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## Type-I dyotropic rearrangement for 1,2-disubstituted cyclohexanes: substitution effect on activation energy

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Nadeem S. Sheikh<sup>a</sup>

For an array of judiciously selected 1,2-disubstituted cyclohexane motifs, the migratory aptitude and contribution of specific structural features of synthetically valuable functional groups and halogen atoms in type-I dyotropic rearrangement are reported by employing quantum chemical calculations. This double migration process requires higher activation barriers for carbon, silicon and nitrogen bearing substituents however, it is thermally allowed and a feasible approach for several important moieties including oxygen, sulphur, phosphorous and halogen atoms bearing migrating fragments. Strong positive correlations are observed by plotting representative activation energy trends against inductive sigma ( $\sigma$ ), field ( $\sigma_f$ ), steric substituent ( $E_s$ ) and polar substituent ( $\sigma^*$ ) constants. Also, an effect of asymmetric combinations of substituents is presented which provides an interesting insight towards captodative substitution pattern.

### Introduction

Type-I dyotropic rearrangement<sup>1</sup> is a highly stereo- and regioselective pericyclic process, which proceeds reversibly through a cyclic transition state in a concerted manner.<sup>2</sup> A distinctive feature of this rearrangement involves one pi ( $\pi$ ) system and a simultaneous intramolecular exchange of two sigma ( $\sigma$ ) bonds (Fig. 1). Based on molecular-orbital and valence-bond analyses, this double migration process for 1,2-disubstituted ethane has been explicitly proposed to proceed either *via* an ethylenic scaffold or a diradical species.<sup>3</sup> Contrary to this, type-II dyotropic rearrangement<sup>4</sup> occurs *via* migration of two substituents to new sites in a molecule. In addition to a usual C–C<sup>5</sup> stationary scaffold, dyotropic reaction has been successfully applied to C–B,<sup>6</sup> C–N,<sup>7</sup> C–O,<sup>8</sup> C–Al,<sup>9</sup> C–Si,<sup>10</sup> C–S,<sup>8,11</sup> C–Cu,<sup>12</sup> C–Zn,<sup>13</sup> C–Zr,<sup>14</sup> C–Pd,<sup>15</sup> C=Si,<sup>16</sup> N–N,<sup>17</sup> O–N,<sup>18</sup> Si=Si,<sup>19</sup> Fe–Pt,<sup>20</sup> and Ge=Sn,<sup>21</sup> used as static frameworks.

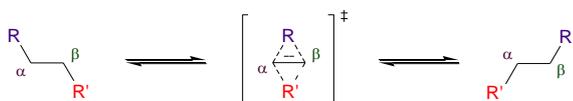


Fig. 1 Generic representation of type-I dyotropic rearrangement.

This double migration approach has been articulately incorporated to construct structurally complex molecules of synthetic and biological relevance such as lacrimin A (**1**),<sup>22</sup> jaspamide (**2**),<sup>23</sup> zoapatanol (**3**),<sup>24</sup> and azafenestrane (**4**, Fig. 2).<sup>25</sup> Moreover, several other bioactive natural products such as milbemycin  $\beta_3$ ,<sup>26</sup> discodermolide,<sup>27</sup> xanthanolides,<sup>28</sup> cephalostatin analogues<sup>29</sup> and a

number of synthetically significant building blocks<sup>30</sup> have also been prepared through this methodology. Additionally, type-II dyotropic rearrangement has also found its applications towards the synthesis of bioactive derivatives including cyclic peptide TCM-95A and B.<sup>31</sup>

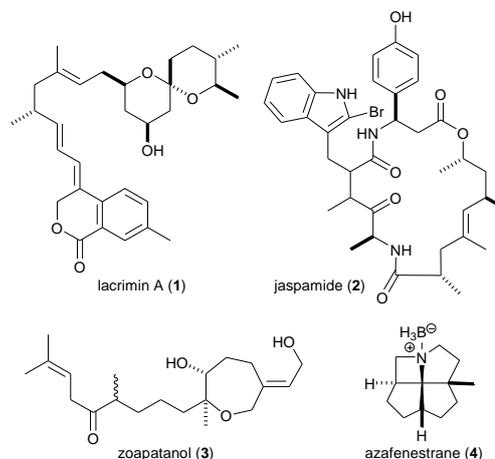


Fig. 2 Synthetic applications of type-I dyotropic rearrangement towards representative bioactive molecules.

