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Communication

Intramolecular London Dispersion Interactions Do Not Cancel in Solution

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ABSTRACT: We present a comprehensive experimental study of a di-*t*-butyl-substituted cyclooctatetraene-based molecular balance to measure the effect of 16 different solvents on the equilibrium of folded versus unfolded isomers. In the folded 1,6-isomer, the two *t*-butyl groups are in close proximity (H···H distance ≈ 2.5 Å), but they are far apart in the unfolded 1,4-isomer (H···H distance ≈ 7 Å). We determined the relative strengths of these noncovalent intramolecular $\sigma-\sigma$ interactions via temperature-dependent nuclear magnetic resonance measurements. The origins of the interactions were elucidated with energy decomposition analysis at the density functional and *ab initio* levels of theory, pinpointing the predominance of London dispersion interactions enthalpically favoring the folded state in any solvent measured.

London dispersion (LD), the attractive part of the van der Waals potential,[1] is ubiquitously present but often underestimated.[2] This is particularly true for molecules in solution, where it is often assumed that LD is overridden by solvent effects.[3] Recently, this view has been carefully refined,[4−9] but an analysis of a nonpolar molecular balance that avoids additional interactions arising from (local) dipoles is still lacking.[10] Hence, by utilizing a pure hydrocarbon balance, we show here that solvents do affect LD interactions, mostly through changes in the solvent reorganization entropy, but that LD enthalpically remains constant and comparable to gas-phase values. We employ the sterically very different bond shift isomers of 1,4- and 1,6-di-*t*-butyl cycloocta-1,3,5,7-tetraene (**1,4-** and **1,6-COT**, Figure 1) and demonstrate that the thermodynamic preference for LD-stabilized but visually more crowded **1,6-COT** isomer is preserved across 16 solvents ranging from polar to apolar as well as from protic to aprotic.

Highly functionalized molecular balances bearing heteroatoms "fold" (having a preference for the more crowded structure) due to a multitude of interactions (polar, induced dipolar, hydrogen bonding, etc.) and therefore make it difficult to discern these effects from unperturbed LD interactions. A case in point is the often employed "Wilcox−Tröger base-torsion balance" that was initially developed to evaluate nonbonding intramolecular interactions between aromatic rings.[11] Rigid and polar *N*-arylamide balances led to the conclusion that LD is only a small component of the aromatic stacking interaction in solution, in contrast with its dominant role *in vacuo*;[12] the theoretically predicted distance dependence (R^{-6}) of the observed LD stabilization was also confirmed.[13]

Strikingly, the often invoked aryl $\pi-\pi$ interactions are also mimicked by nonaromatic, highly polarizable groups such as cyclohexyl and *t*-butyl ("$\sigma-\sigma$ interactions"[14]) that show the same conformational preference for the chemically less intuitive "folded" state.[15] A pertinent example is the favored all-*cis* conformation of 1,3,5-tribromo-2,4,6-trineopentylbenzene in fluorobenzene.[16] Subsequent investigations suggested based on a comparison of perfluoroalkane versus alkane chain folding that the LD contributions are largely attenuated in solution in reference to computed gas-phase values. Whereas LD was deemed non-negligible, solvophobic effects were found to be dominant in driving the association of apolar chains in aqueous solution.[7]

In choosing an optimal balance to determine solvent effects on LD interactions, we followed the suggested guidelines.[19] Such a balance should display high symmetry, show distinguishable NMR signals at variable temperatures, and have a reasonably low barrier for interconversion of the folded

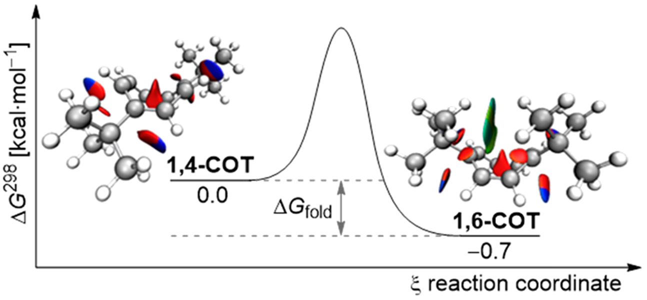

Figure 1. Simplified equilibrium of 1,4- and 1,6-COT. The noncovalent interaction (NCI) surfaces (CCSD(T)/CBS//MP2/cc-pVTZ) are colored on a blue−green−red scale according to an isovalue $s(\rho)$ of 0.35, ranging from $\rho(r)$ −0.025 to 0.025 Å. Blue indicates strong attractive interactions, green corresponds to weak NICs, and red indicates strong repulsion.[17,18] (See the SI.)

