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Computationally forecasting the effect of dibenzylammonium substituents on pseudorotaxane formation with dibenzo[24]crown-8

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ABSTRACT

The ability to predict the relative stabilities of analogous pseudorotaxanes is essential for the synthetic chemist yet simplified computational forecasting approaches remain scarce. Consequently, ten [2]pseudorotaxanes have been assembled (from a series of *para*-substituted dibenzylammonium ions and dibenzo[24]crown-8) and their experimentally-determined stabilities correlated with two computational parameters closely related to complexation energy. The strongest relationship was obtained from density functional theory calculation of binding energy ($R^2 = 0.92$) while determination of the maximum surface electrostatic potential on the dibenzylammonium ions (a proxy indicator of complex stability) afforded comparable results ($R^2 = 0.88$) with great reduction in computational expense.

Introduction

Since Stoddart's initial discovery[1] of the first threaded donor/acceptor complex, we have not only seen the assembly of a myriad of other pseudorotaxanes, but also witnessed their usefulness as precursors to a variety of topologically-fascinating mechanically interlocked molecules (MIMs)[2–8] and functional molecular machinery.[9–13] One of the most outstanding templates which has been developed for MIM synthesis is the hydrogen-bonded dibenzylammonium (DBA)/dibenzo-[24] crown-8 (DB24C8) recognition motif whose remarkable stability[14] has inspired the use of a variety of appropriately-sized crown ethers for DBA ion recognition in numerous intriguing studies.[7,15]

Ashton and co-workers published an interesting keynote article[16] in which they determined the stabilities of several *para*- and *meta*-substituted DBA/DB24C8 pseudorotaxanes and found good correlation between experimental binding energies and the Hammett substituent constants[17] (σ) associated with the *para*-groups on the DBA phenyl rings. This relationship allows the relative stability of these analogous complexes to be predicted, prior to their synthesis, by considering the electronic properties of the substituted DBA threads—effectively allowing the synthetic chemist to 'fine-tune' the strength of complexation at the initial design stage—resulting not only in considerable time- and cost-savings, but also improved control during the final stages of MIM assembly. For instance, stable pseudorotaxane precursors are desirable for the assembly of non-trivial interlocked molecules such as suitanes[2,6] whereas using components which bind less strongly has been noted to be beneficial in the preparation of molecular switches.[18]

As we continue to pursue supramolecules of increasing complexity, the usefulness of the Hammett constant correlation begins to diminish since new studies involve more elaborate DBA templates which bear advanced substituents (such as poly-substituted aromatic units consisting of bridged/extended dibenzylammonium structures) for which σ is unknown. We therefore seek to identify other practical methods for forecasting the relative stabilities of crown ether/DBA threaded systems acknowledging that these computational studies must be simple enough to be routinely used by chemists of all backgrounds and be executable in reasonable timeframes. This preliminary investigation begins by revisiting the Ashton study, focusing only on *para*-substituted DBA ions (Scheme 1). We have expanded the variety of *p*-substituents considered, specifically by including the cyano and iodo analogues (previously unreported to the best of our knowledge), and devised a new synthesis for the bis(4-formylbenzyl)ammonium hexafluorophosphate thread. We proceed with a discussion of data from several computational methods and their correlation with experimental results.