Chemical reactions proceed through one or more transition states and the rate of the reaction depends on the activation energy ( $E_a$ ), which is the free energy difference between the transition state (TS) and the reactants. It is a measure of chemical reactivity and provides a very useful information about the reaction profile. Also, it is directly linked with stability of the TS, which relies on several decisive factors, not just limited to (a) electronic interactions between the reacting centres, (b) charge distributions, (c) steric hindrance caused by substituents, (d) mesomeric, inductive and anomeric effects. In case of type-I dyotropic rearrangement, hybridization of the atoms of the migrating groups directly attached with the stationary scaffold has a pronounced influence on  $E_a$  due

<sup>a</sup> Department of Chemistry, Faculty of Science, King Faisal University  
P.O. Box 380, Al-Ahsa 31982, Saudi Arabia  
Tel: (+966) 13-589-5393, (+966) 58-589-9574; Fax: (+966) 13-588-6437  
E-mail: nsheikh@kfu.edu.sa  
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to associated electronic nature and steric effect. In general,  $sp^3$  hybridized atoms are electron donating moieties whereas both  $sp^2$  and  $sp$  hybridized atoms tend to withdraw electronic density from a molecule. In case of substituted aromatic systems, the electronic influence is controlled by the substituent attached with the aromatic system. The transition states are stabilized/destabilized as a result of all these factors, which have a direct impact on the  $E_a$ ; greater the stability of the TS, lower will be the  $E_a$ . Quantum chemical calculations provide an insightful information towards the elucidation of reaction mechanisms and chemical reactivity descriptors.<sup>32</sup> Application of computational investigations in synthesis has emerged as an indispensable research element and indeed, is a time and cost effective approach. It has been eloquently applied to dyotropic rearrangement and is reported for several structural units such as dithienylethenes,<sup>33</sup> arene/allene cycloadducts,<sup>34</sup> phosphate and sulphate anions,<sup>35</sup> azines,<sup>36</sup> pentalenene,<sup>37</sup> substituted ethane moieties,<sup>38</sup>  $\beta$ -lactones,<sup>39</sup> dimethylaurate,<sup>40</sup> organocuprates and organoargentates,<sup>41</sup> and nitroso acetals.<sup>42</sup>

Undoubtedly, cyclohexane is regarded as one of the most privileged cycloalkane due to associated structural features. It exists in several interconvertible conformations along with a perfectly unstrained and highly stable chair conformation. It is a fairly unreactive molecule with limited applications<sup>43</sup> however, substituted cyclohexane is of substantial synthetic utility and acts as a precursor to numerous organic transformations. Moreover, replacement of hydrogen atoms with larger substituents in cyclohexane skeleton can prevent the interconversion between different conformations and this phenomenon is a common observation in cyclohexane containing structures of biological importance. Considering its significance, a comprehensive investigation towards the migratory aptitude of synthetically significant functional groups/atoms in type-I dyotropic rearrangement for variously functionalized 1,2-disubstituted cyclohexane structures is described.

## Results and Discussion

In general, type-I dyotropic rearrangement occurs at high temperatures as reported for thermal mutarotation of 2,3-dibromo-*tert*-butylcyclohexane,<sup>44</sup> and vicinal dibromides in steroidal structures.<sup>45</sup> The results obtained from this study are in agreement with this experimental observation and 1,2-shifts for the considered groups proceed *via* high energy barriers up to 126 kcal mol<sup>-1</sup>. Such high barriers have also been reported for the type-I dyotropic model systems studied for 1,2-disubstituted ethane structures.<sup>3b</sup> The results for 1,2-disubstituted cyclohexanes bearing migratory groups with  $sp^3$ -hybridized atoms and halogen atoms directly attached with the cyclohexane skeletons are summarized in Table 1 and the optimized structures of the corresponding four-membered transition states are provided in the electronic supplementary information (Fig. 1).

It is evident that 1,2-migration for carbon bearing groups requires higher energy barriers; the maximum for  $CH_3$  groups (entry 1) and it gradually decreases when  $CH_3$  motifs are replaced by  $NH_2$  (entry 2),  $OH$  (entry 3) and  $F$  (entry 4) substituents. In the transition states, the bond distance between the carbon atoms ( $C^\alpha$  and  $C^\beta$ ) bearing  $CH_3$  groups is 1.368 Å, which is an indication of an olefinic bond.

