



# Molecule Formation Energy and Atomic Charge Effectiveness of Membrane-Active Diacyl Derivatives of Dibenzo-18-Crown-6

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**Abstract:** In this study, we present an investigation into the impact of substituent length within the benzene ring of diacyl derivatives of dibenzo-18-crown-6 (DB18C6) on the charges exhibited by oxygen atoms in the macrocycle. Our analysis reveals that the oxygens located at positions 1 and 4 of the nearest pyrocatechol group, situated at a separation of two carbon atoms from the benzene ring substituent, exhibit only minimal changes in charge when compared to oxygens located at positions 3 and 6, located at three carbon atoms. These may indicate that "sandwich" structures form during complex formation. Our research has revealed a correlation between the molecule formation energy of diacyl derivatives of DB18C6 and the enthalpy ( $\Delta H$ ) of complex formation. Specifically, the PM3 method was utilized to calculate the molecule formation energy, which showed an increase in energy from 4',4''-diacetyl-DB18C6 to 4',4''(5'')-divaleryl-DB18C6. Similarly, data obtained from the MM+ technique demonstrated a rise in molecule formation energy from 4',4''-diacetyl DB18C6 to 4',4''(5'')-divaleryl-DB18C6, and in both cases, this value remained at a close level achieved for 4',4''(5'')-divaleryl-DB18C6. Specifically, we observed a gradual increase in molecule formation energy from 4',4''-diacetyl-DB18C6 to 4',4''(5'')-divaleryl-DB18C6, which was consistent with the corresponding increase in  $\Delta H$  and  $\text{Ca}^{2+}$  ionophore activity.

**Keywords:** crown ethers; molecule formation energy; atomic charge; ionophore; calcium; membrane; 4',4''-diacetyl-DB18C6; 4', 4''(5'')-dibutyryl-DB18C6, 4',4''(5'')-divaleryl-DB18C6.

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## 1. Introduction

The promotion of membrane transport by ionophores occurs through a multi-stage process that includes complex formation between the ionophore molecule and the cation, lipophilization, and diffusion of the resulting ionophore-cation complex at the phase boundary between the membrane and surrounding solution [1-6].

In a previous study, we examined the thermodynamic parameters of complexation ( $\Delta G$ ,  $\Delta H$ ,  $\Delta S$ ) [7] and their relationship with the membrane activity of several DB18C6 diacyl derivatives in complexation with calcium ions. Our results indicated a clear correlation between the thermodynamic parameters of complexation and the membrane activity of these compounds, with higher values of  $\Delta H$  and  $\Delta S$  being associated with greater ionophore activity

[8]. We observed an increase in  $\Delta H$  and  $\Delta S$  for 4',4''(5'')-dibutyl-DB18C6 and 4',4''(5'')-divaleryl-DB18C6, indicating that these compounds had a higher ionophore activity compared to their diacetyl counterparts. These findings suggest that the thermodynamic parameters of complexation can provide valuable insight into the ionophore activity of macrocyclic compounds [9] and may inform the design and development of more effective ionophores for use in biomedical applications [10-16].

## 2. Materials and Methods

The synthesis procedures of crown ethers and characterized data are shown in [17,18]. The values of  $\Delta G$  were calculated from the values of  $K$  [19] using the formula:

$$\Delta G = -RT \ln K \quad (1)$$

Complex formation determined by direct calorimetry on an LKB-2107 microcalorimeter (Sweden) [20]. To gain further insight into the structural characteristics of the molecules, we utilized Hyperchem 8.0.10 software [21] to model and optimize the structures using two quantum mechanical methods: PM3 and MM+ level.

The value of  $\Delta S$  was estimated from the values of  $\Delta G$  and  $\Delta H$  using the formula:

$$\Delta G = \Delta H - T\Delta S \quad (2)$$

$$\Delta S = \frac{\Delta H}{\Delta T} - \frac{\Delta G}{T} \quad (3)$$

$$\Delta S = \frac{\Delta H}{T} - R \ln K_{ust} \quad (4)$$

By combining experimental data obtained from calorimetric measurements with computational modeling and optimization, we were able to gain a comprehensive understanding of the complex formation process and underlying molecular mechanisms. Our findings may have important implications for rationalizing new molecules with desired properties and functions [1,22].

## 3. Results and Discussion

Our research has shown that the diacyl derivatives of DB18C6 form "sandwich" complexes with  $Ca^{2+}$ , predominantly in a 2:1 composition. The bond between the  $Ca^{2+}$  ion and the crown ether is formed through the acyl oxygens of the substituents of the DB18C6 diacyl derivatives [19,23]. All reactions involving the interaction between  $Ca^{2+}$  and crown ether were conducted with a high (10-fold) excess of metal to analyze the reactivity of a single type of metal complex with the lowest coordination number.

We found that enthalpy ( $\Delta H$ ) contributes the most to the energy of complex formation. This is in line with previous studies showing that enthalpy plays a dominant role in the thermodynamics of complexation reactions.