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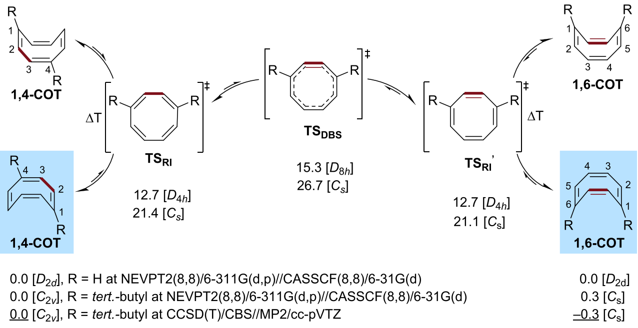
and unfolded states. We found that **1,4-** and **1,6-COT** perfectly fulfill these guidelines and therefore chose this system to determine the effects of LD on its folding preference in a large variety of solvents.[20]

The determination of pure LD interactions in solution is challenging because electrostatic and inductive interactions as well as solvophobic effects favor folding.[21] The energy differences in hydrocarbon configurational isomers are often rather low, and the barriers for their interconversion are high. In most cases, only Gibbs free energies (ΔG) are discussed because they can be determined directly from temperature-dependent equilibrium measurements. Free energies, however, are rather difficult to interpret due to the often encountered enthalpy (ΔH) and entropy (ΔS) compensation.[22] Second, in a first approximation, LD is temperature-independent,[23] so it is instructive to analyze ΔH and ΔS separately. This is important because LD contributes to ΔH, whereas ΔS reflects the disorder of the solute and predominantly solvent reorganization.[24] Our experiments provide the standard isomerization enthalpies ($\Delta_r H^\ominus$) and entropies ($\Delta_r S^\ominus$) assuming that both are temperature-independent within the chosen experimental window (20−80 °C).

The **COT** isomers considered here were first synthesized by Streitwieser et al.,[20] and a molecular mechanics study helped rationalize the unexpected preference for the apparently more crowded isomer in terms of "intramolecular van der Waals attraction"[25] as early as 1982.[26] Shortly thereafter, Paquette et al. synthesized **1,4-** and **1,6-COT** along a different route, confirming the preference of the more crowded diastereomer in C_6D_6[27] and $CDCl_3$.[25] These results were confirmed and refined in 1992 by Anderson and Kirsch, who demonstrated that with increasing substituent size the preference for the more crowded structure increases on the basis of attractive steric interactions.[28] Early semiempirical[29] and force-field studies[26] on a series of disubstituted COT isomers also suggested that LD might be solely responsible for the observed preference. Remarkably, these pivotal studies have largely been overlooked. The advent of modern computational and improved spectroscopic techniques as well as an improved synthetic approach (*vide infra*) prompted us to study this fascinating system in more detail.

Scheme 1 displays an idealized computed version of the complex valence shift isomerization (VSI) in cyclooctatetraenes;[30] there is spectroscopic evidence of the planar singlet double-bond shift transition state $\mathbf{TS_{DBS}}$ of the parent COT that formally violates Hund's rule.[31] Both di-*t*-butyl isomers individually undergo conformational ring isomerization through $\mathbf{TS_{RI}}$ and $\mathbf{TS_{RI}}'$, which are connected via rate-limiting $\mathbf{TS_{DBS}}$, whose description requires multiconfigurational wave functions (such as CASSCF), which do not, however, treat LD in a balanced fashion. The energy of $\mathbf{TS_{DBS}}$ implies that this equilibration will require significant time at ambient temperatures (*vide infra*). The 11.4 kcal mol^{-1} higher energy of the di-*t*-butyl-substituted COT versus the unsubstituted system at TS_{DBS} may be attributed to twice the *t*-butyl strain of ~6 kcal mol^{-1} reported for the axial *t*-butyl ring strain on cyclohexane.[32] Notwithstanding the complexity of the equilibration, only the 1,4- and 1,6-valence bond isomers are observable and can readily be distinguished via NMR spectroscopy (Figure S19). Gratifyingly, the agreement between experimental and computed (enso/xTB) splitting patterns is also in good agreement (Figure S14).

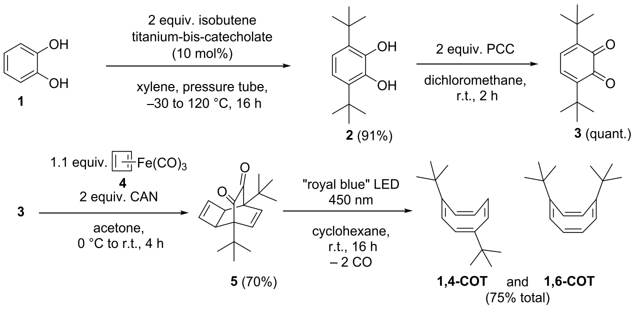
Scheme 1. Computed Double-Bond Valence Shift (DBS) and Ring Inversion (RI) of Cyclooctatetraene Enthalpies (ΔH_0) at the Level Given[a]



[a]See the SI for details.