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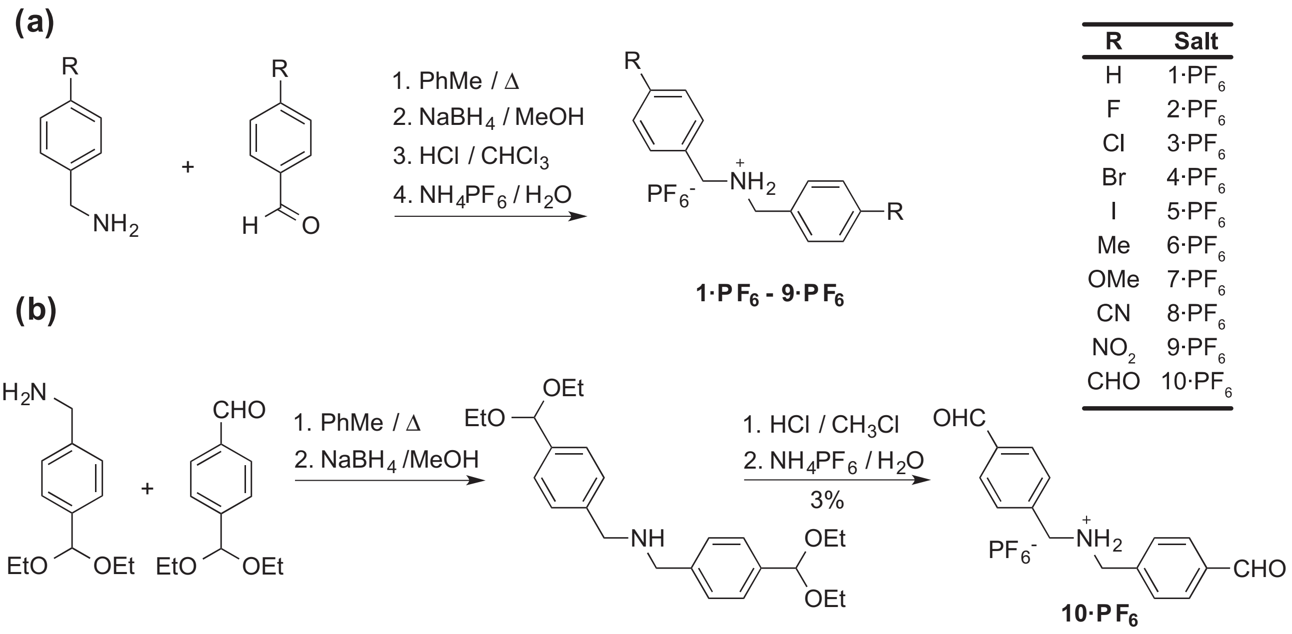


R	Salt
H	$1\cdot PF_6$
F	$2\cdot PF_6$
Cl	$3\cdot PF_6$
Br	$4\cdot PF_6$
I	$5\cdot PF_6$
Me	$6\cdot PF_6$
OMe	$7\cdot PF_6$
CN	$8\cdot PF_6$
NO_2	$9\cdot PF_6$
CHO	$10\cdot PF_6$

Scheme 1. Protocol used in the synthesis of the *para*-substituted DBA threads $1\cdot PF_6$–$9\cdot PF_6$ (a) and synthetic route utilized in the preparation of the formyl-terminated DBA ion $10\cdot PF_6$ (b) involving an acetal-substituted dibenzylamine intermediate.

Synthesis and binding studies

The synthesis of the ten DBA ions was carried out following the four-step procedure (Scheme 1a) outlined by Ashton and co-workers,[16] with the exception of dialdehyde $10\cdot PF_6$. An equimolar mixture of the corresponding benzylamine and benzaldehyde in toluene was heated under reflux overnight with the use of a Dean Stark apparatus. En vacuo concentration of the mixture, followed by treatment with sodium borohydride in a methanol/THF solvent afforded the substituted dibenzylamine which was subsequently protonated using hydrochloric acid. The hydrochloride salt was converted to the hexafluorophosphate species by treatment with ammonium hexafluorophosphate in a boiling mixture of water and methanol. Due to difficulties in reproducing the reported synthesis of $10\cdot PF_6$,[19] we prepared the diethyl acetal-substituted dibenzylamine (Scheme 1b) and treated it with conc. HCl effecting simultaneous deprotection and protonation affording $10\cdot PF_6$ after counterion exchange. Yields were not recorded for the acetal intermediate since the crude product was immediately taken up in chloroform and subjected to treatment with HCl.

Equimolar amounts of the DBA hexafluorophosphate salt and DB24C8 were combined in deuterated acetonitrile to yield a 10 mM solution (Fig. 1a). The ^1H NMR spectra of these solutions were recorded at 297 K five minutes after mixing and the stability constants (K_a) for these dynamic systems subsequently determined via the single point method.[20,21] The typical set of signals observed for systems of this type is illustrated in the ^1H NMR spectrum of the [2]pseudorotaxane assembled from $3\cdot PF_6$ and DB24C8 (Fig. 1b).

