JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b10098 • Publication Date (Web): 25 Oct 2017

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Chasing weak forces: hierarchically assembled helicates as a probe for the evaluation of the energetics of weak interactions

David Van Craen,[†] Wolfgang Hubertus Rath,[†] Marina Huth,[†] Laura Kemp,[†] Christoph Räuber,[†] Jan Wollschläger,[‡] Christoph Schalley,[‡] Arto Valkonen,[§] Kari Rissanen[§] and Markus Albrecht*[†]

† Institut für Organische Chemie, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany, E-mail: markus.albrecht@oc.rwth-aachen.de; ‡ Institut für Chemie und Biochemie - Organische Chemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany; § University of Jyvaskyla, Department of Chemistry, Nanoscience Center, Survontie 9 B, 40014 Jyväskylä, Finland

KEYWORDS Helicate, self-assembly, London dispersion, thermodynamics

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ABSTRACT: London dispersion forces are the weakest interactions between molecules. Because of this, their influence on chemical processes is often low, but can definitely not be ignored and even becomes important in case of molecules with large contact surfaces. Hierarchically assembled dinuclear titanium(IV) helicates represent a rare example in which the direct observation of London dispersion forces is possible in solution even in the presence of strong cohesive solvent effects. Hereby, the dispersion forces do not unlimitedly support the formation of the dimeric complexes. Although they have some favorable enthalpic contribution to the dimerization of the monomeric complex units, large flexible substituents become conformationally restricted by the interactions leading to an entropic disadvantage. The dimeric helicates are entropically destabilized.

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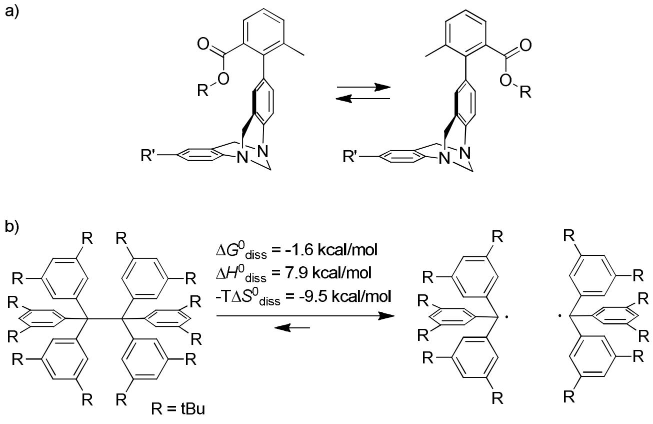
1. *Introduction*

Weak inter- or intramolecular interactions[1] are essential for the properties of molecules. For example, biomaterials are built from covalently connected sub-units (e.g. amino acids) adopting an overall structure which is mainly controlled by weak non-covalent interactions including dispersion forces, solvophobic/-philic effects (e.g. hydrophobicity), or dipole-dipole interactions which finally may result in a special function.[2] Weak forces are essential in chemical reactions and catalysis by stabilizing transition states and thus lead to specific products with high selectivity.[3]

In the solid, crystal structure analysis reveals many intermolecular contacts which indicate weak London dispersion forces.[4,5] Those even can stabilize unusual species.[6] Here, such weak interactions are driving forces e.g. for a specific crystal packing. On the other hand, in the gas phase, non-covalent aggregates based on weak interactions can be observed relatively easily by different techniques and can be characterized[7] by e. g. microwave spectroscopy.[8]

In contrast to this, the situation is much more complicated in solution as in the other two states, due to the presence of many competing interactions like London dipolar interactions and solvent effects. In an intriguing early approach, Wilcox introduced a molecular balance for the determination of weak interactions[9] (Scheme 1, a) which was further applied by Diederich,[10] Hunter,[11] Shimizu[12] and others.[13] Especially, Hunter pointed out that the measured interaction between the alkyl substituents is strongly influenced by solvent effects like solvophobicity and coherence of the solvent molecules.[11,14]

Scheme 1. A molecular balance developed by Wilcox for the determination of weak interactions between substituents R and R' (a) and the dissociation of a *t*-butyl substituted hexaphenyl ethane derivative stabilized by London dispersion interaction of the t-butyl groups.

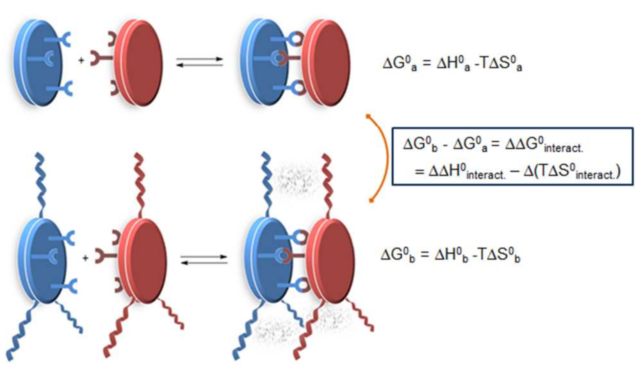


Thus, in order to study weak forces like Van der Waals interactions and London dispersion in solution, strong competitive solvent effects have to be considered. One way to separate the weak binding forces from the latter is to measure solvent-dependent energetics of the process in question.[15] However, variation of the solvent obviously reveals the energetics of the solvent effects and allows only a rough estimation of binding energies, e.g. due to London dispersion. In order to measure London dispersion forces more directly, the focus should be on the molecule which can be varied in a stepwise fashion and is measured in only one solvent. This way, energetics due to London dispersion interactions may become observable.