Our analysis has shown that the enthalpy ( $\Delta H$ ) of the complex formation reaction is dependent on the length of the substituent and that the energy of complex formation drops as the substituent length increases from 4',4''-diacetyl-DB18C6 to 4',4''(5'')-dibutyl-DB18C6. This decrease in enthalpy can be attributed to steric factors that come into play during complex formation. As the length of the substituent increases, the steric factors between the substituent and the  $Ca^{2+}$  ion become stronger, leading to less favorable interactions and a reduction in the enthalpy of complex formation.

The results indicate that in complex formation reactions, the system's entropy does not undergo significant changes. This finding confirms that as the length of the substituents increases, the structure of the generated complexes remains constant, and no conformational changes occur during the binding of  $\text{Ca}^{2+}$  ions. This is consistent with previous studies showing that the entropy change in complexation reactions is often small, as the metal ion's and crown ether's binding does not involve significant changes in molecular structure or reorientation.

It is worth noting that our analysis of the data in Table 1 shows a minor decrease in the value of  $\Delta S$  as the length of the substituent increases from 4',4''(5'')-dibutyryl-DB18C6 to 4',4''(5'')-dinanoyl-DB18C6. This decrease in  $\Delta S$  can be attributed to an increase in systematic order, i.e., creating a denser packing complex. As the length of the substituent increases, the hydrophobic interactions between the hydrocarbon chains become stronger, leading to a more ordered and compact structure.

Our analysis included a correlation analysis between the  $\Delta H$  of complexation for DB18C6 diacyl derivatives and their membrane activity, using the findings of a previous study that investigated the effect of the number of carbon atoms in the side chains of DB18C6 diacyl derivatives on the relative change in mitochondrial permeability for  $\text{Ca}^{2+}$ . The correlation coefficient obtained was  $R=70$ , indicating a moderate positive correlation between the two variables. The coefficient of determination ( $R^2$ ) was 0.50, indicating that the variation in the  $\Delta H$  of complexation could explain 50% of the variation in the membrane activity.

**Table 1.** The thermodynamic parameters of complex formation of diacyl derivatives of DB18C6 with calcium ion in ethanol  $T = 298 \text{ K}$ .

Radical	Structure of radical	K $\text{l}\cdot\text{mol}^{-1}$	$\Delta H$ , $\text{kkal}\times$ $\text{mol}^{-1}$	$\Delta S$ , $\text{kal}\times$ $\text{mol}^{-1}\times\text{grad}^{-1}$	$\Delta G$ , $\text{kal}\times$ $\text{mol}^{-1}$
4', 4''-diacetyl-DB18C6	-CO-CH <sub>3</sub>	$6.77\cdot 10^6$	1.80	25	9.33
4', 4''(5'')-dipropionyl-DB18C6	-CO-CH <sub>2</sub> -CH <sub>3</sub>	$7.76\cdot 10^6$	1.43	26	9.41
4', 4''(5'')-dibutyryl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>2</sub> -CH <sub>3</sub>	$7.39\cdot 10^6$	1.29	27	9.39
4', 4''(5'')-divaleryl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>3</sub> -CH <sub>3</sub>	$5.49\cdot 10^6$	1.47	26	9.20
4', 4''(5'')-dihexanoyl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>4</sub> -CH <sub>3</sub>	$4.90\cdot 10^6$	1.71	25	9.13
4', 4''-diheptanoyl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>5</sub> -CH <sub>3</sub>	$6.99\cdot 10^5$	1.71	21	7.98
4', 5''-dioctanoyl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>6</sub> -CH <sub>3</sub>	$5.95\cdot 10^5$	2.03	20	7.81
4', 4''(5'')-dinanoyl-DB18C6	-CO-(CH <sub>2</sub> ) <sub>7</sub> -CH <sub>3</sub>	$2.30\cdot 10^5$	1.63	19	7.32

Our analysis suggests that the correlation between the  $\Delta H$  of complexation for DB18C6 diacyl derivatives and their membrane activity indicates that one of the primary criteria for implementing membrane activity for these compounds is the complex formation process with the  $\text{Ca}^{2+}$  ion.

The formation and thermodynamic stability of cation-crown ether complexes are influenced by a variety of factors, including the number and type of binding sites in the cycle, the size of the ion and the macrocyclic cavity ratio, spatial obstacles in the ring, the type of solvent and the degree of solubility of the ion, as well as the electric charge of the ion [24]. This implies that there are numerous options for altering the selectivity of complexation and selective membrane transport of ions [25-30].

The number and type of binding sites in the macrocycle, as well as the efficiency of atomic charges and the electrical potential of the crown ether molecule, all play a significant role in the molecule's complexing ability and membrane activity. These factors can affect the complexes' thermodynamic stability, selectivity, binding affinity, and ability to selectively transport cations across membranes. In the case of the DB18C6 diacyl derivatives and  $\text{Ca}^{2+}$ ,

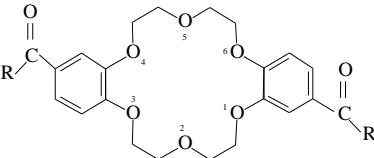
the specific interactions between the crown ether and the ion are determined by the number and location of the binding sites in the macrocycle and the size and charge of the ion.