Each component of the assembly is assigned two sets of resonances corresponding to signals from protons in the free or uncomplexed (uc) state and those in the bound or complexed (c) state. The equilibrium concentrations of chemical species in these slow[22] exchange systems were then determined via the single point method by comparing integrations of peaks corresponding to the 'free' and complexed states of targeted probe protons on each component—specifically the DBA benzylic methylene protons (H_a) and the polyether methylene protons (H_h) which become downfield and upfield shifted, respectively, on pseudorotaxane formation.

Subsequently, $\log[K_a(R)/K_a(H)]$ was plotted against the respective Hammett substituent constants[17] (Fig. 1c), where $K_a(R)/K_a(H)$ represents the ratio of the association constants of a substituted DBA thread to that of its protic analogue and thus effectively sets $1\cdot PF_6$ (R = H) at zero. Unsurprisingly, we observed that electron donating substituents (i.e. those with negative σ values; –OMe and –Me) caused a reduction in affinity for DB24C8 compared with $1\cdot PF_6$, while electron withdrawing groups (those with positive σ values; the halogens, –CHO, $-NO_2$ and –CN) enhanced binding.

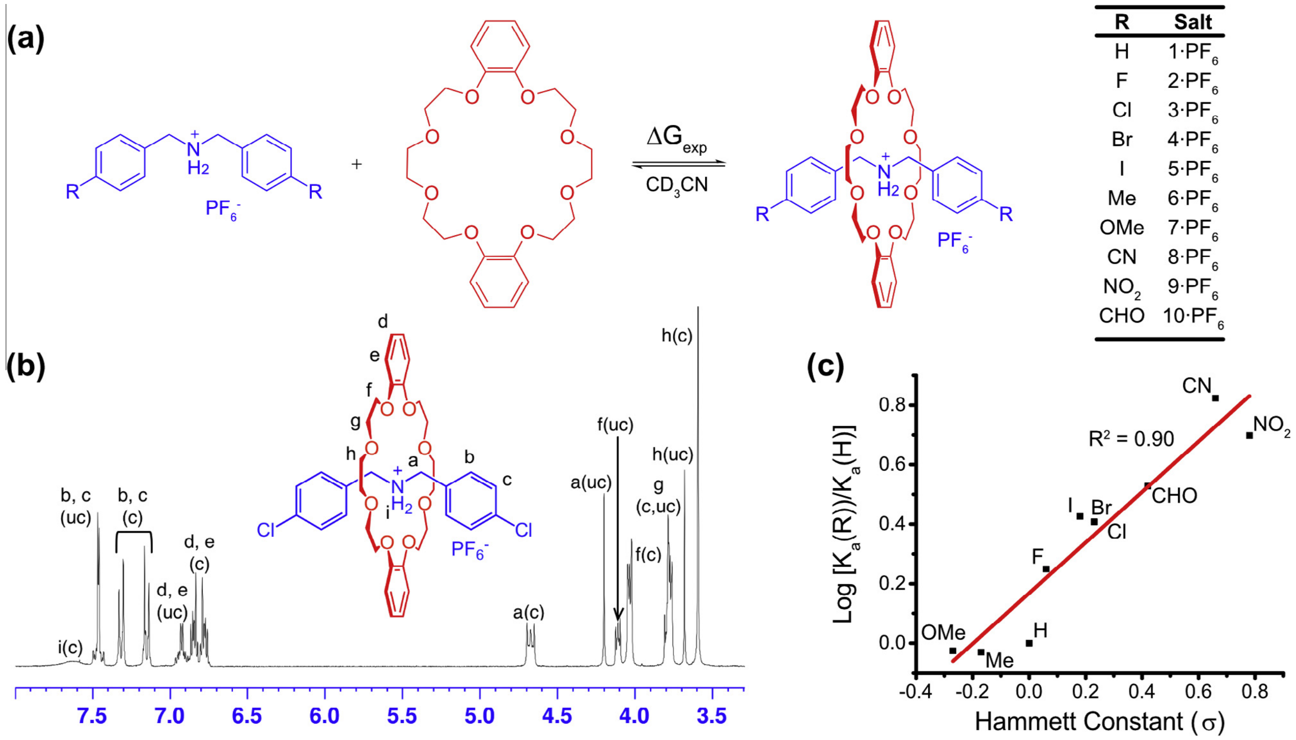
A good correlation (Fig. 1c) between complex stability and the corresponding Hammett substituent constant (σ) was found ($R^2 = 0.8956$) indicating that a linear free energy relationship (LFER) exists between the two quantities, thereby linking the electronic properties of the *para*-substituents to the hydrogen bond donor ability of the ammonium and benzylic methylene protons.