Recently, the Schreiner et al reported a hexaphenylethane derivative which is stable in the solid state due to London dispersion interaction between *t*-butyl groups as substituents.[6a] Upon dissolution in benzene, the "dimer" partly dissociates into the monomeric radicals revealing a monomer-dimer equilibrium (Scheme 1, b). The dissociation energies are determined and it is found that dissociation is entropically highly favored due to restriction of *t*-butyl rotation by attractive London dispersion.[16]

The latter example may act as a blueprint for the development of a new probe for the determination of weak forces in solution. Therefore an easily available and observable dimer-monomer system has to be made and the substituents at the basic units have to be systematically varied. Interaction between the substituents will modulate the monomer-dimer equilibrium in addition to the direct interaction between the two monomers.[16,17]

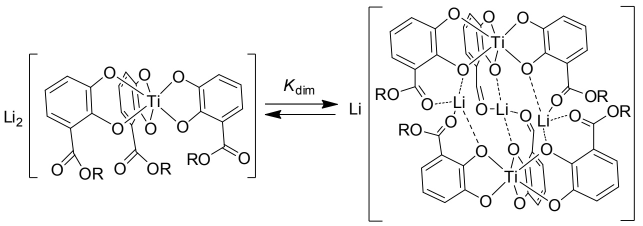
Scheme 2. Schematic representation of a monomer-dimer equilibrium which allows the determination of weak interactions between substituents located at the rim of the molecular components.



In 1987, Lehn introduced the term "helicate" for self-assembled coordination compounds with one or more covalently connected ligand strands twisting around two or more metal centers.[18] Hierarchically assembled helicates with metal ion[19] or hydrogen bridged ligands[20] appeared a few years later. Here, the assembly of the helicates is based on two recognition events: (1) formation of a Werner-type complex and (2) dimerization. In addition, cluster helicates with two terminal complex units being connected by a central metal cluster have to be mentioned.[21] Related covalently linked imine-type helicates were investigated by Hannon and Nitschke within the context of subcomponent self-assembly.[22]

In 2005, we described hierarchically assembled dimeric helicates which in solution are in equilibrium with the corresponding monomers.[23] Those helicates are easy to obtain by self-assembly from synthetically readily available components and provide an ideal platform for the study of weak interactions between appending substituents following the concept presented in Scheme 2. Hereby, a monomeric titanium triscatecholate unit can dimerize in the presence of lithium ions to yield the corresponding dinuclear helicate. The monomer-dimer equilibrium can be easily observed by NMR spectroscopy and K_{dim} as well as other thermodynamic parameters are readily measured.[24] In the monomer the ligands equilibrate fast between syn and anti orientation and the three alkyl groups are well separated, while upon dimerization of the syn isomer to the helicate ester groups of the two monomeric units come into close contact and are able to interact.

Scheme 3. Monomer-dimer equilibrium of ester-substituted catecholate-based hierarchically formed triply lithium-bridged helicates.



In order to determine the dimerization constants of the helicates, some restrictions need to be considered: (i) The complexes are not soluble in non-polar solvents. (ii) In some solvents (e.g. THF, methanol) only the dimer can be observed by NMR spectroscopy due to high dimerization constants. Here, a reliable determination of equilibrium constants is not possible. (iii) Protic solvents (e. g. water, methanol) strongly interfere with dimer formation (by forming hydrogen bonds to the catecholate and ester oxygen atoms) and make the spectroscopic identification of subtle interactions impossible.[23] As an advantage, on the other hand, over Wilcox' molecular balance, the dimeric complexes possess threefold symmetry, leading to a threefold interaction and make very weak energies observable by triplication.

2. *Results and discussion*

Four different series of alkyl-type ester ligands **1-4**-H_2 and the corresponding titanium complexes $Li[Li_3(\mathbf{1\text{-}4})_6Ti_2]$ have been prepared and characterized.[25] Subsequently, thermodynamic studies (determination of K_{dim}, van't Hoff analyses[26]) have been performed in DMSO-d_6.

We are not aware, that similar studies with a systematic variation of the chain length have been performed in case of *n*-alkyl substituted molecular balances. In case of the

Wilcox-type molecular balances, either a restricted number of compounds was investigated in many different solvents or modifications have been done at aromatic substituents to alter their electronics or sterics. Alkyl groups have not been studied with a systematic variation.[9-13]

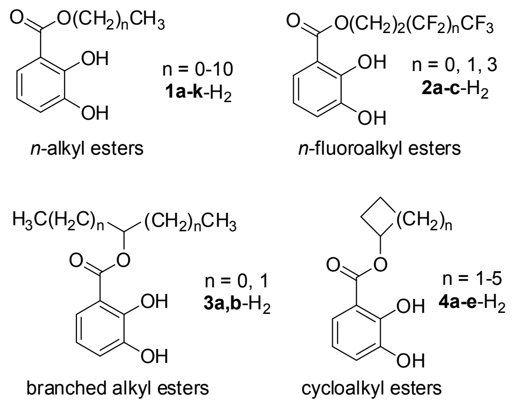


Figure 1. Four different series of ligands as building blocks of hierarchically formed triply lithium-bridged helicates.

Crystal structures of hierarchically formed helicates.