Based on the method we use [31], we present the information obtained on the atomic charge effectiveness (Table 2) and the electronic potentials of diacyl derivatives-DB18C6 molecules (Table 3).

**Table 2.** Molecule formation energy of 4',4''-diacyl derivatives of DB18C6 (kcal/mol).

Crown ethers	Molecule formation energy of 4',4''-diacyl derivatives of DB18C6 (kcal/mol).							
	4', 4''-diacetyl-DB18C6	4', 4''(5'')-dipropionyl-DB18C6	4', 4''(5'')-dibutyryl-DB18C6	4', 4''(5'')-divaleryl-DB18C6	4', 4''(5'')-dihexanoyl-DB18C6	4', 4''-diheptanoyl-DB18C6	4', 5''-dioctanoyl-DB18C6	4', 4''(5'')-dionanoyl-DB18C6
Methods								
PM3	E=-6280	E=-6352	E=-6474	E=- 9079	E=-9083	E=-8521	E= - 9643	E=-10200
	G= 0.087	G=0.097	G= 0.081	G= 0.095	G=0.099	G=0.096	G= 0.097	G=0.082
MM <sup>+</sup>	E=39.80	E=46.70	E=49.27	E=52.06	E=49.45	E=47.75	E=50.75	E=50.90
	G=0.099	G=0.097	G=0.097	G=0.097	G=0.092	G=0.099	G=0.099	G=0.098

**Table 3.** Charges on oxygen atoms of macrocycles of diacyl derivatives of DB18C6.

	1	2	3	4	5	6
dibenzo-18-crown-6	-0.182	-0.255	-0.193	-0.164	-0.251	-0.166
4', 4''-diacetyl-DB18C6	-0.184	-0.248	-0.194	-0.160	-0.255	-0.167
4', 4''(5'')-dipropionyl-DB18C6	-0.168	-0.255	-0.205	-0.199	-0.252	-0.182
4', 4''(5'')-dibutyryl-DB18C6	-0.173	-0.253	-0.173	-0.185	-0.249	-0.170
4', 4''(5'')-divaleryl-DB18C6	-0.171	-0.253	-0.203	-0.183	-0.252	-0.187
4', 4''(5'')-dihexanoyl-DB18C6	-0.159	-0.240	-0.163	-0.192	-0.253	-0.179
4', 4''-diheptanoyl-DB18C6	-0.179	-0.253	-0.192	-0.162	-0.240	-0.160
4', 5''-dioctanoyl-DB18C6	-0.167	-0.253	-0.174	-0.183	-0.252	-0.194
4', 4''(5'')-dionanoyl-DB18C6	-0.183	-0.248	-0.157	-0.168	-0.247	-0.182

Experimental data has revealed that the enthalpy of complex formation of diacyl derivatives of DB18C6 with calcium ions exhibits a distinctive trend. Specifically, as the length of the side chains in the molecule increases from 4',4''-diacetyl-DB18C6 to 4',4''(5'')-divaleryl-DB18C6, the enthalpy of complex formation decreases. However, beyond 4',4''(5'')-divaleryl-DB18C6, the enthalpy of the complex formation increases again, reaching a minimum at a certain point (Table 1, ΔH).

The energy required for forming 4',4''-diacyl derivatives of DB18C6 exhibits a similar trend to the complex formation enthalpy ΔH. Specifically, when the molecule formation energy is calculated using the PM3 method, an increase is observed from 4',4''-diacetyl DB18C6 to 4',4''(5'')-divaleryl-DB18C6. Similarly, the MM<sup>+</sup> technique also calculates an increase in energy for molecule production from diacetyl to divaleryl-DB18C6, although in both cases, the

values remain close to the results obtained for 4',4''(5'')-divaleryl-DB18C6 (Supplementary material. Figures S1-S9).

A clear relationship exists between the molecule formation energy of diacyl derivatives of DB18C6 and the enthalpy of complex formation  $\Delta H$ . Specifically, the optimal side chain length for diacyl derivatives of DB18C6, which leads to the most stable and efficient complexes with calcium ions, is closely related to the energy required for molecule formation.

#### 4. Conclusion

In this study, we investigate the effect of substituent length in the benzene ring of acyl substituents in diacyl derivatives of DB18C6 on the charges of oxygen atoms in the macrocycle. Our results demonstrate that the maximum change in atom charge occurs on the nearest pyrocatechol oxygens 1 and 4, located 2 carbon atoms from the substituent in the benzene ring, as compared to the charges on the macrocycle oxygens 3 and 6, placed 3 carbon atoms away.

Our results suggest the possible formation of "sandwich" structures during complexation, which may accompany significant changes in the geometry of the macrocycle itself. The data on complexation thermodynamics support these observations. Specifically, the significant changes in enthalpy and entropy of complex formation indicate that the formation of the complexes is accompanied by significant structural reorganization (Table 1).