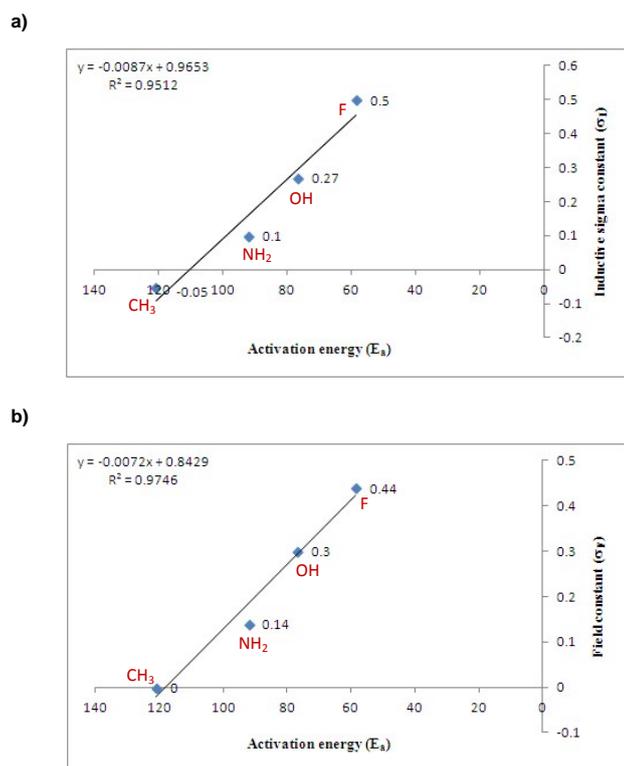
However for  $NH_2$ ,  $OH$  and  $F$  migrating groups, it is in the range of 1.416–1.445 Å.<sup>46</sup> Also, the average bond distance for  $C^\alpha/C^\beta-R/R'$  is comparatively higher for  $CH_3$  groups (2.425 Å) as compared to  $NH_2$ ,  $OH$  and  $F$  moieties (1.909–2.065 Å).

Entry	Substituents (R and R')	Activation energy ( $E_a$ ), <sup>[a]</sup> kcal mol <sup>-1</sup>	Bond distance ( $r$ ), <sup>[b]</sup> Å		Average bond distance ( $r$ ), <sup>[a,b]</sup> Å	Average bond angle ( $\theta$ ), <sup>[a,b]</sup>  $C^\alpha-R-C^\beta$ and $C^\alpha-R'-C^\beta$
			$C^\alpha-C^\beta$	$C^\alpha/C^\beta-R/R'$		
1	$CH_3$	120.9	1.368	2.425	32.77	
2	$NH_2$	92.02	1.445	2.065	43.15	
3	$OH$	76.85	1.416	1.973	42.04	
4	$F$	58.56	1.423	1.909	43.77	
5	$SiH_3$	88.62	1.371	2.879	27.52	
6	$PH_2$	63.67	1.376	2.814	28.28	
7	$SH$	49.00	1.418	2.492	33.04	
8	$Cl$	36.24	1.434	2.384	35.00	
9	$CH_2CH_3$	120.2	1.362	2.541	31.28	
10	$CH(CH_3)_2$	109.4	1.353	2.700	29.03	
11	$C(CH_3)_3$	95.83	1.345	3.107	25.00	
12	$CH_2CHCH_2$	90.16	1.353	3.039	25.54	
13	$Si(CH_3)_3$	97.00	1.362	3.010	26.13	
14	$P(CH_3)_2$	68.22	1.361	2.934	26.81	
15	$OCH_3$	71.29	1.418	1.967	42.25	
16	$SCH_3$	50.14	1.417	2.461	33.45	
17	$OC(CH_3)_3$	89.28	1.431	2.011	41.67	
18	$OCH_2Ph$	79.10	1.422	2.000	41.65	
19	$OCH_2OCH_3$	77.53	1.422	2.033	40.90	
20	$OSi(CH_3)_3$	71.10	1.424	1.975	42.27	
21	$OC(O)CH_3$	63.88	1.420	2.059	40.32	
22	$OPh$	60.99	1.420	2.021	41.14	
23	$OC(O)Ph$	50.42	1.432	2.084	40.20	
24	$Br$	31.50	1.428	2.506	33.11	

**Table 1** Type-I dyotropic reactions for migratory substituents with  $sp^3$ -hybridized atoms and halogen atoms directly attached with the cyclohexane unit. <sup>[a]</sup>For a detailed information about energies, bond distances and bond angles (see ESI). <sup>[b]</sup>the values are for the corresponding transition states.