These results are consistent with those reported in the literature[16]—however, as previously mentioned, the applicability of this prediction method falls off on departure from simple complexes.

Computational studies

We next turned our attention to computational studies of the synthesized complexes, in the hope that useful relationships between the experimentally-determined Gibbs free energies of complexation and the computational results could be obtained, allowing us to avoid the limited scope and pitfalls associated with the Hammett constant correlation approach.

The theoretical work consisted of density functional theory (DFT) calculations of binding energies and free energies of complexation for the various complexes. The ten substituted DBA ions, free DB24C8 and the corresponding 1:1 complexes were drawn in Spartan 14.1.1.4[23] and the lowest energy conformations were subjected to geometry optimization and harmonic vibrational frequency calculations (Fig. 2a). The binding energies for each of the complexes were then calculated as the difference between the energy of the 1:1 complex and the total energy of the free components. Free energies of complexation were calculated using the enthalpies and entropies obtained from the frequency calculations.



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Me	$6\cdot PF_6$
OMe	$7\cdot PF_6$
CN	$8\cdot PF_6$
NO_2	$9\cdot PF_6$
CHO	$10\cdot PF_6$

Figure 1. (a) Schematic of the complexation of a *para*-substituted DBA ion with DB24C8 and table of the substituents considered in this study, (b) Sample ^1H NMR spectrum of $[3\cdot PF_6][DB24C8]$ with peak assignments where (c) and (uc) correspond to protons in the complexed and uncomplexed species, respectively, and (c) Correlation of stability constants determined experimentally via the single point method with known Hammett substituent constants (σ).

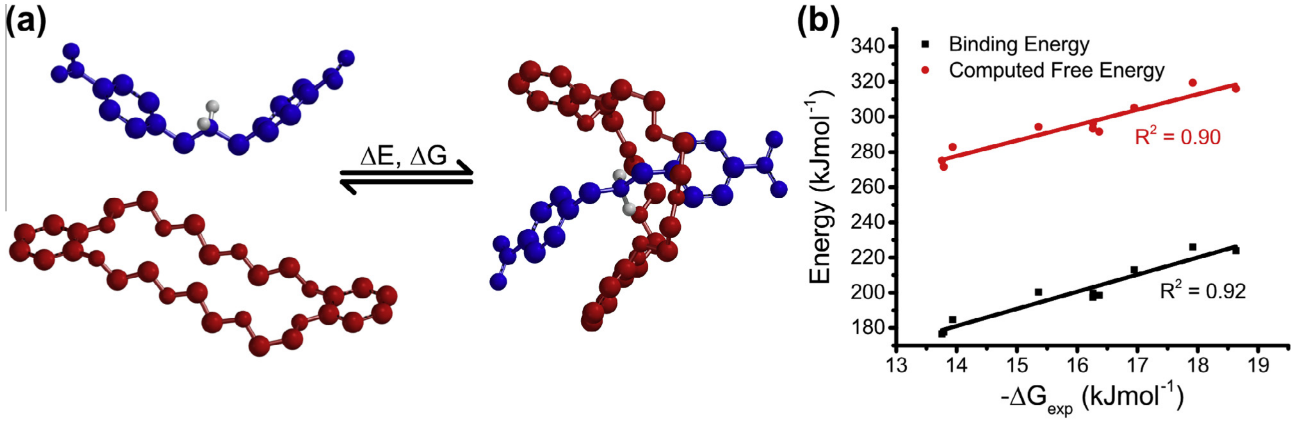

Figure 2. (a) Optimized structures of $9\cdot PF_6$, DB24C8 and $[9\cdot PF_6][DB24C8]$ (H atoms except $R_2NH_2^+$ omitted for clarity) and (b) Correlation of computational binding energy and free energy with experimentally-determined free energies of complexation (ΔG_{exp}) for the [2]pseudorotaxanes prepared.

DFT calculations were carried out at the B3LYP level with the 6-31G* basis set. In the case of $5\cdot PF_6$ and $[5\cdot PF_6][DB24C8]$, the LANL2DZ basis set was applied to the iodine atoms while the 6-31G* basis set was applied to all other atoms.