Our study reveals that there is a clear dependence of the enthalpy  $\Delta H$  on the substituent length, which suggests that as the length of the acyl substituent in the benzene ring increases, the energy of complexation from 4',4''-diacetyl-DB18C6 to 4',4''(5'')-divaleryl-DB18C6 decreases. However, further increases in the substituent length to 4', 4''(5'')-dinonanoyl-DB18C6 lead to an increase in the energy of complexation (Table 1). This trend can be attributed to the rise in calcium ionophore activity for 4',4''(5'')-dibutyryl-DB18C6 and 4',4''(5'')-divaleryl-DB18C6. The observed decrease in the energy of complexation appears to be responsible for the enhanced activity of these ionophores, as it forms more stable and selective complexes with calcium ions [25,32,33].

Previously, we demonstrated that 4',4''(5'')-dibutyryl-DB18C6 and 4',4''(5'')-divaleryl-DB18C6 exhibit significant calcium ionophore activity on both artificial and biological membranes. Specifically, these ionophores were found to be highly effective in facilitating the transport of calcium ions across the membrane, as compared to other tested compounds. The enhanced selectivity, efficiency, and stability of complexes formed between 4',4''(5'')-dibutyryl-DB18C6 and 4',4''(5'')-divaleryl-DB18C6 and calcium ions were found to be responsible for their superior ionophore activity.

Our calculated findings on the atomic charge effectiveness and molecule formation energy provide valuable insights into the underlying mechanisms of diacyl derivatives-DB18C6 complexation with calcium ions and their membrane activity on artificial and biological membranes. Specifically, the observed correlation between these calculated parameters and the thermodynamic parameters of complexation suggests that the optimal length of the acyl substituent in the benzene ring plays a crucial role in determining the selectivity, efficiency, and stability of ionophore complexes with calcium ions.

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## Conflict of Interest

The authors declare no conflict of interest. The funding sponsors had no role in the design of the study, in the analyses, in the writing of the manuscript, and in the decision to publish the results.

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Supplementary Materials

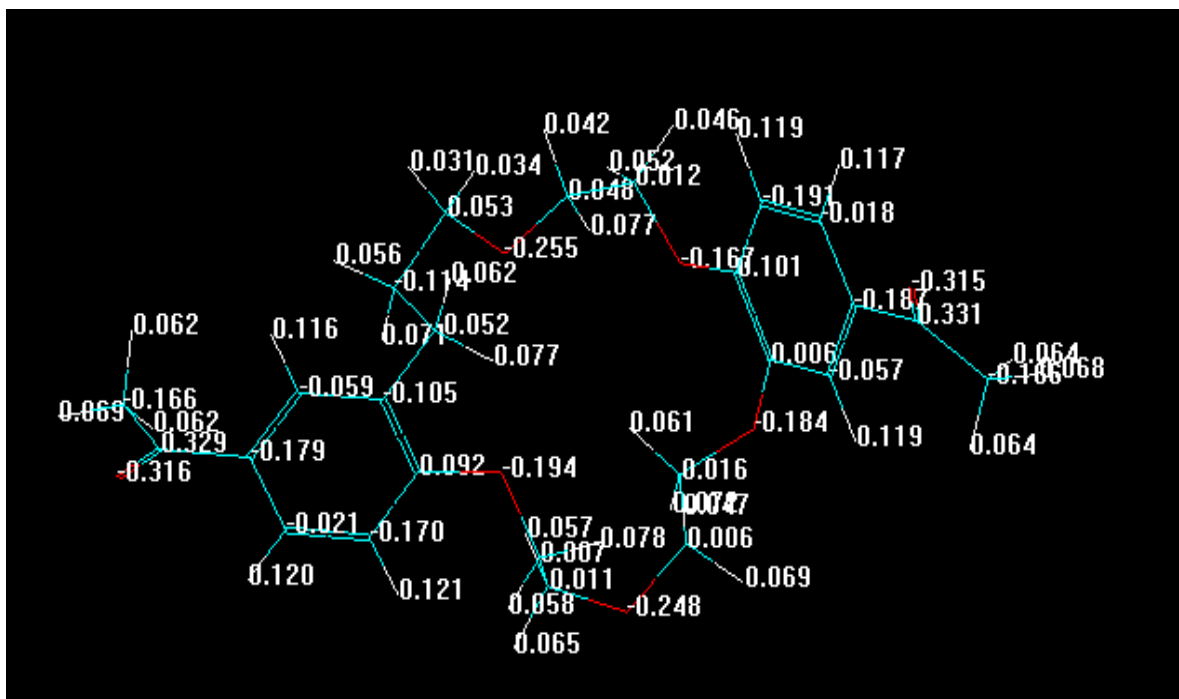


Figure S1. Effective atomic charges of 4',4''-diacetyl-DB18C6.