This decrease in the computed activation barrier in going from  $CH_3$  to  $F$  substituents may be ascribed to the increase in the bond polarity or inductive effect, which is in an order of  $CH_3 < NH_2 < OH < F$ . It significantly influences to stabilize the transition states and decreases the  $E_a$ . Also, it has been proposed for 1,2-disubstituted

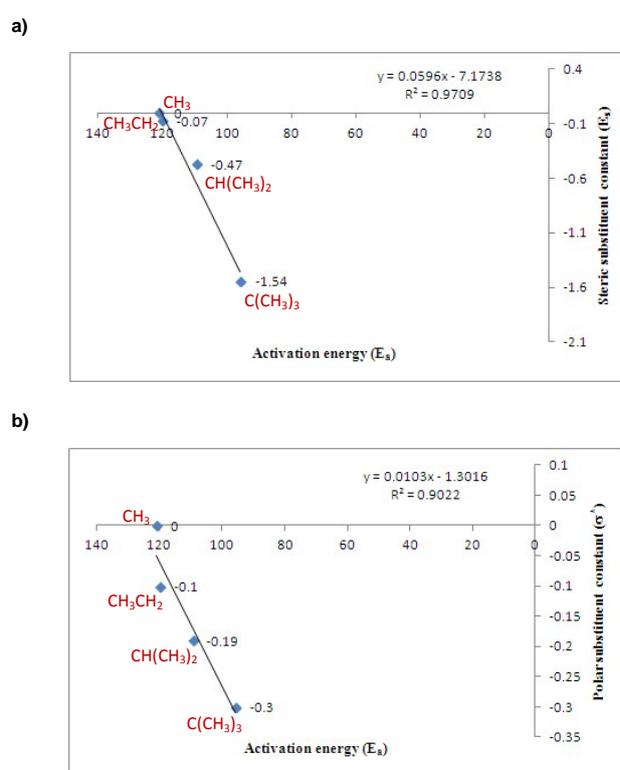
ethane molecules that halogen atoms as migrating groups provide better stabilization to the transition states through an additional donor–acceptor orbital interaction between the lone pairs of halogen atoms and the newly formed ethylenic  $\pi^*$  LUMO.<sup>3b</sup> This additional stabilization completes the pericyclic circuit and consequently, a lower activation barrier is observed. In addition to this, linear free-energy correlations for the energy barriers and inductive sigma ( $\sigma_I$ ) and field ( $\sigma_F$ ) constants for CH<sub>3</sub>, NH<sub>2</sub>, OH and F groups/atoms are shown in Figure 3.<sup>47</sup> From the positive correlation coefficients obtained, it can be concluded that the energy barrier has a strong relationship with the corresponding Hammett constants. Replacing with the substituents bearing the atoms belonging to the third period of the periodic table (entries 5–8), a similar trend is observed;  $E_a$  is in an order of SiH<sub>3</sub> > PH<sub>2</sub> > SH > Cl. Also, the presence of a weaker C–R bond in the reactants corresponds to a lower  $E_a$  and it has been noticed for the pairs SiH<sub>3</sub> and CH<sub>3</sub>, PH<sub>2</sub> and NH<sub>2</sub>, OH and SH, F and Cl. Similar observations for the type-I dyotropic rearrangement barrier have been reported for the pairs CH<sub>3</sub> and F, SiH<sub>3</sub> and Cl substituted ethane molecules and explained in terms of activation-strain and molecular-orbital analyses.<sup>3b</sup>



**Fig. 3** The correlation between the activation energy ( $E_a$ ) of CH<sub>3</sub>, NH<sub>2</sub>, OH and F as migrating groups with their corresponding (a) inductive sigma constants ( $\sigma_I$ ) and (b) field constants ( $\sigma_F$ ).

Interestingly, sequential exchange of hydrogen atoms with CH<sub>3</sub> groups in CH<sub>3</sub> substituents significantly reduces the energy barrier (entries 9–11). For this particular case of carbon bearing migrating fragments, an increase in the steric crowding (by replacing hydrogen atoms with CH<sub>3</sub> groups) result in an increase in the

average bond distances (2.541–3.107 Å) between the carbon atoms (C <sup>$\alpha$</sup>  and C <sup>$\beta$</sup> ) and the substituents (R and R') involved in the transition states. It is conceivable to infer that this increase in the bond distances leads to lower the steric interactions between the substituents and the carbon atoms, which consequently stabilize the corresponding transition states and result in decreasing the  $E_a$  for this double migration process. Notably, the bond angles between carbon atoms (C <sup>$\alpha$</sup>  and C <sup>$\beta$</sup> ) and the substituents (R and R') seem to be related with the steric crowdedness as a gradual decrease in the bond angles is recorded from CH<sub>3</sub> to C(CH<sub>3</sub>)<sub>3</sub> substituents (31.28–25.00°). These results are also supported by linear free-energy relationship described by the Taft equation and strong positive correlations are observed between the activation energy and steric substituent ( $E_s$ ) and polar substituent ( $\sigma^*$ ) constants for CH<sub>3</sub>, CH<sub>3</sub>CH<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub> and C(CH<sub>3</sub>)<sub>3</sub> as shown in Figure 4.<sup>48</sup>



**Fig. 4** The correlation between the activation energy ( $E_a$ ) of CH<sub>3</sub>, CH<sub>3</sub>CH<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub> and C(CH<sub>3</sub>)<sub>3</sub> as migrating groups with their corresponding (a) steric substituent constants ( $E_s$ ) and (b) polar substituent constants ( $\sigma^*$ ).