We synthesized **1,4-** and **1,6-COT** utilizing a modification of Paquette's route starting with an ortho-alkylation of **1** using the method of Ershov et al. (Scheme 2).[33] This was followed by a Corey−Suggs oxidation[34] of 3,6-di-*t*-butyl-pyrocatechol (**2**) to 3,6-di-*t*-butyl-*o*-benzochinone (**3**). The Diels−Alder reaction of **3** with cyclobutadiene iron(II) tricarbonyl (**4**), synthesized via Pettit's method,[35] gave 1,6-di-*t*-butyltricyclo[4.2.2.0$^{0.25}$]-deca-3,7-diene-9,10-dione (**5**) as a storable COT precursor from which the target compounds **1,4-** and **1,6-COT** can be prepared cleanly right before the NMR measurements via Strating−Zwanenburg photodecarbonylation.[36] For the synthesis, see the SI.

Scheme 2. Synthesis of the Target Structures[a]



[a]PCC, pyridinium chlorochromate; CAN, ceric(IV) ammonium nitrate; LED, light-emitting diode.

We decided to take 16 of the most common organic solvents covering most parameters of the empirical solvent polarizability (SP) and solvent polarity−polarizability (SPP) scale established by Catalán and Hopf[37] to estimate their influence on the COT equilibrium. Because **1,4-** and **1,6-COT** are barely soluble in water and hexafluorobenzene, the equilibrium constant (K_{eq}) could not be determined in these.[38] We allowed the isomeric mixtures to equilibrate for at least 1 h at each temperature inside the NMR spectrometer (see details in the SI) by initially warming the sample to the highest possible temperature for a given solvent and decreasing it in 5−10 °C steps immediately thereafter. The resulting experimental data are summarized in Figure 2. Whereas the values of neither Streitwieser et al.[25] nor Paquette et al.[39] (both are different) were reproduced, our results agree well with the most recent measurements of Anderson and Kirsch in the same temperature regime (Figure S1).[28]

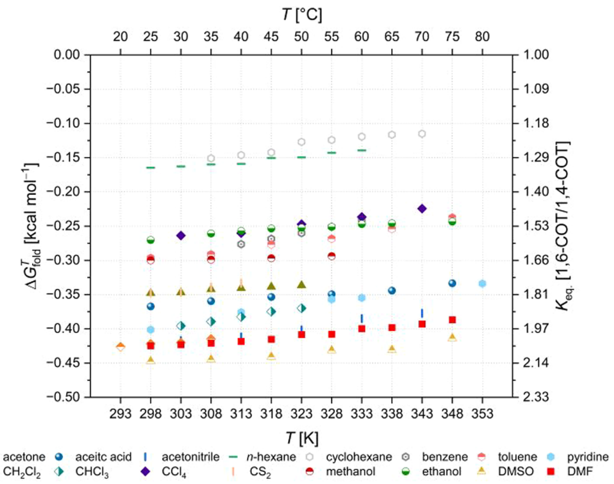


Figure 2. Temperature-dependent Gibbs free energies and equilibrium constants of the **1,4-** and **1,6-COT** equilibrium in various solvents.

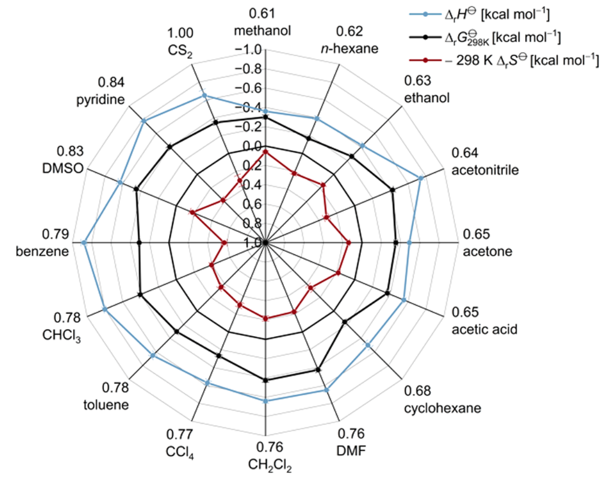


Figure 3. Correlation of thermodynamic quantities at 298 K in kcal mol^{-1} with clockwise increasing relative solvent polarizabilities (min = 0.00 vacuum, max = 1.00 CS_2) (Catalán−Hopf SP scale[37]).