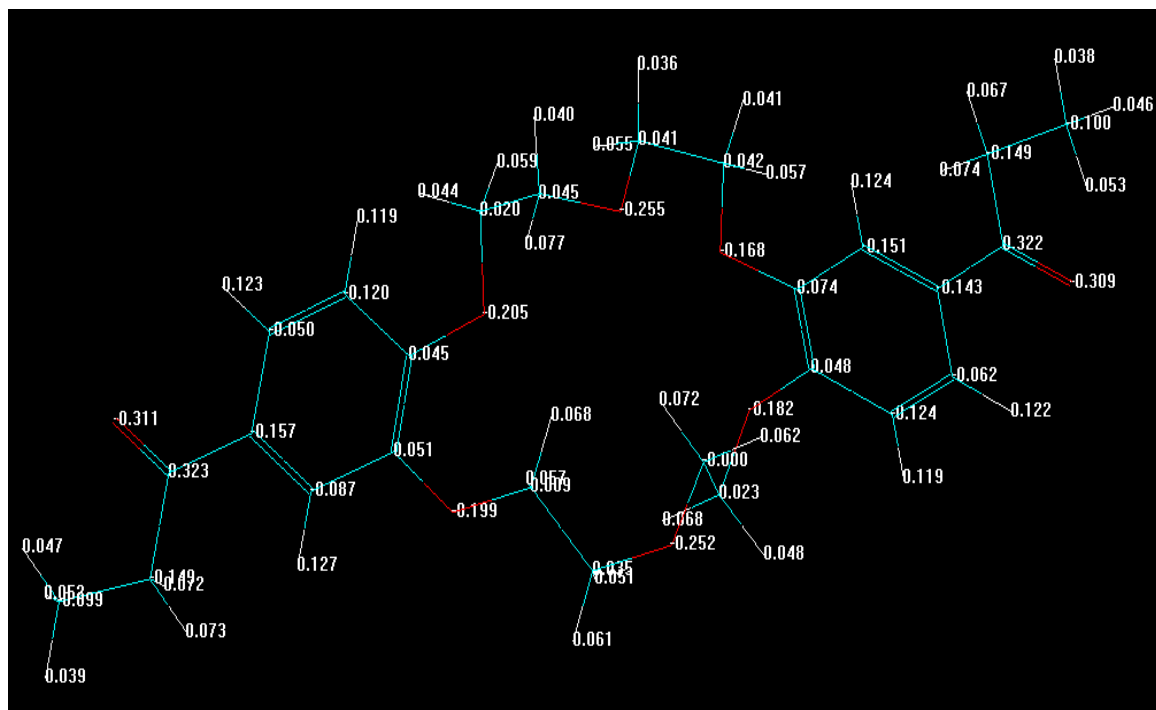


Figure S2. Effective atomic charges of 4',4''-dipropionyl-DB18C6.

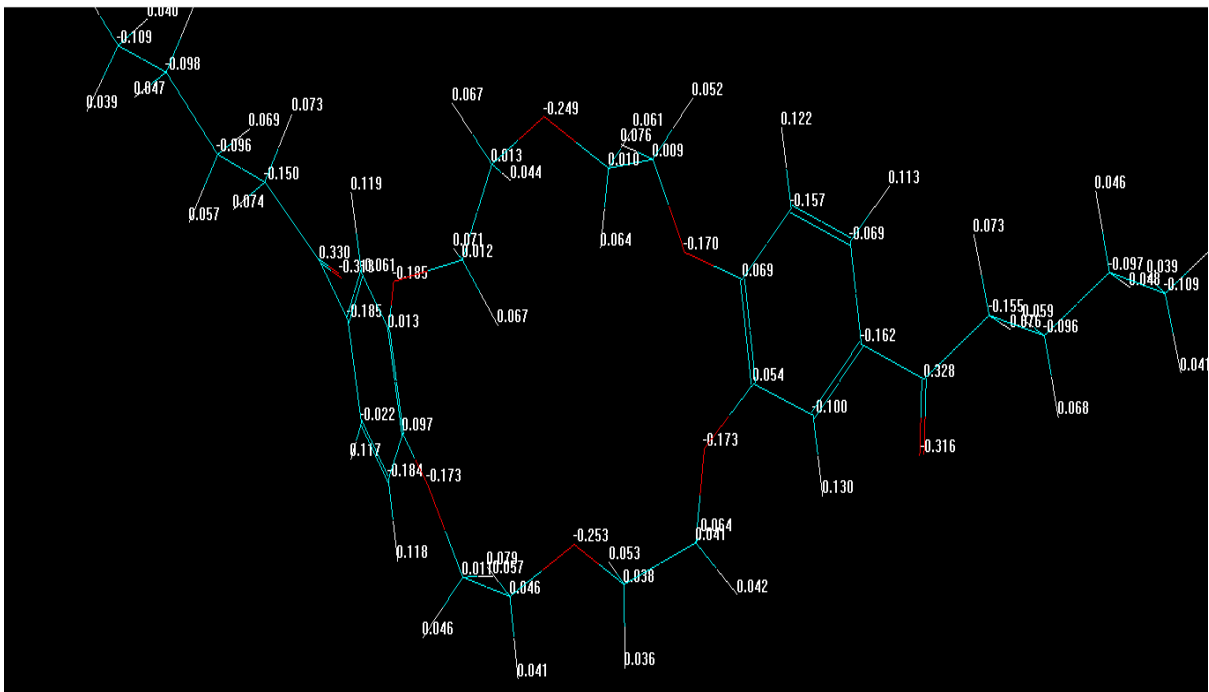


Figure S3. Effective atomic charges of 4',4''-dibutyl-DB18C6.