Crystals of sufficient quality for the single X-ray diffraction analysis of the ethyl $\mathrm{Li[Li_3(\mathbf{1b})_6Ti_2]}$, cyclobutyl $\mathrm{Li[Li_3(\mathbf{4a})_6Ti_2]}$ and cyclopentyl esters $\mathrm{Li[Li_3(\mathbf{4b})_6Ti_2]}$ have been obtained by slow evaporation of the mother solvent. The corresponding structures of methyl $\mathrm{Li[Li_3(\mathbf{1a})_6Ti_2]}$[23] and isopropylesters $\mathrm{Li[Li_3(\mathbf{3a})_6Ti_2]}$[24e] were published earlier. For the ethyl compound $\mathrm{Li[Li_3(\mathbf{1b})_6Ti_2]}$, close contacts of the ethyl substituents to neighboring catechol units are observed, while no interactions between adjacent ethyl groups can be found ($\mathrm{CH_{ethyl}\cdots C_{aryl}}$ = 2.78, 2.90 or 3.05 Å, closest $\mathrm{CH_{ethyl}\cdots CH_{ethyl}}$ = 5.41 Å). The more bulky isopropyl substituents of $\mathrm{Li[Li_3(\mathbf{3a})_6Ti_2]}$ are filling up the cleft of the helicate much better and alkyl-alkyl contacts are observed in addition to short alkyl-aryl distances ($\mathrm{CH_{iPr}\cdots C_{aryl}}$ = 3.34 Å, $\mathrm{CH_{iPr}\cdots CH_{iPr}}$ = 2.62 Å). In the cyclobutyl derivative $\mathrm{Li[Li_3(\mathbf{4a})_6Ti_2]}$, the $\mathrm{CH_2\text{-}CH\text{-}CH_2}$ angle at the methine carbon ($\mathrm{CH_2\text{-}CH\text{-}CH_2}$ = 90°) is smaller as in isopropyl ($\mathrm{CH_2\text{-}CH\text{-}CH_2}$ = 110°) due to the small ring size. This compression at the secondary carbon atom leads to longer distances between neighboring cyclobutyl groups ($\mathrm{CH_{cy\text{-}Bu}\cdots C_{aryl}}$ = 2.92, 3.03 Å, shortest $\mathrm{CH_{cyBu}\cdots CH_{cyBu}}$ = 3.97 Å). The cyclopentyl substituent of $\mathrm{Li[Li_3(\mathbf{4b})_6Ti_2]}$ is a bit more expanded ($\mathrm{CH_2\text{-}CH\text{-}CH_2}$ = 106°) than the corresponding four membered ring, but somewhat smaller than isopropyl. Short alkyl-alkyl contacts are observed ($\mathrm{CH_{cyPent}\cdots CH_{cyPent}}$ = 2.66, 2.88 Å, $\mathrm{CH_{cyPent}\cdots C_{aryl}}$ = 3.01 Å).

The results of X-ray diffraction studies indicate London dispersion interactions between the ester side chains in the solid state.[27] However, they highly depend on the size of the corresponding moiety. In the described examples, ethyl groups are not ideal for interalkyl London interactions because they are too separated in the dimeric complex. However, they show some CH-π interactions.[28] In case of longer *n*-alkyl chains dispersion interactions indeed become possible between the peripheral parts of the alkyl groups. In case of the branched secondary alkyl ester the ability for alkyl-alkyl interactions highly depends on the $\mathrm{CH_2\text{-}CH\text{-}CH_2}$ angle[29] controlling the bulkiness of the substituent.

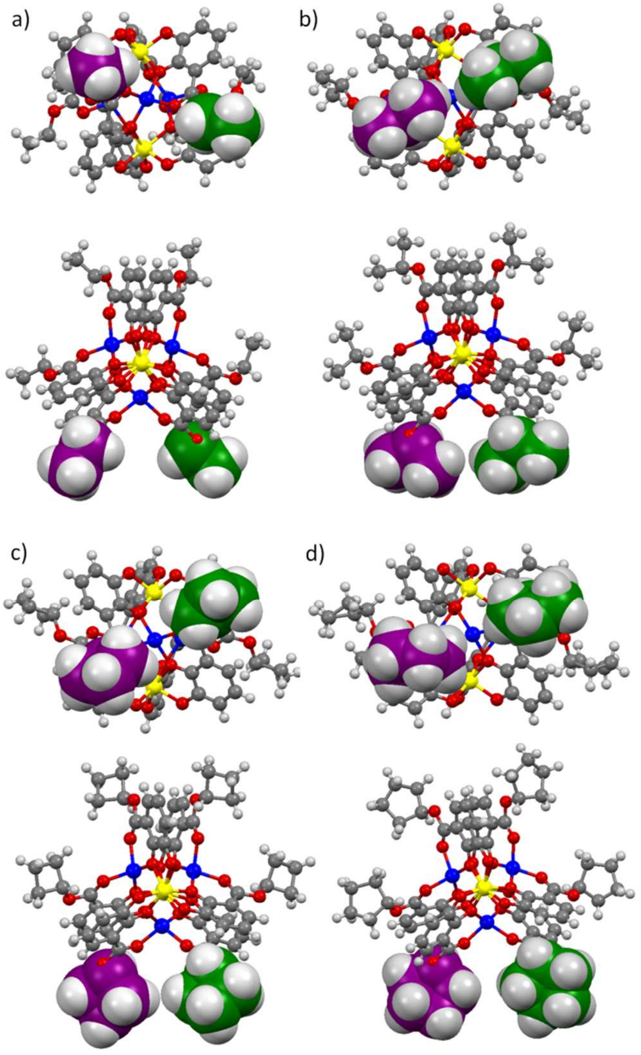


Figure 2. Structures of the anions $\mathrm{[Li_3(\mathbf{1b})_6Ti_2]^-}$ (a), $\mathrm{[Li_3(\mathbf{3a})_6Ti_2]^-}$ (b), $\mathrm{[Li_3(\mathbf{4a})_6Ti_2]^-}$ (c), and $\mathrm{[Li_3(\mathbf{4b})_6Ti_2]^-}$ (d). Side view (top) and view down the Ti-Ti axis. Ti: yellow, Li: blue, C: grey, H: white, C-atoms of representative neighboring alkyl groups are colored in purple and green.

