) Grochala, W.; Hoffmann, R.; Feng, J.; Ashcroft, N. W. *Angew. Chem., Int. Ed.* **2007**, 46, 3620. doi:10.1002/anie.200602485. (b) Hemley, R. J. *Annu. Rev. Phys. Chem.* **2000**, 51, 763. doi:10.1146/annurev.physchem.51.1.763. (c) Bini, R. *Acc. Chem. Res.* **2004**, 37, 95. doi:10.1021/ar030015c. (d) Schettino, V.; Bini, R. *Chem. Soc. Rev.* **2007**, 36, 869. doi:10.1039/b515964b. (e) Bini, R.; Ceppatelli, M.; Citroni, M.; Schettino, V. *Chem. Phys.* **2012**, 398, 262. doi:10.1016/j.chemphys.2011.04.021.
4. Planck, M. *Ann. Phys.* **1887**, 268, 462. doi:10.1002/andp.18872681108.

5. (a) Taniguchi, Y.; Takaya, H.; Wong, P. T. T.; Whalley E. *J. Chem. Phys.* **1981**, *75*, 4815. doi:10.1063/1.441908. (b) Nomura, H.; Murasawa, K.; Ito, N.; Iida, F.; Udagawa, Y. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 3321. doi:10.1246/bcsj.57.3321. (c) Ikawa, S.; Whalley, E. *J. Chem. Phys.*, **1984**, *81*, 1620. doi:10.1063/1.447876. (d) McClain, B. L.; Ben-Amotz, D. *J. Phys. Chem. B* **2002**, *106*, 7882. doi:10.1021/jp0140973. (e) Sabharwal, R. J.; Huang, Y.; Song, Y. *J. Phys. Chem. B* **2007**, *111*, 7267. doi:10.1021/jp068287v
6. (a) Nomura, H.; Udagawa, Y.; Murasawa, K. *J. Molec. Struct.* **1985**, *126*, 229. doi:10.1016/0022-2860(85)80116-2. (b) Nomura, H.; Koda, S. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 2917. doi:10.1246/bcsj.58.2917. (c) Gardiner, D. J.; Jackson, R. W.; Straughan, B. P. *J. Chem. Soc. Chem. Commun.* **1981**, 159. doi:10.1039/c39810000159.
7. (a) Evans, M. J.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875. doi:10.1039/tf9353100875. (b) Stearn, A. E.; Eyring, H. *Chem. Rev.* **1941**, *29*, 509. doi:10.1021/cr60094a007.
8. (a) Vidugiris, G. J. A.; Markley, J. L.; Royer, C. A. *Biochemistry* **1995**, *34*, 4909. doi:10.1021/bi00015a001. (b) Kunugi, S.; Kitayaki, M.; Yanagi, Y.; Tanaka, N.; Lange, R.; Balny, C. *Eur. J. Biochem.* **1997**, *248*, 567. doi:10.1111/j.1432-1033.1997.t01-1-00567.x. (c) Mohana-Borges, R.; Silva, J. L.; Ruiz-Sanz, J.; de Prat-Gay, G. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 7888. doi:10.1073/pnas.96.14.7888. (d) Pappenberger, G.; Saudan, C.; Becker, M.; Merbach, A. E.; Kiefhaber, T. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 17. doi:10.1073/pnas.97.1.17. (e) Woenckhaus, J.; Köhling, R.; Thiyagarajan, P.; Littrell, K. C.; Seifert, S.; Royer, C. A.; Winter, R. *Biophys. J.* **2001**, *80*, 1518. doi:10.1016/s0006-3495(01)76124-3. (f) Herberhold, H.; Marchal, S.; Lange, R.; Scheyhing, C. H.; Vogel, R.F.; Winter, R. *J. Mol. Biol.* **2003**, *330*, 1153. doi:10.1016/s0022-2836(03)00657-0. (g)