In addition to this, the migrating ability of allyl group (entry 12) requires higher  $E_a$ , which is probably because of the repulsive interaction between the  $\pi$ -bonds present in the allylic substituents and the newly formed  $\pi$ -bond in the corresponding transition state (TS12, Fig. 1, ESI). Such a repulsion leads to destabilize the TS and causes an increase in the energy barrier. However, the steric effect becomes more pronounced when there is a slight increase in the bond distances between the carbon atoms (C <sup>$\alpha$</sup>  and C <sup>$\beta$</sup> ) and the substituents (R and R') involved in the transition states. It is the case when SiH<sub>3</sub> (entry 5) is substituted with Si(CH<sub>3</sub>)<sub>3</sub> (entry 13); the

difference for average bond distance is of 0.131 Å and for CH<sub>3</sub> and C(CH<sub>3</sub>)<sub>3</sub> groups, it is 0.682 Å. It is plausible that an increase in the steric crowding by replacing H atoms with CH<sub>3</sub> groups result in an enhanced steric repulsion between the substituents and the stationary scaffold, which destabilizes the resultant transition states. This explains why rearrangement of Si(CH<sub>3</sub>)<sub>3</sub> substituent is linked with a higher E<sub>a</sub> than the corresponding [1,2]-shifts for SiH<sub>3</sub> group. Comparing to their respective hydrogenated equivalents, similar effect towards an increase in E<sub>a</sub> has been computed for P(CH<sub>3</sub>)<sub>2</sub> (entry 14), OCH<sub>3</sub> (entry 15) and SCH<sub>3</sub> (entry 16).

At this juncture, an investigation was carried out to understand the behaviour of commonly used OH protecting groups for this [1,2]-shifts approach and a regular pattern can be envisaged. From OH (entry 3) to OC(CH<sub>3</sub>)<sub>3</sub> (entry 17), introduction of the steric bulk significantly increases the energy barrier and this agrees well with other findings of this study, where the steric factor is a dominant contributor. The functional groups OCH<sub>2</sub>Ph (entry 18) and OCH<sub>2</sub>OCH<sub>3</sub> (entry 19) have E<sub>a</sub> values similar to OH groups (entry 3). For OSi(CH<sub>3</sub>)<sub>3</sub> substituents (entry 20), a lower energy barrier of 71.10 kcal mol<sup>-1</sup> is calculated as compared to OH migrating fragments (76.85 kcal mol<sup>-1</sup>). This decrease in the E<sub>a</sub> may be ascribed to the presence of a more polarized O–Si bond than an O–H bond. A significant decrease in the activation barrier is computed for OC(O)CH<sub>3</sub> migrating units (entry 21), where the TS receives better stabilization due to the presence of carbonyl groups. Stabilization of the TS caused by delocalization of the lone pairs of oxygen substituents over aromatic system renders a lower barrier (60.99 kcal mol<sup>-1</sup>) and it has been noticed for OPh groups (entry 22). As anticipated, the energy barrier for OC(O)Ph (entry 23) substituents is remarkably lower than the corresponding OH groups by 26.43 kcal mol<sup>-1</sup> due to additional stabilization, which is clear from the TS23 (Fig. 1, ESI). It is the lowest activation barrier for the considered OH protecting groups, which is a consequence of more stabilized TS due to the presence of improved delocalization. The most feasible migrating fragments for the type-I dyotropic rearrangement among the considered systems are Br atoms (entry 24) with a reaction barrier of 31.5 kcal mol<sup>-1</sup>. This is due to weaker C–Br bonds in the reactant and it is one of the consistent aspects of this study; weaker the C–R bond in the reactants, lower will be the energy barrier.