Thermodynamic investigations

Thermodynamic studies of the dimerization process are mainly performed by NMR spectroscopy (DMSO-d_6). K_{dim} of the monomer dimer equilibrium $\mathrm{Li_2[(\mathbf{1\text{-}4})_3Ti]/Li[Li_3(\mathbf{1\text{-}4})_6Ti_2]}$ are shown in Figure 3. In the *n*-alkyl ester series, the methyl ester $\mathrm{Li[Li_3(\mathbf{1a})_6Ti_2]}$ possesses the lowest dimerization constant which rises upon elongation of the chain and reaches a maximum with heptyl ($\mathrm{Li[Li_3(\mathbf{1g})_6Ti_2]}$), beyond which it drops again. The dramatic change from the methyl ($\mathrm{Li[Li_3(\mathbf{1a})_6Ti_2]}$) to the ethyl

(Li[Li_3(**1b**)$_6$$Ti_2$]) derivative can be explained with different inductive effects of the alkyl groups on the lithium coordination at the ester carbonyl. This electronic effect becomes less important upon elongation of the chain and does not play a significant role starting with propyl or butyl.[30] Fluorination of the outer alkyl chain leads to complexes Li[Li_3(**2**)$_6$$Ti_2$] with dimerization constants K_{dim} much lower than those of the non-fluorinated analogues. In the fluorinated series, K_{dim} increases somewhat from the trifluoropropane derivative to the nonafluoro hexane.

For open chain branched systems Li[Li_3(**3**)$_6$$Ti_2$], K_{dim} drops from the isopropyl ester to the 3-pentyl derivative for sterical reasons. In case of the cyclic esters, K_{dim} increases from smaller (cyclobutyl) Li[Li_3(**4a**)$_6$$Ti_2$] to bigger (cyclooctyl) ring size Li[Li_3(**4e**)$_6$$Ti_2$].

Interestingly, the sterically highly demanding isopropyl ester Li[Li_3(**3a**)$_6$$Ti_2$] possesses the same dimerization constant as the corresponding *n*-propyl ester Li[Li_3(**1c**)$_6$$Ti_2$]. The even bigger *t*-butyl ester-substituted complex is sterically so congested that the dimer cannot be formed anymore while the dimerization constant drops dramatically for the 3-pentyl ester Li[Li_3(**3b**)$_6$$Ti_2$] as compared to isopropyl Li[Li_3(**3a**)$_6$$Ti_2$].

Table 1. K_{dim} [L/mol] as well as ΔG°, ΔH° and -TΔS° [kJ/mol] measured by ^{1}H NMR for the monomer-dimer equilibrium of Li[Li_3(L)$_6$$Ti_2$].

Complex	K_{Dim}	ΔG°	ΔH°	-TΔS°
Li[Li_3{(**1a**)$_3$Ti}$_2$]	175±20	-12,82	-10,95	-1,87
Li[Li_3{(**1b**)$_3$Ti}$_2$]	830±100	-16,67	-17,32	0,67
Li[Li_3{(**1c**)$_3$Ti}$_2$]	1095±135	-17,35	-18,13	0,83
Li[Li_3{(**1d**)$_3$Ti}$_2$]	1195±145	-17,57	-18,82	1,32
Li[Li_3{(**1e**)$_3$Ti}$_2$]	1920±240	-18,74	-19,83	1,14
Li[Li_3{(**1f**)$_3$Ti}$_2$]	1530±190	-18,17	-20,92	2,89
Li[Li_3{(**1g**)$_3$Ti}$_2$]	2690±345	-19,58	-20,78	1,27
Li[Li_3{(**1h**)$_3$Ti}$_2$]	2330±300	-19,22	-22,75	3,59
Li[Li_3{(**1i**)$_3$Ti}$_2$]	2410±300	-19,30	-23,28	4,02
Li[Li_3{(**1j**)$_3$Ti}$_2$]	1080±125	-17,32	-21,71	4,47
Li[Li_3{(**1k**)$_3$Ti}$_2$]	810±90	-16,60	-21,76	5,31
Li[Li_3{(**2a**)$_3$Ti}$_2$]	200±20	-13,15	-15,83	-2,67
Li[Li_3{(**2b**)$_3$Ti}$_2$]	205±20	-13,21	-14,70	-1,46
Li[Li_3{(**2c**)$_3$Ti}$_2$]	750±90	-16,41	-17,12	-0,75
Li[Li_3{(**3a**)$_3$Ti}$_2$]	1010±120	-17,14	-17,91	0,85
Li[Li_3{(**3b**)$_3$Ti}$_2$]	50±5	-9,79	-14,65	4,85
Li[Li_3{(**4a**)$_3$Ti}$_2$]	140±15	-12,29	-9,58	-2,68
Li[Li_3{(**4b**)$_3$Ti}$_2$]	560±65	-15,67	-14,49	-1,12
Li[Li_3{(**4c**)$_3$Ti}$_2$]	415±50	-14,94	-15,42	0,52
Li[Li_3{(**4d**)$_3$Ti}$_2$]	970±120	-17,04	-16,89	-0,16
Li[Li_3{(**4e**)$_3$Ti}$_2$]	1145±140	-17,46	-18,50	1,14

The 3-pentyl derivative Li[Li_3(**3b**)$_6$$Ti_2$] may be compared with the cyclopentane ester Li[Li_3(**4b**)$_6$$Ti_2$], in which the terminal groups of 3-pentyl are tethered within the ring system. However, the corresponding dimerization constant of Li[Li_3(**4b**)$_6$$Ti_2$] is found somewhere inbetween the one of the isopropyl and the 3-pentyl-substituted complexes. For the cycloalkane esters, a dimerization constant similar to the isopropyl derivative Li[Li_3(**3a**)$_6$$Ti_2$] is only reached starting with the cycloheptyl derivative Li[Li_3(**4d**)$_6$$Ti_2$]. Obviously, isopropyl fills up the cleft of the helicate as efficiently as cycloheptyl does, while the smaller rings cannot do this due to the smaller angles within the ring.