- Tan, C.-Y.; Xu, C.-H.; Wong, J.; Shen, J.-R.; Sakuma, S.; Yamamoto, Y.; Lange, R.; Balny, C.; Ruan, K.-C. *Biophys. J.* **2005**, *88*, 1264. doi:10.1529/biophysj.104.050435. (h) Brun, L.; Ison, D. G.; Velu, P.; Garcia-Moreno, B.; Royer, C. A. *Biochemistry* **2006**, *45*, 3473. doi:10.1021/bi052638z. (i) Font, J.; Torrent, J.; Ribó, M.; Laurents, D. V.; Balny, C.; Vilanova, M.; Lange, R. *Biophys. J.* **2006**, *91*, 2264. doi:10.1529/biophysj.106.082552. (j) Kimura, T.; Sakamoto, K.; Morishima, I.; Ishimori, K. *J. Am. Chem. Soc.* **2006**, *128*, 670. doi:10.1021/ja055084w. (k) Jenkins, D. C.; Pearson, D. S.; Harvey, A.; Sylvester, I. D.; Geeves, M. A.; Pinheiro, T. J. T. *Eur. Biophys. J.* **2009**, *38*, 625. doi:10.1007/s00249-009-0420-6. (l) Osváth, S.; Quynh, L. M.; Smeller, L. *Biochemistry* **2009**, *48*, 10146. doi:10.1021/bi900922f. (m) Rouget, J.-B.; Aksel, T.; Roche, J.; Saldana, J.-L.; Garcia, A. E.; Barrick, D.; Royer, C. A. *J. Am. Chem. Soc.* **2011**, *133*, 6020. doi:10.1021/ja200228w. (n) Roche, J.; Dellarole, M.; Caro, J. A.; Norberto, D. R.; Garcia, A. E.; Garcia-Moreno, B.; Roumestand, C.; Royer, C. A. *J. Am. Chem. Soc.* **2013**, *135*, 14610. doi:10.1021/ja406682e.
9. (a) le Noble, W. J. *Rev. Phys. Chem. Jpn.* **1980**, *50*, 207. (b) Stochel, G.; van Eldik, R. *Coord. Chem. Rev.* **1999**, *187*, 329. doi:10.1016/s0010-8545(99)00009-0. (c) Hubbard, C. D.; van Eldik, R. *J. Coord. Chem.* **2007**, *60*, 1. doi:10.1080/00958970601089200. (d) Hubbard, C.; van Eldik, R. *Inorg. Chim. Acta.* **2010**, *363*, 2357. doi:10.1016/j.ica.2009.09.042.
10. (a) Wiebe, H.; Weinberg, N. *J. Chem. Phys.*, **2014**, *140*, 124105. doi:10.1063/1.4868549. (b) Wiebe, H.; Louwerse, M.; Weinberg, N. *J. Chem. Phys.*, **2017**, *146*, 104107. doi:10.1063/1.4977732.
11. (a) Spooner, J.; Wiebe, H.; Boon, N.; Deglint, E.; Edwards, E.; Yanciw, B.; Patton, B.; Thiele, L.; Dance, P.; Weinberg, N. *Phys. Chem. Chem. Phys.* **2012**, *14*, 2264.