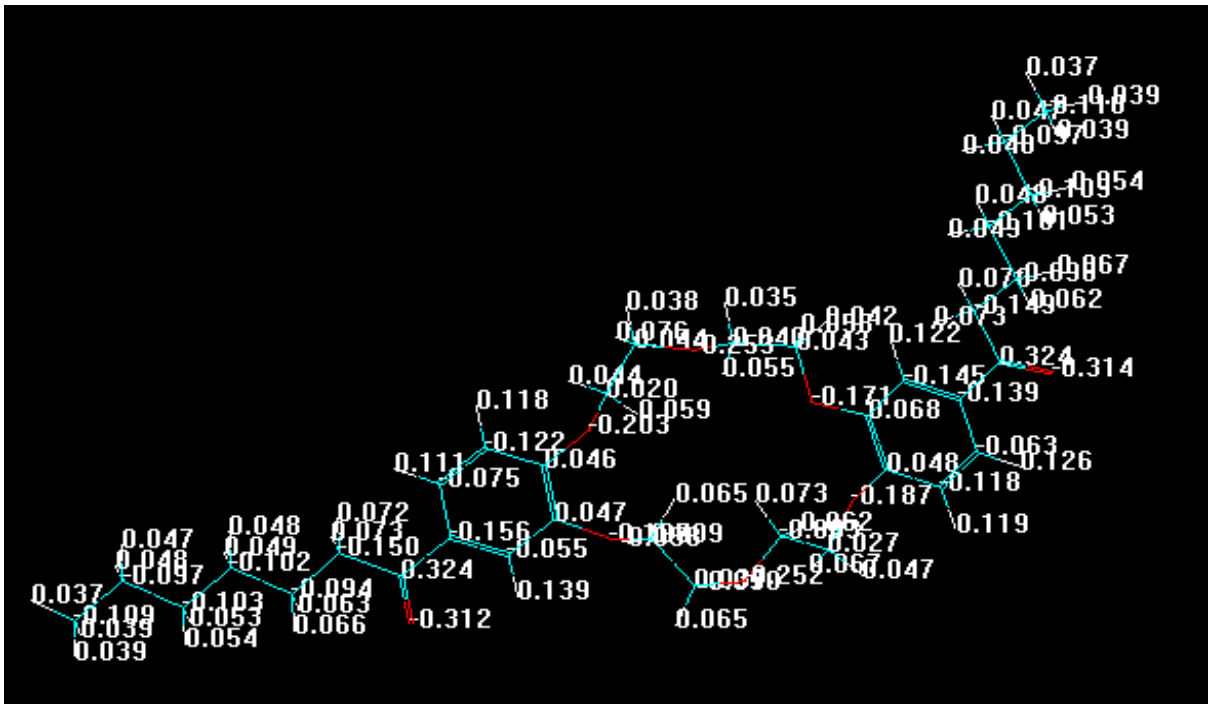
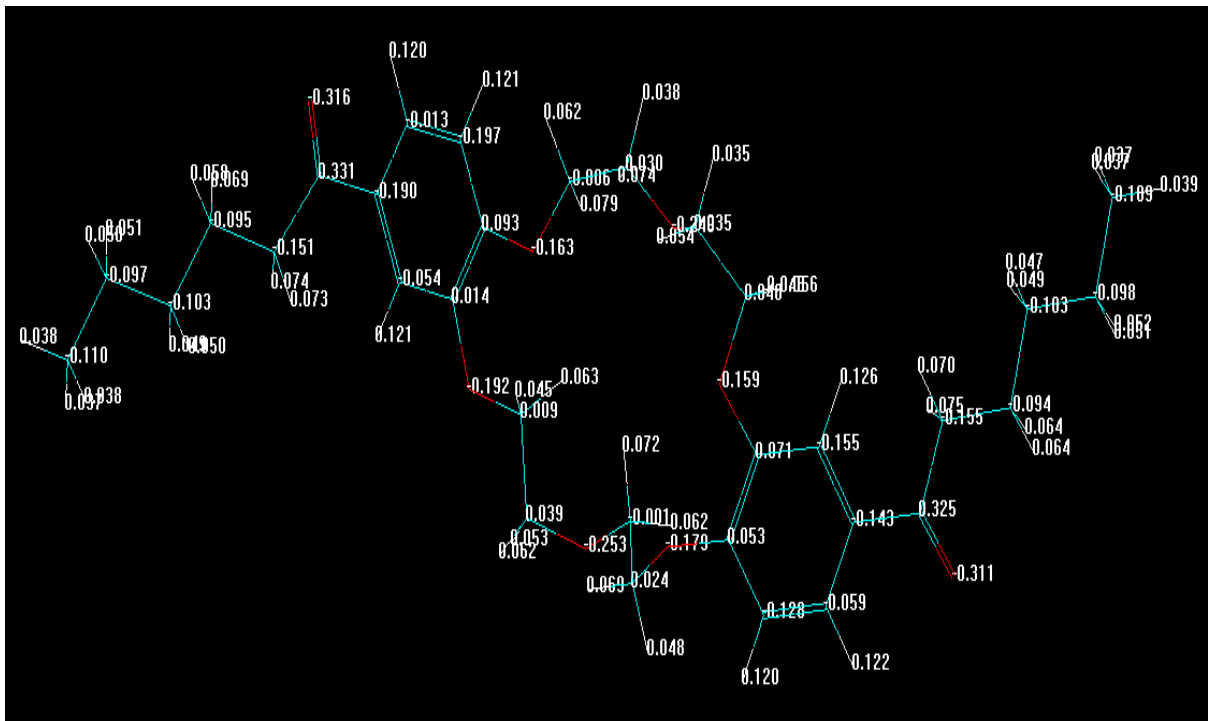