Although these theoretical calculations of binding energy ($R^2 = 0.9161$) and free energy of complexation ($R^2 = 0.8985$) were well-correlated with experimental data (Fig. 2b), we found it necessary to explore other theoretical methods that would better fit the criteria for speed, high accuracy and ease of use. We noted that reducing the overall system size being considered greatly reduced the timeframe in which these calculations could be executed. In reality, the design of new pseudorotaxanes is greatly restricted by the small window of opportunity for modification of the macrocycle cavity size since interrupting the –O–C–C–O– repeating units hinders the affinity of crown ethers for DBA ions.[24,25] Contrastingly, we have considerable flexibility in making significant modifications to the dibenzylammonium threads allowing us to fine-tune their binding to crown ethers. To this end, we decided to move forward by assessing the cationic threads in isolation, resulting in a significant reduction in computational effort thereby facilitating the possibility of improved accuracy through calculations at higher levels of theory or larger basis sets.

We subsequently focused on the response of the maximum of the molecular electrostatic potential on the thread's surface ($V_{s,max}$) to changes in the electron-withdrawing/-donating nature of the DBA *p*-substituents. The ammonium centre binds to crown ethers through intermolecular hydrogen bonding and Coulombic interactions with the crown's electron-rich (negative) ligating atoms; both of these binding mechanisms being dependent on the degree of positive charge at the ammonium centre, easily

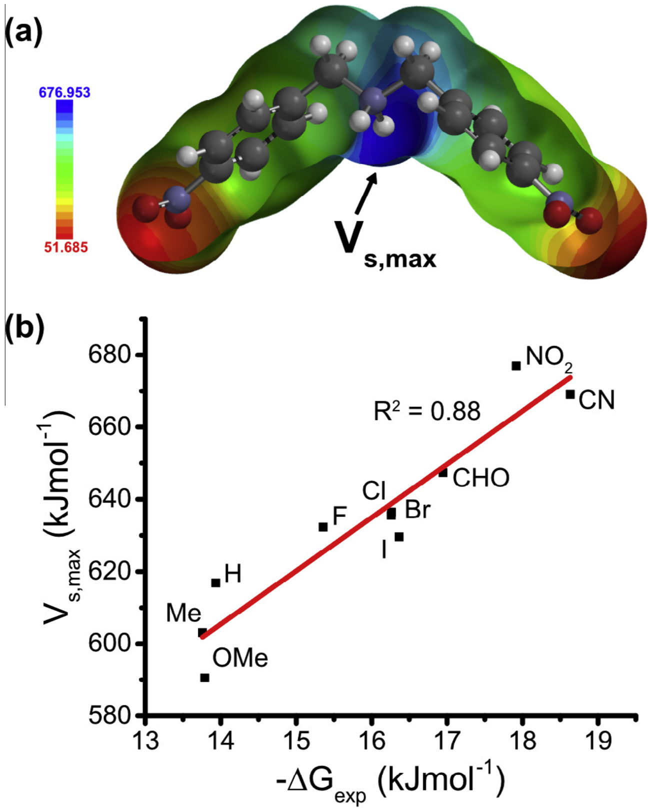

Figure 3. (a) Molecular electrostatic potential map of the nitro-substituted DBA thread, 9·PF_6, illustrating the positive potential (blue) concentrated at the $R_2NH_2^+$ portion of the molecule and (b) Correlation of $V_{s,max}$ values with experimental data.