- doi:10.1039/c2cp22949h. (b) Wiebe, H.; Spooner, J.; Boon, N.; Deglint, E.; Edwards, E.; Dance, P.; Weinberg, N. *J. Phys. Chem. C* **2012**, *116*, 2240. doi:10.1021/jp209088u. (c) Deglint, E.; Martens, H.; Edwards, E.; Boon, N.; Dance, P.; Weinberg, N. *Phys. Chem. Chem. Phys.* **2011**, *13*, 438. doi:10.1039/c0cp01570a.
12. (a) Berendsen, H. J. C.; van der Spoel, D.; van Drunen, R. *Comput. Phys. Commun.* **1995**, *91*, 43. doi:10.1016/0010-4655(95)00042-e. (b) Lindahl, E.; Hess, B.; van der Spoel, D. *J. Mol. Model.* **2001**, *7*, 306. doi:10.1007/s008940100045. (c) van der Spoel, D.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J. *J. Comput. Chem.* **2005**, *26*, 1701. doi:10.1002/jcc.20291. (d) Hess, B.; Kutzner, C.; van der Spoel, D.; Lindahl, E. *J. Chem. Theory Comput.* **2008**, *4*, 435. doi:10.1021/ct700301q.
13. Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684. doi:10.1063/1.448118.
14. (a) Verlet, L. *Phys. Rev.* **1967**, *159*, 98. doi:10.1103/physrev.159.98. (b) Leach, A. R. *Molecular Modelling: Principles and Applications*, 2nd ed., Prentice Hall: Upper Saddle River, NJ, 2001.
15. Darden, T.; York D.; Pedersen, L. *J. Chem. Phys.* **1993**, *98*, 10089. doi:10.1063/1.464397.
16. (a) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657. doi:10.1021/ja00214a001. (b) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225. doi:10.1021/ja9621760.
17. Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33. doi:10.1016/0263-7855(96)00018-5.

18. Frisch, M. J.; Trucks, G.W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J.J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision E.01*, Gaussian, Inc., Wallingford CT, **2009**.
19. GaussView, Version 5, Dennington, R.; Keith, T. A.; Millam, J. M. Semichem Inc., Shawnee Mission, KS, **2009**.
20. (a) Viana, C. A. N.; Reis, J. C. R. *Pure Appl. Chem.*, **1996**, 68, 1541. doi:10.1351/pac199668081541. (b) Spooner, J.; Weinberg, N. *Can. J. Chem.*, **2017**, 95, 149. doi:10.1139/cjc-2016-0454.
21. (a) Sawin, S. P. Ph.D. Thesis, University of Illinois, Urbana, 1971. (b) Eckert, C. A. *Ann. Rev. Phys. Chem.*, **1972**, 23, 239. doi:10.1146/annurev.pc.23.100172.001323. (c) Kelm H.; Palmer, D. A. In: *High Pressure Chemistry*; Kelm, H., Ed., Dordrecht: Reidel, **1978**, 281. doi:10.1007/978-94-009-9888-9_11. (d) El'yanov B. S.; Gonikberg, E. M. *J. Chem. Soc., Faraday Trans. 1*, **1979**, 75, 172. doi:10.1039/f19797500172. (e) El'yanov B. S.;