In looking at K_{eq} always being larger than unity, it is clear that **1,6-COT** is *always* favored, just to different degrees depending on the solvent. Whereas solvents of low polarity show the smallest preference for the folded isomer, it is highly favored in polar and chlorinated solvents, which shows that the inductive effect of the dipole moment also is present. Remarkably, the $\Delta_r H^{\ominus}$ values cover a range of only −0.4 to −0.9 kcal mol^{-1} over this wide range of solvents, indicating that the preference for **1,6-COT** is an intrinsic structural property. We therefore conclude that the isomer structures are comparable in different solvents and that the enthalpic intramolecular LD stabilization of **1,6-COT** must be rather similar. The $\Delta_r S^{\ominus}$ values extrapolated from the intercepts with the ordinate vary considerably and thereby have a much larger effect on the $\Delta_r G^{\ominus}$ values. Entropy consistently favors **1,4-COT**, which is at odds with simple symmetry considerations that would favor the C_s over the C_2 symmetric structure due to its reduced rotational symmetry number.[40] Thus we attribute the entropy changes to solvent reorganization. Because of the small changes in enthalpy and the large entropic contributions, we estimate an enthalpy−entropy compensation temperature range of 291 ± 57 K over all 16 solvents (Figure S4). This indicates that only at elevated temperatures, for all solvents above their boiling point, is LD overcome by entropy. We choose 298 K as the temperature for comparing our results for $\Delta_r G^{\ominus}$ (Figure 3).

The $\Delta_r H^{\ominus}$ values increase steadily with increasing solvent polarizabilities, with the exception of a few outliers like DMSO and acetonitrile (Figure 3). This intriguing finding is hard to rationalize and strongly contradicts the importance of competitive dispersive solute−solvent interactions that are thought to diminish LD interactions in solution.[41] Accordingly, comparing the results within solvent groups, we do see trends: In hydrocarbons, the **1,6-COT** preference is proportional to increasing polarizability, hexane < cyclohexane < toluene < benzene. The same is true for chlorinated solvents, CH_2Cl_2 < CCl_4 < $CHCl_3$, and for alcohols with methanol < ethanol. This contradicts the expected simple correlation between solvent polarizability and LD interactions with and within the solute.

Because only LD interactions play a role in solute−solvent interactions, the polar effects of permanent dipole moments have to be taken into account as well. A benchmark study showed that the best results for dipole computations are obtained by the ωB97xD/cc-pVQZ level of theory.[42] The computed gas-phase dipole moments of **1,4-** and **1,6-COT** are rather small (**1,6-COT**, 0.6 D; **1,4-COT**, 0.1 D) but might favor **1,4-COT** in the gas phase and nonpolar solvents. For comparison, the difference in dipole moments between toluene (0.4 D)[43] and benzene (0.0 D)[43] is similar. Taking solvent polarity into account, we find that highly polar solvents indeed favor the population of the higher dipole moment **1,6-COT** isomer. However, this cannot necessarily be traced back to an increased enthalpic interaction but to a favorable entropic origin. One might envision that competition of the solute for dipolar interactions with the solvent disrupts the organized internal structure of the solvent, resulting in a favorable solvent entropy contribution. Because the computed solvent-accessible area of **1,4-COT** (260 Å^2) is even larger than that of **1,6-COT** (256 Å^2), solvent interactions should favor **1,4-COT**.

Having established the given preference for the more crowded isomer irrespective of the environment, we returned to a more detailed molecular analysis and took the B3LYP-D3(BJ)/def2-QZVPP optimized geometries, removed the COT moiety, and saturated the resulting radicals with hydrogen (Figure S18). This should bring the "isolated" interactions of the alkyl groups depicted in the NCI plot in Figure 1 as a green surface to the fore by excluding the COT moiety. To separate electrostatic and inductive effects from the LD, we used symmetry-adapted perturbation theory (DF-SAPT2/aug-cc-pVTZ),[44] which revealed that LD is the largest component of all evaluated interactions, in particular, in **1,6-COT**. Apart from Pauli exchange repulsion, all other contributors (electrostatics and induction together) favor **1,6-COT** by ∼0.5 kcal mol^{-1}, in good agreement with our other energy evaluations (summarized in the SI). In line with this finding, the **1,4-** and **1,6-COT** isomers are almost isoenergetic at the Hartree−Fock level, and the preference for the more crowded structure only comes from the electron correlation, which is the quantum-mechanical origin of LD.

Counterintuitively, intramolecular LD interactions favor the visually sterically more demanding **1,6-COT** isomer in all solvents measured. This preference is assisted by induction and electrostatics, which, in sum, counterbalance the Pauli exchange repulsion. LD is thereby the largest single energy

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contributor. The equilibrium $\Delta_r H^\ominus$ values vary from −0.4 to −0.9 kcal mol^{-1}, whereas $\Delta_r G^\ominus$ values at 298 K (−0.2 to −0.4 kcal mol^{-1}) attenuate these by a positive entropy contribution arising from solvent reorganization. Even though this partial enthalpy−entropy compensation is apparent, it does not qualitatively change the preference for the more crowed structure that is stabilized through intramolecular LD interactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09597.

Comparison with previous measurements as well as synthetic and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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