Figure S4. Effective atomic charges of 4',4''-divaleryl-DB18C6.



**Figure S5.** Effective atomic charges of 4', 4''(5'')-dihexanoyl-DB18C6.



**Figure S6.** Effective atomic charges of 4', 4''-diheptanoyl-DB18C6

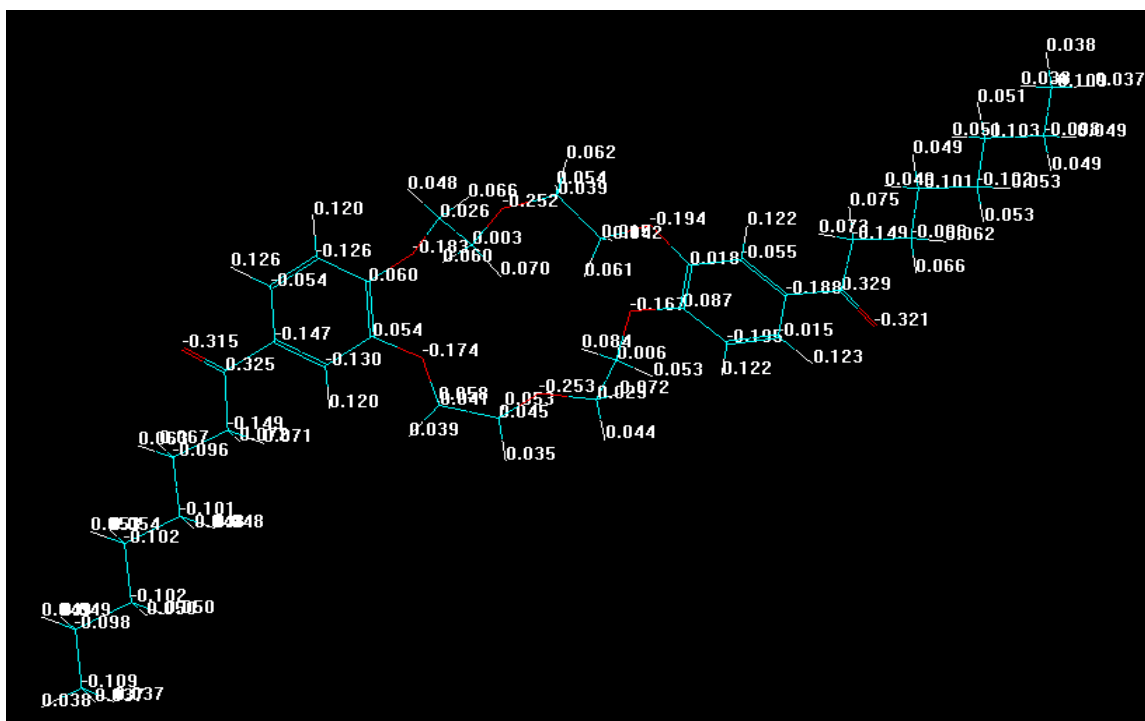