- Vasylyvitskaya, E. M. *Rev. Phys. Chem. Japan*, **1980**, *50*, 169. (f) Asano T.; Okada, T. *J. Phys. Chem.*, **1984**, *88*, 238. doi:10.1021/j150646a015. (g) Viana, C. A. N.; Calado, A. R. T.; Pinheiro, L. M. V. *J. Phys. Org. Chem.*, **1995**, *8*, 63. doi:10.1002/poc.610080202.
22. (a) Kramers, H. A. *Physica* **1940**, *7*, 284. doi:10.1016/s0031-8914(40)90098-2. For reviews, see: (b) Hanggi, P.; Talkner, P.; Borkovec, M. *Rev. Mod. Phys.* **1990**, *62*, 251. doi:10.1103/revmodphys.62.251. (c) Bagchi, B. *Annu. Rev. Phys. Chem.* **1989**, *40*, 115. doi:10.1146/annurev.pc.40.100189.000555. (d) Hanggi, P.; Jung, P. In *Adv. Chem. Phys.*; Prigogine, I., Rice, S. A., Eds.; Wiley: New York, 1995; 89, pp. 239-326. (e) Schweizer, K. S. *J. Chem. Phys.* **2005**, *123*, 244501. doi:10.1063/1.2137701. (f) Pollak, E. Talkner, P. *Chaos* **2005**, *15*, 026116. doi:10.1063/1.1858782. See also: (g) Langer, J. S. *Ann. Phys.* **1969**, *54*, 258. doi:10.1016/0003-4916(69)90153-5. (h) Grote, R. F.; Hynes, J. T. *J. Chem. Phys.* **1980**, *73*, 2715. doi:10.1063/1.440485. (i) Agmon, N.; Hopfield, J. J. *J. Chem. Phys.* **1983**, *78*, 6947. doi:10.1063/1.444643. (j) Agmon, N.; Hopfield, J. J. *J. Chem. Phys.* **1983**, *79*, 2042. doi:10.1063/1.445988. (k) Weidenmuller, H. A.; Zhang, J.-S. *J. Stat. Phys.* **1984**, *34*, 191. doi:10.1007/bf01770354. (l) Zwanzig, R. *Acc. Chem. Res.* **1990**, *23*, 148. doi:10.1021/ar00173a005. (m) Berezhkovskii, A. M.; Zitserman, V. Yu. *Chem. Phys. Lett.* **1989**, *158*, 369. doi:10.1016/0009-2614(89)87353-1. (n) Berezhkovskii, A. M.; D'yakov, Yu. A.; Zitserman, V. Yu. *J. Chem. Phys.* **1998**, *109*, 4182. doi:10.1063/1.477024.
23. See, for example, Asano, T. *Pure Appl. Chem.* **1999**, *71*, 1691. doi:10.1351/pac199971091691. and references therein.
24. Bridgman, P. W. *The Physics of High Pressure*; G. Bell: London, 1949.

25. (a) Hasha, D.L.; Eguchi, T.; Jonas, J. *J. Chem. Phys.*, **1981**, *75*, 1571. doi:10.1063/1.442193. (b) Hasha, D.L.; Eguchi, T.; Jonas, J. *J. Amer. Chem. Soc.*, **1982**, *104*, 2290. doi:10.1021/ja00372a029.
26. Perkins, J.; Edwards, E.; Kleiv, R.; Weinberg, N. *Mol. Phys.*, **2011**, *109*, 1901. doi:10.1080/00268976.2011.598136.
27. For recent reviews, see (a) Nielsen, C. B.; McCulloch, I. *Prog. Polym. Sci.* **2013**, *38*, 2053. doi:10.1016/j.progpolymsci.2013.05.003. (b) Mehmood, U.; Al-Ahmed, A.; Hussein, I. A. *Renew. Sustainable Energy Rev.* **2016**, *57*, 550. doi:10.1016/j.rser.2015.12.177. (c) Yamamoto, T. *NPG Asia Mater.* **2010**, *2*, 54. doi:10.1038/asiamat.2010.37. (d) Das, S.; Routh, P.; Ghosh, R.; Chatterjee, D. P.; Nandi, A. K. *Polym. Int.* **2016**, *66*, 623. doi:10.1002/pi.5295. (e) Kline, R. J.; McGehee, M. D. *J. Macromol. Sci. Polymer Rev.* **2006**, *46*, 27. doi:10.1080/15321790500471194. (f) Bolinger, J. C.; Traub, M. C.; Brazard, J.; Adachi, T.; Barbara, P. F.; Vanden Bout, D. A. *Acc. Chem. Res.* **2012**, *45*, 1992. doi:10.1021/ar300012k. (g) Kane-Maguire, L. A. P.; Wallace, G. G. *Chem. Soc. Rev.* **2010**, *39*, 2545. doi:10.1039/b908001p.
28. (a) Diaz-Quijada G. A.; Weinberg, N.; Holdcroft, S.; Pinto, B. M. *J. Phys. Chem. A*, **2002**, *106*, 1266. doi:10.1021/jp011783t. (b) Diaz-Quijada, G. A.; Weinberg, N.; Holdcroft, S.; Pinto, B. M. *J. Phys. Chem. A*, **2002**, *106*, 1277. doi:10.1021/jp011784l. (c) Meng, S.; Ma, J.; Jiang, Y. *J. Phys. Chem. B*, **2007**, *111*, 4128. doi:10.1021/jp067745x.
29. (a) Flyvbjerg, H.; Petersen, H. G. *J. Chem. Phys.*, **1989**, *91*, 461. doi:10.1063/1.457480. (b) Hess, B. *J. Chem. Phys.*, **2002**, *116*, 209. doi:10.1063/1.1421362.