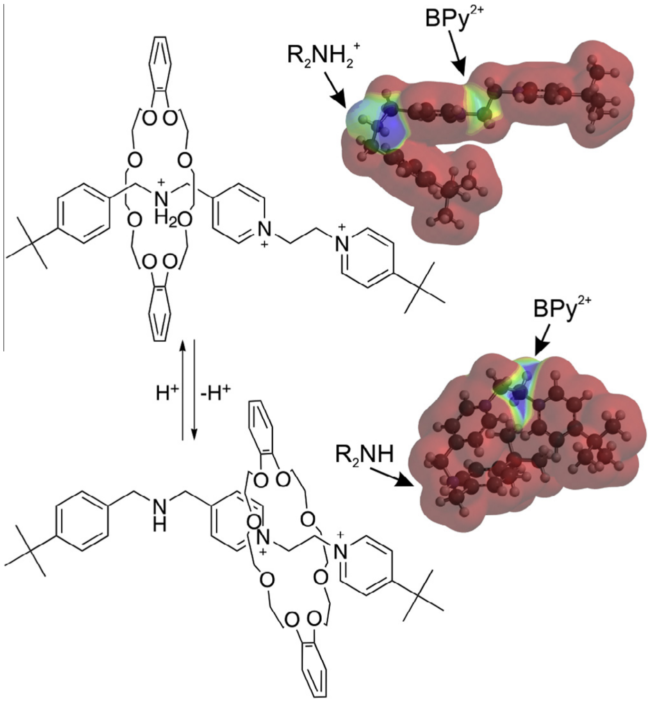

Figure 4. Schematic of pH-switchable rotaxane[26] beside the corresponding individual threads showing the computed surface electrostatic potentials.

determined by molecular electrostatic potential (MEP) studies. Electrostatic potential maps were consequently generated for the ten previously optimized DBA ions with an example of the map for 9·PF_6 illustrated in Figure 3a.

We expected that electron-withdrawing substituents would enhance the electron deficiency of the ammonium centre, which would be reflected in the magnitude of the positive potential observed on the MEP map. Thus, it follows that the magnitude of the maximum surface potential ($V_{s,max}$) at the ammonium centre should be proportional to the binding affinity of these DBA ions for crown ethers. Indeed a good correlation between $V_{s,max}$ at the $R_2NH_2^+$ binding sites and experimentally-determined free energies of complexation was obtained ($R^2 = 0.8804$, Fig. 3b). While the binding and free energy data gave slightly stronger correlations with experimental data, the tremendous reduction in computational expense due to the dramatic reduction in system size renders the MEP method far more practical as we pursue higher order supramolecular assemblies, especially for applications in planning the synthesis of mechanically interlocked molecules.

In order to test the viability of the method, we sought a simple model system, namely a pH-sensitive molecular switch reported by Eizarov.[26] On the thread, there is competition for binding of DB24C8 between bipyridinium and pH-dependent dialkylamine/-dialkylammonium sites. Under acidic conditions, the ammonium site shows higher affinity towards DB24C8 and therefore is the preferential binding site (Fig. 4). Deprotonation from treatment with base shifts the equilibrium towards docking on the bipyridinium thus effectively creating a molecular switch.

Using the method for calculating and plotting the surface electrostatic potentials, we modelled the threads of the rotaxanes shown in Figure 4. The colour thresholds have been modified to highlight the regions of high surface potential (i.e., possible binding locations for DB24C8). In the protonated thread, the positive potential is concentrated mostly over the ammonium with the bipyridinium site also showing positive potential, albeit to a lesser extent. Upon deprotonation, the map shows that there is a shift in the location of the maximum positive potential from the ammonium to the bipyridinium, an observation in line with the movement of the crown ether with change in pH. Furthermore, in the protonated thread, the region of positive potential over the bipyridinium would indicate partial occupancy, which is in agreement with the ^1H NMR experiments performed on the rotaxane.[26] While the method can highlight potential binding regions, it must be noted that prediction for the binding affinities in multiply charged species is currently only qualitative as the range of the surface potentials on the molecule is influenced by the charge.

Conclusion

Noting the limitations of using the LFER (which correlates the Hammett substituent constants and DBA/crown association constants) to predict the stability of pseudorotaxanes, we have investigated computational methods to predict the binding affinity of a variety of *p*-substituted dibenzylammonium ions to crown ethers. Calculation of binding energies and free energies by DFT provided data well-correlated with experimental results. Owing to the computational expense of optimizing the assembled pseudorotaxanes by DFT, we proceeded with determination of the maximum surface molecular electrostatic potential at the ammonium centres of the DBA threads. We found that $V_{s,max}$ afforded a strong correlation with experimental data—comparable to that of the binding and free energy results but with a significant reduction in computer time and the surface potential maps can also be used to highlight preferential binding sites in a rotaxane molecular switch. These, coupled with the visually stimulating maps obtained from the MEP computations, leads us to believe that $V_{s,max}$ computation is a fitting tool for the non-theoretical chemist to predict relative stabilities of DBA/Crown supramolecular complexes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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