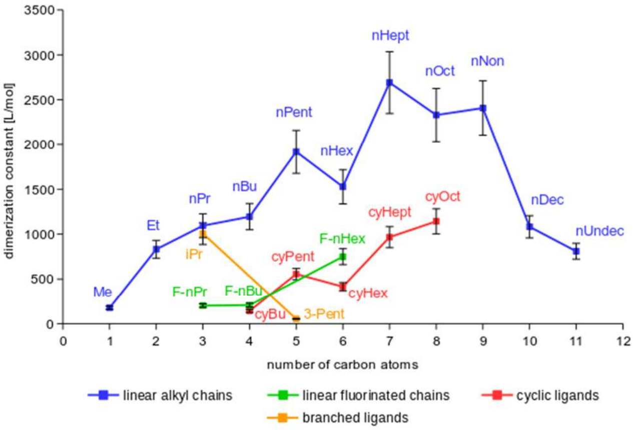


Figure 3. Dimerization constants K_{dim} [L/mol] of *n*-alkyl (blue), branched acyclic alkyl (orange), cycloalkyl (red) and fluorinated alkyl (green) ester derivatives of $[Li_3L_6Ti_2]^-$ depending on the number of carbon atoms of the ester side chain. K_{dim} was determined by NMR at 298 K in DMSO-d_6 containing 0.12 ± 0.04 mol/l of water. Concentrations were 0.002 mol L^{-1}, except for the nonyl-, decyl- and undecyl-substituted helicates, for which the concentration had to be decreased due to low solubility.

In order to get a more profound insight into the thermodynamics, Van't Hoff analyses were performed by NMR.[26] It is found that the dimerization of the *n*-alkyl Li[Li_3(**1**)$_6$$Ti_2$] as well as fluoroalkyl esters Li[Li_3(**2**)$_6$$Ti_2$] are enthalpically more favored with increasing chain length. The plateau and eventually the slight increase in ΔH° for the very long alkyl substituents (**1j,k**) is tentatively assigned to their ability to backfold.[31] For the fluoroalkyl esters, Li[Li_3(**2**)$_6$$Ti_2$] only minor changes can be observed depending on the chain length. The cycloalkane derivatives also show the increase of ΔH° with bigger ring size. Only in case of the branched systems Li[Li_3(**3**)$_6$$Ti_2$] a decrease of enthalpic dimer stabilization is observed due to a strong steric effect in case of the 3-pentyl esters.

The liberation of lithium bound solvent molecules is an entropic advantage for dimerization.[23] In case of the ethyl ester Li[Li_3(**1b**)$_6$$Ti_2$], however, the restrictions of alkyl group flexibility override this effect and entropy becomes unfavorable. Surprisingly, it becomes even more unfavorable by the stepwise elongation of the alkyl chain, even upon elongation far out of the cleft of the molecule. This can be explained by an "attractive" interaction between the alkyl groups leading to an enthalpic favorization of the dimerization, but restricting the flexibility of the chains.

For the fluorinated compounds, effects of chain variation are very small. Dimerization becomes enthalpically slightly more favorable and slightly less favored entropically with longer chain length. The very small energetic differences indicate that here no strong interactions between the side groups occur and that parts pointing out of the cleft are not restricted in flexibility by interaction with other chains.

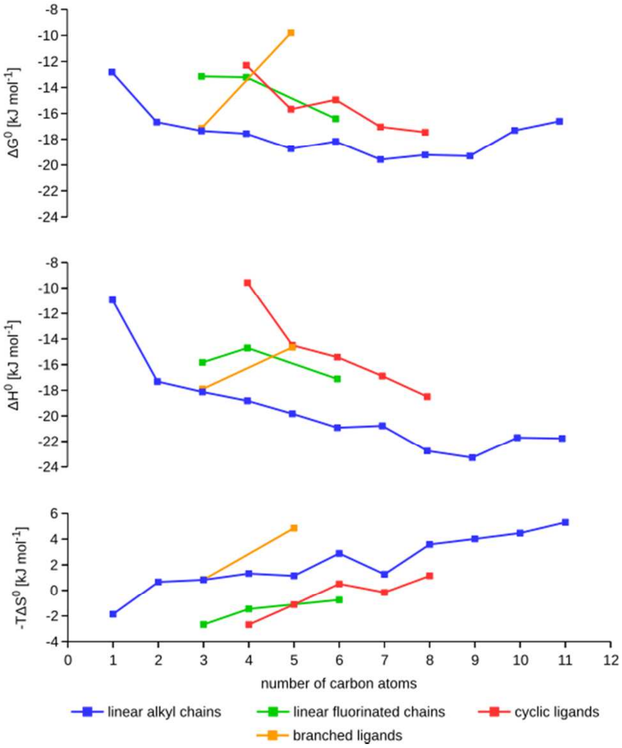


Figure 4. Gibbs free energy (ΔG^o, enthalpy (ΔH^o), as well as entropy ($-T\Delta S^o$) changes for the dimerization of substituted complexes $[Li_3\mathbf{L}_6Ti_2]^-$ in DMSO-d$_6$.