30. Burrows, H. D.; Hartshorn, R. M. *Pure Appl. Chem.* **2016**, *88*, 917. doi:10.1515/pac-2016-2005.
31. See, for example, (a) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines - A Journey into the Nano World*; Wiley-VCH: Weinheim, 2003, doi/10.1002/3527601600. For recent reviews, see (b) Kassem, S.; van Leeuwen, T.; Lubbe, A. S.; Wilson, M. R.; Feringa, B. L.; Leigh, D. A. *Chem. Soc. Rev.* **2017**, *46*, 2592. doi:10.1039/c7cs00245a. (c) Kay, E. R.; Leigh, D. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 10080. doi:10.1002/anie.201503375. (d) Abendroth, J. M.; Bushuyev, O. S.; Weiss, P. S.; Barrett, C. J. *ACS Nano* **2015**, *9*, 7746. doi:10.1021/acsnano.5b03367. (e) Rapenne, G.; Joachim, C. *Top. Curr. Chem.* **2014**, *354*, 253. doi:10.1007/128_2013_510. (f) Leigh, D. A.; Perez, E. M. *Top. Curr. Chem.* **2006**, *265*, 185. doi:10.1007/128_039. (g) Browne, W. R.; Feringa, B. L. *Nat. Nanotechnol.* **2006**, *1*, 26. doi:10.1038/nnano.2006.45.
32. (a) Kelly, T. R.; De Silva, H.; Silva, R. A. *Nature* **1999**, *401*, 150. doi:10.1038/43639. (b) Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harad, N.; Feringa, B. L. *Nature* **1999**, *401*, 152. doi:10.1038/43646. (c) Koumura, N.; Geertsema, E. M.; van Gelder, M. B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 5037. doi:10.1021/ja012499i. (d) Fletcher, S. P.; Dumur, F.; Pollard, M. M.; Feringa, B. L. *Science* **2005**, *310*, 80. doi:10.1126/science.1117090. (e) Perera, U. G. E.; Ample, F.; Kersell, H.; Zhang, Y.; Vives, G.; Echeverria, J.; Grisolia, M.; Rapenne, G.; Joachim, C.; Hla, S.-W. *Nat. Nanotechnol.* **2013**, *8*, 46. doi:10.1038/nnano.2012.218. (f) Greb, L.; Lehn, J.-M. *J. Am. Chem. Soc.* **2014**, *136*, 13114. doi:10.1021/ja506034n. (g) Kistemaker, J. C. M.; Štacko, P.; Visser, J.; Feringa, B. L. *Nat. Chem.* **2015**, *7*, 890. doi:10.1038/nchem.2362. (h) Collins, B. S. L.; Kistemaker, J. C. M.; Otten, E.; Feringa, B. L. *Nat. Chem.* **2016**, *8*, 860.

doi:10.1038/nchem.2543. (i) Nikiforov, A.; Gamez, J. A.; Thiel, W.; Filatov, M. *J. Phys. Chem. Lett.* **2016**, 7, 105. doi:10.1021/acs.jpcclett.5b02575. (j) Burkhardt, C.; Haberhauer, G. *Eur. J. Org. Chem.* **2017**, 1308. doi:10.1002/ejoc.201601371. (k) Wang, J.; Oruganti, B.; Durbeej, B. *Phys. Chem. Chem. Phys.* **2017**, 19, 6952. doi:10.1039/c6cp08484b. (l) Astumian, R. D. *Chem. Sci.*, **2017**, 8, 840. doi:10.1039/c6sc04806d. (m) Kassem, S.; van Leeuwen, T.; Lubbe, A. S.; Wilson, M. R.; Feringa, B. L.; Leigh, D. A. *Chem. Soc. Rev.*, **2017**, 46, 2592. doi:10.1039/c7cs00245a.