Figure S7. Effective atomic charges of 4', 5''-dioctanoyl-DB18C6

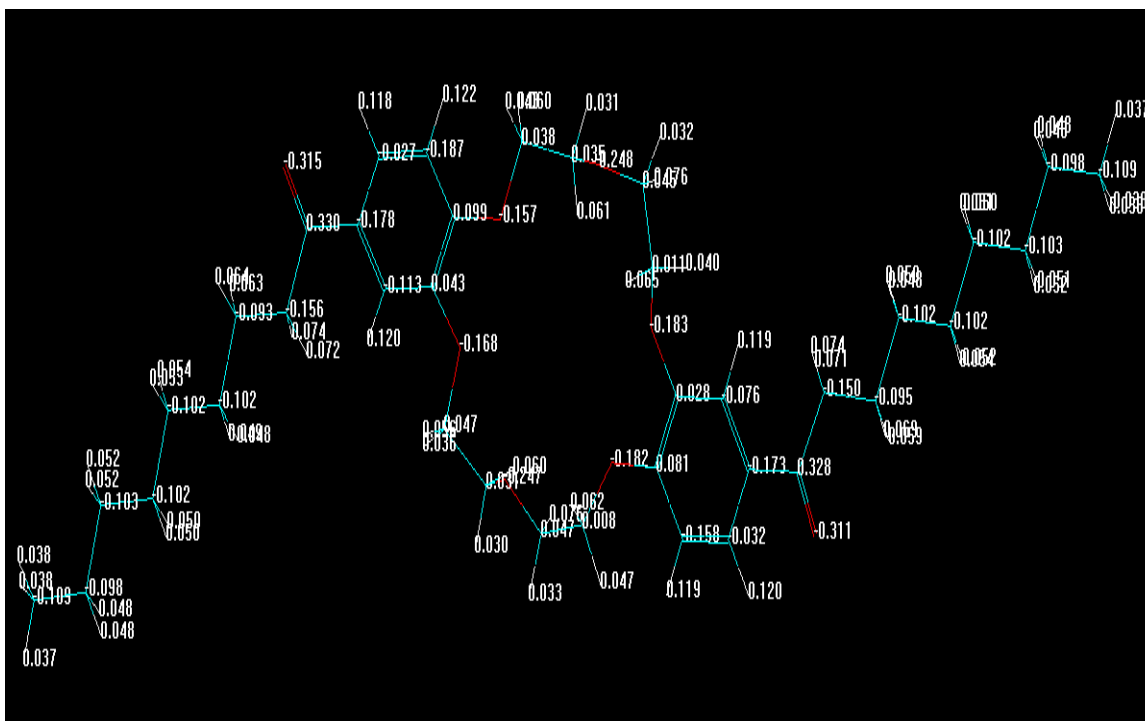
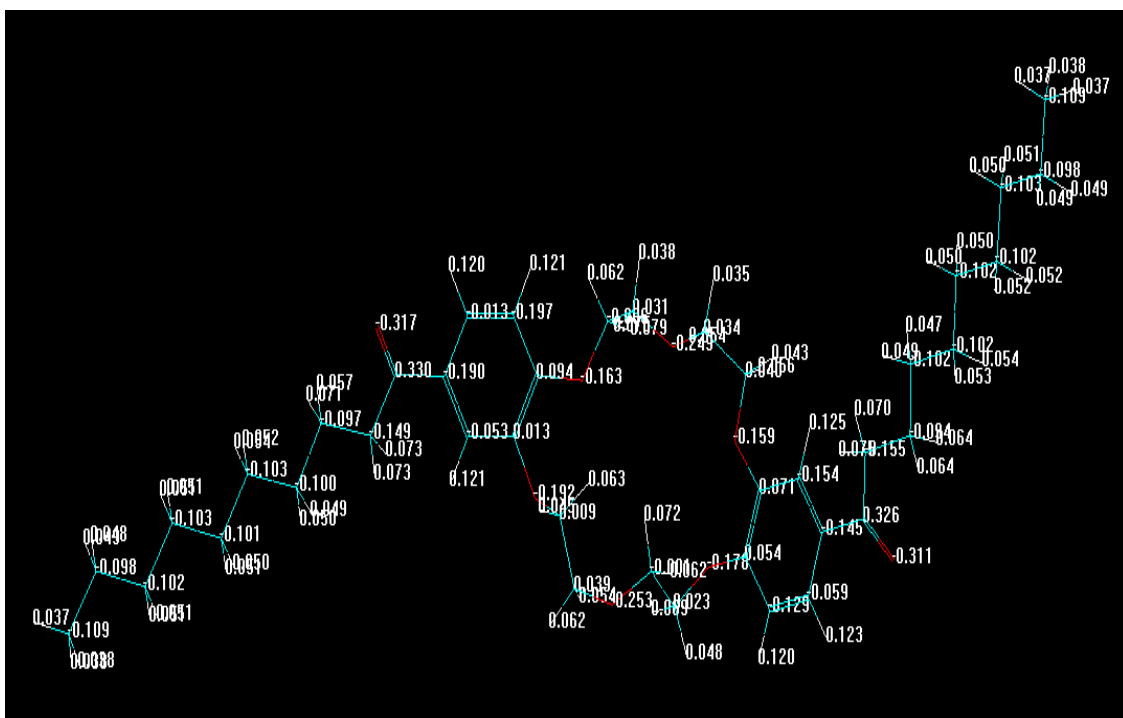


Figure S8. Effective atomic charges of 4', 4''(5'')-dinonanoyl-DB18C6



**Figure S9.** Effective atomic charges of 4', 4''(5'')-didecanoyl-DB18C6