The thermodynamic trends within series of different ester substituted complexes can thus be summarized in the following way:

n-Alkyl derivatives: In the dimers, the ester alkyl groups undergo weak interactions with each other adding some enthalpic stabilization to the dimer which increases with the length of the alkyl chain. The entropy of dimerization becomes more unfavorable with increasing chain length due to the restriction of the chain mobility.

n-Fluoroalkyl derivatives: In case of the fluorinated compounds, hardly any interaction occurs between the side chains leading to no significant difference in the enthalpic contribution. Entropy of dimerization is always favorable which is traced back to the liberation of solvent molecules upon dimerization. However, a slight increase of $-T\Delta S^o$ is based on slight steric restrictions of the chain mobility.

Open-chain branched alkyl derivatives: The decrease of K_{dim} from the isopropyl to the 3-pentyl ester is dominated by the increasing steric demand of the substituents.

Cycloalkyl derivatives: The cycloalkyl derivatives possess only restricted flexibility at the substituents and the enthalpic contribution becomes dominant over the entropic contribution. The latter becomes slightly unfavorable with larger ring size. Enthalpically, the dimer formation is favored with increasing ring size due to higher contact areas for weak interactions and due to more favorable angles at the methine carbon atom of the ring in order to allow efficient interactions between the substituents. This is also observed in the alkyl-alkyl contacts found in the crystal structures of the cyclobutyl versus the cyclopentyl complexes.

Kinetic studies in THF by ESI mass spectrometry.

Differences in weak interactions may not only be expressed thermodynamically in binding constant differences, but can also have a kinetic effect on the barriers and thus the rates for the exchange of monomers. Such an exchange reaction in solution can easily be monitored by ESI mass spectrometry as the dimeric helicates are singly negatively charged after the abstraction of the lithium counterion that is not incorporated in the helicate structure.[23] This technique opens up a way to study the effect of minor changes of the substituents on the dimerization behavior in solvents which are not appropriate for NMR studies (e.g. THF).

The exchange mechanisms at the dimeric helicates are quite complex as no direct exchange of single catecholate ligands is observed for the dimers. Instead, the dimeric helicates first dissociate into the two monomeric titanium tris-catecholate complexes, which then undergo ligand exchange reactions. Depending on the nature of the solvent, the relative rates of the dimer-to-monomer dissociation and the ligand exchange on the monomers differ. In aprotic solvents, the first reaction is usually faster than the latter, while protic solvents speed up the ligand exchange on the monomers.[23] Irrespective of these details, any exchange – that of intact monomers without a subsequent fast ligand exchange as well as the fast exchange of individual ligands on the monomers – begins with the dissociation of the dimeric helicates into the monomeric titanium tris-catecholates as the rate determining step. These two exchange reactions should therefore both be affected in the same manner by differences in weak forces affecting the transition state for the dimer-to-monomer dissociation.

When two separately generated homodimeric helicates $[Li_3\mathbf{L}^{\mathbf{A}}{}_6Ti_2]^-$ and $[Li_3\mathbf{L}^{\mathbf{B}}{}_6Ti_2]^-$ are mixed, the signal intensity I for the $[Li_3(\mathbf{L}^{\mathbf{A}}{}_3Ti)(\mathbf{L}^{\mathbf{B}}{}_3Ti)]^-$ heterodimeric helicate will increase between $[Li_3\mathbf{L}^{\mathbf{A}}{}_6Ti_2]^-$ and $[Li_3\mathbf{L}^{\mathbf{B}}{}_6Ti_2]^-$, when the exchange of intact monomers is significantly faster than the exchange of individual ligands on the monomers. If instead the ligand exchange on the monomers is fast compared to the dissociation of the dimers into monomers, the signal for $[Li_3(\mathbf{L}^{\mathbf{A}}{}_3Ti)(\mathbf{L}^{\mathbf{B}}{}_3Ti)]^-$ at the same m/z will also grow together with a statistical distribution of all other possible complexes. Without the need to distinguish both processes, we can therefore follow the trends caused by weak interactions by monitoring the signal for the 3:3 heterodimer $[Li_3(\mathbf{L}^A{}_3Ti)(\mathbf{L}^B{}_3Ti)]^-$.

As shown in Figure 5, an exchange parameter Q_{ex} can be defined as the quotient of the intensity *I* of the exchange product $[Li_3(\mathbf{L}^A{}_3Ti)(\mathbf{L}^B{}_3Ti)]^-$ divided by the product of the intensities of the homodimeric helicate ions $[Li_3\mathbf{L}^A{}_6Ti_2]^-$ and $[Li_3\mathbf{L}^B{}_6Ti_2]^-$. The smaller this parameter at a given reaction time, the slower the exchange proceeds and the higher is thus the dissociation barrier for the dimeric helicate into monomeric tris-catecholate complexes.

Figure 5 visualizes the progress of the ligand exchange reaction after 60 minutes reaction time over the average chain length of the helicate side chains for homologous pairs of *n*-alkyl substituted helicates (i.e. Me/Et: chain length 1.5, Et/Pr: chain length 2.5 etc.). Clearly, the Q_{ex} parameter decreases with chain length and thus the dissociation barriers increase in the same series. This indicates stabilizing weak interactions to have an observable effect on the transition state for dimer-to-monomer dissociation. Very interestingly, the decrease of Q_{ex} is more pronounced for side chains of medium length, while the effect decreases for the longer chains. This parallels the thermodynamic contributions of the weak interactions to the stability of the dimeric helicates discussed above.