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Figure 1. 1,2-dichloroethane in *anti* (left) and *gauche* (right) conformations immersed in a solvent (represented here by an overlay of solvent particles, positions of which are sampled along the MD trajectory). Top: side view; bottom: Newman projection. Due to a short-range repulsion, the solvent avoids the solute, which results in the creation of a solvent cavity of size and shape specific to the solute conformation. Color scheme: H – white, C – light blue, Cl – green, solvent – light grey.

Figure 2. Convergency of the conformational volume changes calculated using the displacement volume method.¹² The level of convergency is measured by the deviation $\Delta\Delta V(t) = \Delta V(t) - \Delta V_\infty$ of the cumulative average $\Delta V(t)$ from the trajectory average ΔV_∞ .

Figure 3. Convergency of the ambient pressure equilibrium constants obtained by MD simulations of conformational equilibria. The level of convergency is measured by the deviation $\Delta \ln K(t) = \ln K(t) - \ln K_\infty$ of the cumulative average $K(t)$ from the trajectory average K_∞ . In the energy scale, $\Delta \ln K = 0.05$ corresponds to the Gibbs energy difference of only 0.12 kJ/mol.

Figure 4. Calculated (blue diamonds) and experimental (red circles and green triangles) equilibrium constants at 298K and various pressures for (a) 1,2-dichloroethane, eq. (13); (b) 2-chlorobutane, eq. (14); (c) 1-bromobutane, eq. (17); (d) 1-bromopentane, eq. (17); (e) 1-bromohexane, eq. (17). The sources of the experimental data are referenced in Table 4.

Figure 5. Calculated rate constants at 298K and various pressures (filled circles) and their approximations by eq. (18)-(22) for (a) 1,2-dichloroethane, eq. (13) (the inset displays the fit by eqs.(19) and (21)); (b) 1-bromobutane, eq. (17); and (c) 1-bromohexane, eq. (17).

Figure 6. Three-point volume profiles for (a) 1,2-dichloroethane, eq. (13) – red; (b) 1-bromobutane, eq. (17) – green; and (c) 1-bromohexane, eq. (17) – blue. Note the difference in signs of the activation volumes and thus the shapes of the volume profiles obtained using two different techniques: dashed lines – activation volumes estimated from simulated kinetics using eq. (4); solid lines – activation volumes obtained from eq. (5) using displacement volume model. The value of $\Delta V^\ddagger = 2.6 \text{ cm}^3/\text{mol}$ for 1,2-dichloroethane is an average of 2.0 and $3.2 \text{ cm}^3/\text{mol}$ obtained from eqs. (19) and (21) respectively.

Figure 7. Pressure dependence of the diffusion coefficient for 1,2-dichloroethane.

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Figure 8. Torsion angle φ describing mutual orientation of thiophene rings in bithiophene **1**.

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Figure 9. Gas phase B3LYP/6-31++G(d,p) inter-ring torsion profile $U_0(\varphi)$ for 3-methyl-2,2'-bithiophene **1**. Torsion angle φ is the dihedral angle S-C-C-S as defined in Figure 8.

Figure 10. Polynomial approximations to the ambient pressure Gibbs energy torsion profile $G_0(\varphi)$ for 3-methyl-2,2'-bithiophene **1** (green solid line), and its gas-phase $U_0(\varphi)$ (blue dashed line, blue diamonds) and solvation Gibbs energy $G_{\text{solv}}(\varphi)$ (red dotted line, red circles) component.