For comparative purposes and to comprehensively document this investigation, the migratory aptitude for the groups bearing sp<sup>2</sup>- and sp-hybridized carbon atoms was explored. A range of valuable functional moieties were selected, which provides an important information about the specific behaviour of the substituents in this double migration process and the results are summarized in Table 2. In the presence of these functional groups, type-I dyotropic rearrangement for cyclohexanes as stationary scaffolds proceeds *via* high activation barriers (more than 100 kcal mol<sup>-1</sup>) with an exception of C(O)Cl groups. Vinyl groups as migrating substituents require the highest energy barrier (126.1 kcal mol<sup>-1</sup>, entry 1) that is probably due to an increased electronic interaction between the olefinic bonds of the substituents and the newly formed π-bond in

the corresponding TS (TS25, Fig. 1, ESI). A significant decrease of 8.9 kcal mol<sup>-1</sup> is observed when H atoms of the carbon atoms of vinyl groups attached with the cyclohexane unit are swapped by CH<sub>3</sub> groups. By doing this, the steric crowdedness is increased, which generally results in higher E<sub>a</sub>. However, the average distance between the newly formed π-bond in the TS and the substituents increases from 2.31 to 2.372 Å. Probably, this increase stabilizes the TS by reducing the interactions, which would lead to a lower E<sub>a</sub>. The net effect of this replacement is a decrease in the activation barrier and it is in accordance with the findings for other carbon bearing groups such as going from CH<sub>3</sub> to C(CH<sub>3</sub>)<sub>3</sub> substituents, entries 1 and 11 of Table 1 respectively.

Entry	Substituents (R and R')	Activation energy (E <sub>a</sub> ), <sup>[a]</sup> kcal mol <sup>-1</sup>	Bond distance (r), <sup>[b]</sup> Å C <sup>α</sup> –C <sup>β</sup>	Average bond distance (r), <sup>[a,b]</sup> Å C <sup>α</sup> /C <sup>β</sup> – R/R'	Average bond angle (θ), <sup>[a,b]</sup> C <sup>α</sup> –R–C <sup>β</sup> and C <sup>α</sup> –R'–C <sup>β</sup>
1	CHCH <sub>2</sub>	126.1	1.378	2.310	34.73
2	C(CH <sub>3</sub> )CH <sub>2</sub>	117.3	1.375	2.372	33.70
3	C(O)H	111.6	1.364	2.582	30.64
4	C(O)CH <sub>3</sub>	104.5	1.362	2.697	29.24
5	C(O)NH <sub>2</sub>	109.4	1.369	2.539	31.27
6	C(O)NHPh	105.1	1.369	2.597	30.57
7	C(O)OCH <sub>3</sub>	111.1	1.378	2.421	33.06
8	C(O)OH	110.6	1.380	2.410	33.27
9	C(O)OC(O)CH <sub>3</sub>	108.6	1.381	2.417	33.18
10	C(O)F	108.5	1.387	2.372	34.00
11	C(O)Cl	92.50	1.385	2.417	33.31
12	Ph	119.8	1.379	2.328	34.44
13	CCH	115.1	1.431	2.197	40.40
14	CN	106.9	1.410	2.183	37.69

**Table 2** Type-I dyotropic reactions for migratory fragments with sp<sup>2</sup>- and sp-hybridized atoms directly attached with the cyclohexane unit. <sup>[a]</sup>For a detailed information about energies, bond distances and bond angles (see ESI). <sup>[b]</sup>the values are for the corresponding transition states.

The presence of carbonyl groups as migrating substituents withdraw the electronic density from the newly formed π-bonds in a TS, which promotes destabilization of the TS and increases the E<sub>a</sub>. Another factor is steric hindrance offered by bulky substituents attached with the carbonyl groups, which leads to an increased bond distances between the carbon atoms (C<sup>α</sup> and C<sup>β</sup>) and the substituents (R and R') involved in the transition states. This results in lowering the steric interactions hence a decrease in activation barrier as observed for carbon bearing groups as migrating

substituents. So, the carbonyl substituents behave differently and the resultant energy barrier is directly linked with the extent of electron withdrawal and the steric hindrance. The computed activation barriers for C(O)H (entry 3) and C(O)CH<sub>3</sub> (entry 4) are 111.6 and 104.5 kcal mol<sup>-1</sup> respectively. These values are lower than vinyl groups (entry 1) due to increased bond distances and lower repulsive interactions for carbonyl bearing groups as compared to vinyl substituents. The average computed bond distance for C(O)CH<sub>3</sub> substituents is 2.697 Å, while for C(O)H groups is 2.582 Å. Also, CH<sub>3</sub> groups tend to reduce the electron withdrawing ability of the carbonyl group due to hyperconjugation, which leads to stabilize the TS and consequently E<sub>a</sub> is decreased. In case of nitrogen containing substituents like C(O)NH<sub>2</sub> (entry 5) and C(O)NHPH (entry 6), there is a difference of 2.5 kcal mol<sup>-1</sup>. This may be ascribed to a possible extended delocalization of electronic cloud through the involvement of π-electrons from the Ph ring, which can reduce the electron withdrawing ability of the carbonyl group (TS30, Fig. 1, ESI). This can assist to stabilize the TS as compared to the situation when no Ph group is present and consequently, E<sub>a</sub> is significantly decreased.