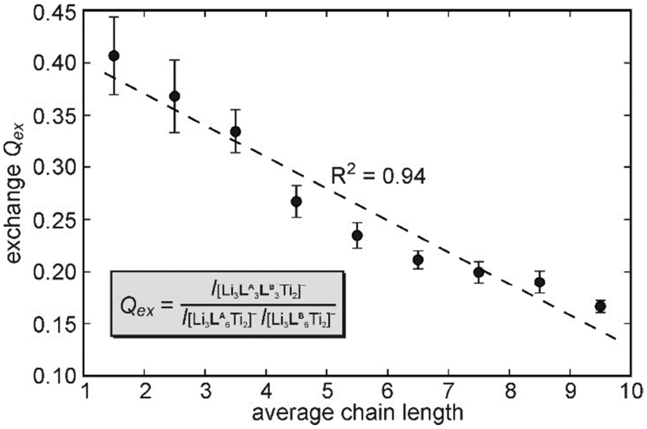


Figure 5. Based on the equation in the inset, an exchange parameter Q_{ex} is defined, which expresses the progress of the exchange reaction after a certain reaction delay (here 60 min). The lengths of the *n*-alkyl side chains attached to the helicates is expressed as the averaged chain length. Data points are plotted for the Me/Et, Et/Pr, Pr/Bu, etc. pairs.

The nature of the inter-substituent interaction in the dimer

The studies described above show that the ester substituents of the titanium catecholates interact with each other in the dimers giving some enthalpic contribution to the dimerization which increases with increasing "size" of the alkyl group. Only in case of the fluorinated complexes $Li[Li_3(\mathbf{2})_6Ti_2]$ as well as of the sterically highly congested derivative $Li[Li_3(\mathbf{3b})_6Ti_2]$, this trend cannot be observed. Parallel to the increase of enthalpy with substituent size the entropic contribution to the dimerization becomes unfavorable.

This behavior shows that the ester substituents undergo some weak interaction overall stabilizing the dimer but resulting in a restriction of chain flexibility leading to a "negative" entropic effect.

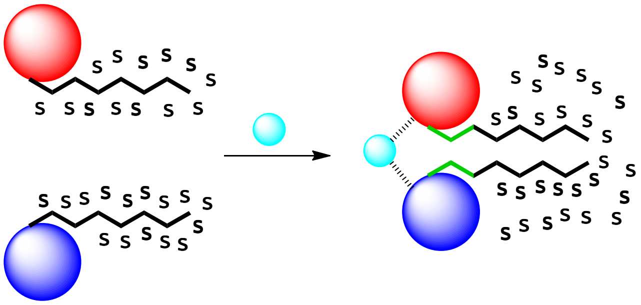


Figure 6. Schematic representation of the alkyl-alkyl interaction upon dimerization of the titanium triscatecholate complexes involving solvent (S) alkyl contact areas which are reduced in the dimer. The green bonds are located within the cleft formed in the dimer and do not have significant solvent contacts.

The question remains as to what the nature of the interaction between the alkyl side groups is. Two different effects can be responsible for the weak interaction which has been observed: (i) London dispersion and (ii) solvophobic effects due to cohesive properties of the solvent. The latter should be especially pronounced in DMSO, but should not be strong in THF which has been used for the ESI MS study.[32]

An answer to the question cannot be given by interpretation of the four separate series of complexes with ligands **1**-**4** as shown in Figures 3 and 4. However, comparison of well-selected examples from the different series provides valuable information. Therefore, complexes from the four different classes of compounds with similar dimerization constants have to be considered. Dimerization constants between 1000 M^{-1} and 1150 M^{-1} have been observed for the *n*-propyl $Li[Li_3(\mathbf{1c})_6Ti_2]$, isopropyl $Li[Li_3(\mathbf{3a})_6Ti_2]$, cyclooctyl $Li[Li_3(\mathbf{4e})_6Ti_2]$ and *n*-decyl $Li[Li_3(\mathbf{1j})_6Ti_2]$ substituted systems. The *n*-propyl as well as isopropyl esters show dimerization constants of $K_{dim}{}^{nPr}$ = 1095 M^{-1} and $K_{dim}{}^{iPr}$ = 1010 M^{-1} with similar enthalpic ($\Delta H^o{}_{nPr}$ = -18.13 kJ/mol, $\Delta H^o{}_{iPr}$ = -17.91 kJ/mol) as well as entropic contributions ($-T\Delta S^o{}_{nPr}$ = 0.83 kJ/mol, $-T\Delta S^o{}_{iPr}$ = 0.85 kJ/mol). From the crystal structure of $Li[Li_3(\mathbf{3a})_6Ti_2]$, it can be seen that the isopropyl substituent is well embedded in the cavity which is formed in the dimer. Thus, solvent exposure is much lower in the dimer as in the monomer. Based on this, the dimerization, which minimizes contact areas, should be favored by solvophobicity of the alkyl groups especially in DMSO.[11,13f] Simple models of the *n*-propyl derivative $Li[Li_3(\mathbf{1c})_6Ti_2]$ as well as the X-ray structure of the corresponding ethyl compound Li[Li_3(**1b**)$_6Ti_2$] show that with short alkyl groups like ethyl or *n*-propyl no effective inter-alkyl London dispersion can take place, but some strong interaction occurs between the alkyl groups and adjacent catecholates. Because of their bulkiness, isopropyl groups come in close contact to each other and enable strong alkyl-alkyl London dispersion interactions. On the other hand, the steric demand of isopropyl might reduce the dimerization energy.