Figure 11. MD-generated ambient pressure volume profile $\Delta V(\phi)$ for 3-methyl-2,2'-bithiophene **1** (black circles) and its quadratic approximation (dashed line). The error bars are standard deviations obtained over an MD trajectory using the block averaging technique.²⁹

Figure 12. Pressure dependent Gibbs energy torsion profiles $G(\varphi, P)$ of 3-methyl-2,2'-bithiophene **1** for a series of increasing pressures. The images on the top are Newman projections of the minima of those profiles.

Figure 13. A hypothetical prototype molecular rotor system described by a four-fold ambient Gibbs energy torsion profile $G_0(\varphi)$ (green) and a two-fold volume profile $\Delta V(\varphi)$ (red). The first minimum of $\Delta V(\varphi)$ is slightly shifted to the right, past the first maximum of $G_0(\varphi)$. For convenience of discussion, both $G_0(\varphi)$ and $\Delta V(\varphi)$ are dimensionless. Letters **A** to **I** serve to relate conformations of the rotor to the respective maxima and minima of the Gibbs energy profile.

Figure 14. A triangular pressure pulse sequence designed to propel the molecular rotor of Fig. 13.

Figure 15. Progression of the pressure-dependent Gibbs energy torsion profiles $G(\varphi, P) = G_0(\varphi) + P\Delta V(\varphi)$ for $G_0(\varphi)$ and $\Delta V(\varphi)$ of Fig. 13 modified in response to the change in the hydrostatic pressure P applied to the system in the form of the pressure pulse shown in Fig. 14. The red-filled circles trace the time evolution of a local minimum of the pressure-dependent Gibbs energy profile corresponding to its left-most minimum at the ambient pressure. The sequence of shifts of this local minimum adds up to a full unidirectional rotation. Similar to Figs. 13-14, for convenience of discussion, $G_0(\varphi)$, $\Delta V(\varphi)$, P , and the resultant $G(\varphi, P)$ are dimensionless.

Figure 16. Two candidate molecular rotor systems. In both cases, the moving part is a benzene ring clamped within a pericondensed strap.

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Figure 17. B3LYP/6-31G energy profiles for rotors **3** (blue diamonds) and **4** (red circles) of Fig. 16. In both cases, the energy maxima at the flat conformations are due to steric repulsion and the additional maxima at the orthogonal positions of the benzene ring are due to the loss of its π -electron conjugation with the strap.

Figure 18. Volume profiles for rotors **3** (blue diamonds and green triangles) and **4** (red circles) of Fig. 16. These profiles were obtained using Lennard Jones solvents with $\epsilon = 2.0$ kJ/mol and $\sigma = 0.35$ nm (blue diamonds and red circles) and 0.25 nm (green triangles). The dashed lines are “ideal” profiles with a single maximum for the orthogonal conformations ($\varphi = 90^\circ$ or 270°).

Figure 19. Cavity images for rotor **3** of Fig. 16 with a $\sigma = 0.35$ nm solvent: Top – flat conformation ($\varphi = 0^\circ$); bottom – orthogonal conformation ($\varphi = 90^\circ$); left – front view; right – side view.

Figure 20. Cavity images for rotor **3** of Fig. 16 with a $\sigma = 0.25$ nm solvent: Top – flat conformation ($\varphi = 0^\circ$); bottom – orthogonal conformation ($\varphi = 90^\circ$); left – front view; right – side view.

Figure 21. Cavity images for rotor 4 of Fig. 16 with a $\sigma = 0.35$ nm solvent: Top – flat conformation ($\varphi = 0^\circ$); bottom – orthogonal conformation ($\varphi = 90^\circ$); left – front view; right – side view.

Table 1. Calculated and experimental conformational volume changes, ΔV , for selected neat halogenated hydrocarbons.