For oxygen bearing carbonyl groups such as C(O)OCH<sub>3</sub> (entry 7), C(O)OH (entry 8) and C(O)OC(O)CH<sub>3</sub> (entry 9), the energy barriers are 111.1, 110.6 and 108.6 kcal mol<sup>-1</sup> respectively. Moving from C(O)OC(O)CH<sub>3</sub> substituents to C(O)OCH<sub>3</sub>, a decrease of 4.1 kcal mol<sup>-1</sup> that is probably related to better stabilization of newly formed π-bond in the TS by the oxonium species through hyperconjugation. A significant difference of 16.0 kcal mol<sup>-1</sup> in the energy barrier is observed for C(O)F (entry 10) and C(O)Cl (entry 11), which seems to be due to the repulsive interaction of lone pairs on F and Cl atoms with the newly formed π-bond. The average bond distances between the substituents and the carbon atoms (C<sup>α</sup>-C<sup>β</sup>) suggest that these interactions are higher for C(O)F substituents as it is 2.372 Å compared to 2.417 Å for C(O)Cl migrating groups. In addition to this, higher electronegativity of F over Cl atom can destabilize the corresponding TS by withdrawing electronic density from the newly formed π-bond, and cause a higher E<sub>a</sub> for C(O)F substituents.

An installation of Ph groups (entry 12) as migrating substituents show higher value of E<sub>a</sub>, 119.8 kcal mol<sup>-1</sup>, which is significantly lower than the vinyl substituents (entry 1). This seems to be as a result of delocalized π-bonds in the aromatic system, which renders lower electronic interactions between the newly formed π-bond and the π-bonds in the Ph rings. For other synthetic transformations, the existence of *ortho/para* and/or *meta* directing groups on an aromatic ring plays a decisive rule to determine the reactivity and selectivity. In case of type-I dyotropic rearrangement for 1,2-disubstituted cyclohexane, there seems to be a very minor contribution offered by these *ortho/para* and *meta* directors located on Ph substituents.<sup>49</sup> For CCH (entry 13) and CN (entry 14) groups, activation barriers of 115.1 and 106.9 kcal mol<sup>-1</sup> and bond distances (C<sup>α</sup>-C<sup>β</sup>) of 1.431 and 1.41 Å are observed respectively.<sup>46</sup> This decrease in E<sub>a</sub> in going from CCH to CN may be rationalized on the basis of their optimized transition state structures (TS37 and

TS38, Fig. 1, ESI). It is reasonable to suggest that in the case of CN as migrating groups, planarity of the substituents in the TS renders better stabilization and lower repulsive interactions in the TS as compared to CCH groups. Consequently, a lower activation barrier is noticed for CN migrating groups in type-I dyotropic rearrangement of cyclohexanes.

Finally, an investigation towards the energy barriers for asymmetric combinations of substituents was carried out and the results are summarized in Table 3. It provides an interesting information towards captodative substitution, which demonstrates a combined effect of electron withdrawing (captor) and electron donating (dative) substituents attached to the same substrate.<sup>50</sup>

Entry	Substituents		Activation energy (E <sub>a</sub> ), <sup>[a]</sup> kcal mol <sup>-1</sup>	Bond distance (r), <sup>[b]</sup> Å
	R	R'		
1	CH <sub>3</sub>	NH <sub>2</sub>	105.0	1.399
2	CH <sub>3</sub>	OH	90.5	1.388
3	CH <sub>3</sub>	F	77.2	1.385
4	NH <sub>2</sub>	OH	72.7	1.449
5	NH <sub>2</sub>	F	57.3	1.443
6	OH	F	62.0	1.421
7	CH <sub>3</sub>	C(O)CH <sub>3</sub>	113.2	1.367
8	NH <sub>2</sub>	C(O)CH <sub>3</sub>	99.3	1.404
9	OH	C(O)CH <sub>3</sub>	86.9	1.389
10	F	C(O)CH <sub>3</sub>	73.8	1.385
11	CH <sub>3</sub>	CN	94.7	1.394
12	NH <sub>2</sub>	CN	73.5	1.463
13	OH	CN	86.4	1.427
14	F	CN	81.5	1.415
15	C(O)CH <sub>3</sub>	CN	93.0	1.387
16	F	Cl	47.5	1.432
17	F	Br	45.2	1.430
18	Cl	Br	33.9	1.431

**Table 3** Effect of asymmetric combinations of substituents on the activation barriers of 1,2-disubstituted cyclohexanes. <sup>[a]</sup>For a detailed information about energies, bond distances and bond angles (see ESI). <sup>[b]</sup>the values are for the corresponding transition states.