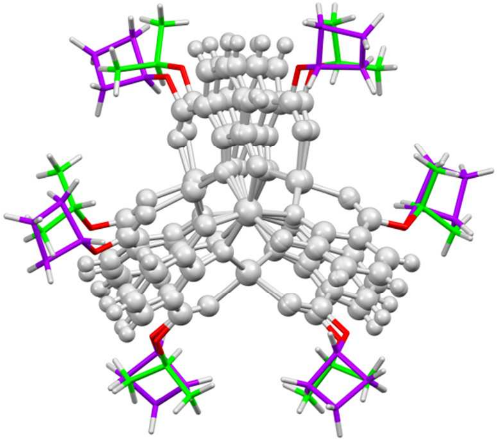


Figure 7. Overlayed structures of the isopropyl Li[Li_3(**1c**)$_6Ti_2$] (green) and the cyclo-butyl derivatives Li[Li_3(**4a**)$_6Ti_2$] (magenta) showing similar sizes of the ester substituents.

Following this, a similar dimerization constant as for isopropyl Li[Li_3(**1c**)$_6Ti_2$] would be expected for the cyclobutyl Li[Li_3(**4a**)$_6Ti_2$] and cyclopentyl derivatives Li[Li_3(**4b**)$_6Ti_2$] if the observed enhancement of the dimerization is based on solvophobic effects. However, the small ring systems show dramatically lower K_{dim} (K_{dim}^{cyBu} = 140 M^{-1}, K_{dim}^{cyPent} = 560 M^{-1}) which is mainly due to a much lower enthalpic contribution to the dimerization while entropy even is favorable for the relatively rigid rings (ΔH^{o}_{cyBu} = -9.6 kJ/mol, $-T\Delta S^{o}_{cyBu}$ = -2.7 kJ/mol; (ΔH^{o}_{cyPent} = --14.5 kJ/mol, $-T\Delta S^{o}_{cyPent}$ = -1.1 kJ/mol). Because of the similar space requirements of the isopropyl and cyclobutyl / cyclopentyl derivatives in the cleft (Figure 7), solvophobic effects cannot cause such a big difference in dimerization energies. The differences can be rather explained by London dispersion interaction between the substituents within the cleft for the cyclic compared to the isopropyl derivative. Upon expansion of the ring size to cycloheptyl or cyclooctyl, the substituent becomes bulky enough for strong London dispersion interactions and the dimerization constant becomes similar to those of the *n*-/isopropyl substituted complexes (K_{dim}^{cyOct} = 1145 M^{-1}) with a strong enthalpic contribution on dimerization (ΔH^{o}_{cyOct} = -18.50 kJ/mol). In this case, the London dispersion interactions probably experience some support by alkyl solvophobicity.

The *n*-decyl derivative Li[Li_3(**1j**)$_6Ti_2$] shows K_{dim}^{nDec} = 1145 M^{-1}. In contrast to the earlier discussed examples, a very strong enthalpic stabilization (ΔH^{o}_{nDec} = -21.71 kJ/mol) occurs while the dimerization is entropically strongly disfavored ($-T\Delta S^{o}_{nDec}$ = 4.47 kJ/mol). This is due to strong London dispersion interactions between the alkyl side chains supported by cohesive forces of the solvent molecules.[33] The mobility of the alkyl chains is reduced by the interaction leading to the entropic penalty.

3. Conclusion

The energetics of lithium cation-dependent dimerization of titanium(IV) triscatecholates bearing esters as substituents in the 3-position of the catecholate ligands is strongly influenced by the nature of the ester substituent. Thermodynamic investigations reveal that side chains weakly interact. In solution, interacting groups may be highly dynamic and their interaction is strongly covered by solvent effects (e.g. solvophobicity). In the case of the hierarchically assembled helicates discussed here, the interaction energies are amplified by the 3-fold symmetry of the system leading to a 3-fold interaction and correspondingly to a much larger interaction energy. This energy contribution to the dimerisation can be observed in the trends of the equilibrium constants depending on chain lengths and structures and thermodynamic as well as exchange parameters can be determined. In case of the linear alkyl substituents, London dispersion forces are observed with more than three or four carbon atoms in the chain. Starting from this chain length, the through-bond inductive effects do not anymore alter the binding of the lithium cations and the groups diverge from the complex. Thus, they have negligible different steric demand in respect to the dimerization. The detailed study of hierarchically assembled dimeric helicates reveals that alkyl substituents typically – and superficially – thought of as innocent, show significant solvophobicity-supported London dispersive interactions in solution. However, enthalpic stabilization is accompanied by a destabilising entropic effect due to conformational fixation of the chain getting more pronounced with longer chain length. Fluorinated derivatives cannot undergo such interactions significantly and do not show this effect. With the more rigid cycloalkanes the entropic effect is significantly reduced. In summary, London dispersion forces are enthalpically beneficial for stabilizing chemical structures, but some significant entropic cost has to be paid.[34]

ASSOCIATED CONTENT

Supporting Information. Synthetic procedures, details on the thermodynamic studies, spectroscopic and spectrometric investigations and on the crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org." For instructions on what should be included in the Supporting Information as well as how to prepare this material for publication, refer to the journal's Instructions for Authors.

AUTHOR INFORMATION

Corresponding Author

* Markus Albrecht, RWTH Aachen University, Institut für Organische Chemie, Landoltweg 1, 52074 Aachen, Germany; markus.albrecht@oc.rwth-aachen.de

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

Deutsche Forschungsgemeinschaft (DVC, MA), Academy of Finland (K.R.: grants no. 263256, 265328 and 292746)

ACKNOWLEDGMENT

We are grateful for funding by the international graduate school Seleca (Deutsche Forschungsgemeinschaft) and the Collaborative Research Center 765 (Deutsche Forschungsgemeinschaft) the Academy of Finland (K.R.: grants no. 263256, 265328 and 292746) and the University of Jyväskylä. We thank Prof. Gerhard Raabe for collection of the data set of $Li[Li_3(\mathbf{1b})_6Ti_2]$.

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