Halogenated hydrocarbon	Conformational transformation	ΔV , cm ³ /mol		Literature source
		Calculated ^a	Experimental	
1,2-dichloroethane	eq. (13)	-3.6	-2.7	Ref 5b
			-0.6	Ref 5e
2-chlorobutane	eq. (14)	-0.9	-1.5	Ref 6a
	eq. (15)	-0.3	-0.8	Ref 6a
2-bromobutane	eq. (14)	-0.8	2.0	Ref 6a
	eq. (15)	-0.4	0.6	Ref 6a
1-chloro-2-methylpropane	eq. (16)	-0.8	0.5	Ref 6a
1-bromo-2-methylpropane	eq. (16)	-1.2	-1.7	Ref 6a
1-bromobutane	eq. (17)	-1.0	-0.8	Ref 6c
1-bromopentane		-1.0	-1.0	Ref 6c
1-bromohexane		-0.9	-0.5	Ref 6c

^a ΔV values calculated using the displacement volume method¹¹ using eq. (2)

Table 2. Conformational volume changes, ΔV , reported for the *anti-gauche* isomerization of 1,2-dichloroethane by different authors.⁵

Literature source	Solvent	Pressure range, kbar	Rough appearance of $K(P)$	ΔV , cm ³ /mol	
				Reported ^a	Linearly estimated ^b
Ref 5a	20% in hexane	0 – 4	linear	–3.5	–3.2
	30% in hexane	0 – 5	linear	–3.8	–3.8
Ref 5b	neat	0 – 2.3	linear	–2.7	–3.1
Ref 5c	2-methylbutane	0 – 7.5	linear	–2.9	–2.7
Ref 5d	diethyl ether	0 – 26.4	nonlinear	–2.4 ^c	–
		0 – 5.2	linear	–	–5.1
		0.6 – 5.2	linear	–	–3.7
		5.2 – 26.4	linear	–	–1.4
Ref 5e	neat	0.6 – 5.0	linear	–0.6	–0.6

^a ΔV value as reported in the literature source

^b ΔV value obtained in the present work by linear regression based on $K(P)$ values reported in the literature source

^c ΔV value reported in the literature source based on the exponential fit to $K(P)$ data

Table 3. Experimental conformational volume changes, ΔV , for selected halogenated hydrocarbons in hexane.

Halogenated hydrocarbon	Conformational transformation	ΔV , cm ³ /mol ^a
2-chlorobutane	eq. (14)	−1.8
	eq. (15)	−0.5
2-bromobutane	eq. (14)	−1.4
	eq. (15)	−0.9
1-chloro-2-methylpropane	eq. (16)	−0.6
1-bromo-2-methylpropane	eq. (16)	−0.5

^a Ref 6b

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Table 4. Conformational volume changes, ΔV (in cm^3/mol), obtained from eq. (3) using linear regression and nonlinear functions (18)-(22) fitted to the experimental and simulated $K(P)$ data of Fig. 4

System	$K(P)$ data	Fitting function					
		Linear	eq (18)	eq (19)	eq (20)	eq (21)	eq (22)
1,2-dichloroethane	experimental ^{5b}	-2.7	-4.3	-4.2	-4.3	-4.2	-4.3
	experimental ^{5e}	-0.6	-1.1	-2.0	-2.1	-2.3	-2.1
	simulated	-1.8	-2.7	-3.0	-3.4	-3.2	-3.5
2-chlorobutane	experimental ^{6a}	-1.5	-1.1	-1.5	-1.1	-1.5	-1.5
	simulated	-0.8	-1.3	-2.0	- ^a	-2.7	- ^a
1-bromobutane	experimental ^{6c}	-0.8	-1.6	-1.6	-1.6	-1.6	- ^a
	simulated	-0.6	-0.7	-0.7	-0.7	-0.7	-0.7
1-bromopentane	experimental ^{6c}	-1.0	-1.2	-1.3	-1.2	-1.3	-1.2
	simulated	-0.6	-0.9	-1.0	-0.9	-1.0	-0.9
1-bromohexane	experimental ^{6c}	-0.5	-0.6	-0.6	- ^a	-0.6	- ^a
	simulated	-0.5	-0.6	-0.6	- ^a	-0.6	- ^a

^a Failed fit (see text).