Certain captodative substitution patterns have been found effective in decreasing the activation barriers for several pericyclic transformations.<sup>51</sup> An explanation of the results presented in Table 3 appear somewhat intricate however, couple of aspects can be clearly seen:

1. For most of the substitution patterns studied, the activation energies for unsymmetrical disubstituted cyclohexanes are in between the barrier values obtained for the corresponding individual symmetrical disubstituted cyclohexane systems.

2. An acceleration effect is observed for certain combinations where the energy barriers of asymmetric 1,2-disubstituted cyclohexanes are significantly lower than the analogous symmetrical disubstituted cyclohexanes. These combinations include the presence of two mesomerically electron donating substituents such as NH<sub>2</sub> and OH (entry 4), an electron donating and an electron withdrawing species like CH<sub>3</sub> and CN (entry 11) and both electron withdrawing migrating fragments such as C(O)CH<sub>3</sub> and CN (entry 15).

## Conclusions

A comprehensive investigation towards type-I dyotropic rearrangement for a range of 1,2-disubstituted cyclohexane molecules is presented. The results obtained for the considered groups/atoms are in good agreement with the experimental observations and reported DFT based calculations for the related systems. To establish a free-energy linear relationship, representative activation energy trends are plotted against inductive sigma ( $\sigma_I$ ), field ( $\sigma_F$ ), steric substituent ( $E_s$ ) and polar substituent ( $\sigma^*$ ) constants, which provide a strong positive correlation. The salient conclusions drawn from this double migration process include:

(a) Inductive effect of the substituents plays a substantial role in determining the feasibility of this approach and it is a thermally allowed process for 1,2-dihalogenated cyclohexanes due to added stabilization by the interaction of halogen lone pairs with the newly formed  $\pi$ -bond.

(b) Oxygen, sulphur and phosphorus bearing migrating fragments require moderate levels of activation barriers and these have also been computed for the most common OH protecting groups. The most convenient OH protecting group for type-I dyotropic reaction of 1,2-disubstituted cyclohexane is O(CO)Ph with an activation barrier of 50.42 kcal mol<sup>-1</sup>, which is 26.43 kcal mol<sup>-1</sup> lower than the corresponding OH substituted system.

(c) Installation of carbon, silicon and nitrogen bearing migrating groups proceed *via* higher energy barriers; the maximum is for carbon atoms.

(d) The presence of carbonyl groups as migrating units result in higher activation energies for the considered groups because of enhanced destabilization of the transition states.

(e) Phenyl (Ph) rings as migrating substituents have higher energy barriers and there is a slight difference in the  $E_a$  caused by the synergistic effect of electron donating and withdrawing groups.

(f) Increase in steric bulk of the substituents lead to higher energy barriers and increase in the bond distances between the carbon atoms (C <sup>$\alpha$</sup>  and C <sup>$\beta$</sup> ) and the substituents (R and R') involved in the transition states decreases the activation barrier.

(g) Asymmetric combinations of substituents usually proceed with an energy barrier related to the corresponding individual symmetrically disubstituted systems however for certain unsymmetrical combinations, such as NH<sub>2</sub> and OH, CH<sub>3</sub> and CN, and C(O)CH<sub>3</sub> and CN, an extra acceleration effect is observed which leads to a significant decrease in the activation energy of 1,2-asymmetric disubstituted cyclohexane molecules.

## Methods

All calculations were performed with the Gaussian 09W programme<sup>52</sup> and the results were produced with GaussView 5.0. Density functional theory (DFT)<sup>53</sup> calculations using the B3LYP functional<sup>54</sup> were used to locate all the stationary points involved. Geometries were optimized at B3LYP/6-31+G(d,p) level of theory, which has been successfully applied to related dyotropic reactions.<sup>37,42</sup> The frequency calculations were run at the same level of theory to confirm each stationary point to be either a minimum or a transition structure. The transition states were also linked to their corresponding minima through the intrinsic reaction coordinate (IRC)<sup>55</sup> calculations (see ESI for details), which confirm the connection of transition structures with the reactants and products. Zero-point energy (ZPE) values were computed from the optimized geometries at 298.15 K and are not corrected.

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## Type-I dyotropic rearrangement for 1,2-disubstituted cyclohexanes: substitution effect on activation energy

### Short statement and graphical abstract

Migratory aptitude and contribution of specific structural features of synthetically valuable functional groups and halogen atoms in type-I dyotropic rearrangement for both symmetric and unsymmetrical 1,2-disubstituted cyclohexanes are computed.

