

Full Length Research Paper

# Theoretical study of phthalane oxidation and effect of substituents by using Hyperchem program

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The effect of substituents on the relative stabilization energy ( $E_{RS}$ ) of phthalane-X carbocations has been studied with PM3 semi-empirical molecular orbital theory. The results show that the amino group gives  $E_{RS}$  less than zero for very big amount and that will increase stability of carbocation by  $\pi$ -electron donation, whereas the nitro group gives height amount of  $E_{RS}$  more than zero and that will lead to difficulties of an intermediate carbocation formation because of its strong  $\sigma$ - and  $\pi$ -accepting nature.  $E_{RS}$  decreases with increase in the phenyl rings attached to cation. When electron withdraws substituents attached, it will destabilize the cation, because they act as  $\pi$ -electron donors.

**Key words:** Relative stabilization energy ( $E_{RS}$ ), PM3 semi-empirical, isodesmic reactions.

## INTRODUCTION

Phthalane (1,3-dihydroisobenzofuran or 1,3-dihydro-2-benzofuran) also known as isocoumaran, is a bicyclic aromatic organic compound and it can be oxidized to phthalic acid (Schulz, 1959). Phthalic acid is an isomer of isophthalic and terephthalic acid (Christensen et al., 1977). In inhibiting the amine pump in adrenergic neurons, phthalane is approximately equipotent with tricyclic compounds like antidepressants (Maxwell et al., 1980). For full potency to be expressed, it requires the presence of a phenyl ring on the bicyclic nucleus (Heudorf et al., 2007; Kolarik et al., 2008). Phthalane contained methyl groups on their bicyclic ring system which are involved in binding to the receptor (Sathyanarayana et al., 2008). Derivatives are found in the drug candidate Lu 10 to 171 and drug citalopram (Hernández-Díaz, 2009).

Thermochemistry is the study of nature of energy, energy change in chemical reactions, enthalpy, calorimetry, standard enthalpy of formation and reaction and thermodynamics-thermochemistry (Lomenick et al., 2010).

In chemical reaction, the energy could be release or absorb (Getman, 1918), also, a phase could be changed

as melting or boiling. Thermochemistry could be used to predict if the reaction is going to forward direction or back direction (Laidler and Meiser, 1982). The system in thermochemistry is the part that has been studied from the universe (Perrot, 1998). Heat is absorbed in endothermic reactions and it release in exothermic reactions (Atkins and Paula, 2006).

Hehre et al. (1970) defined isodesmic reactions as "chemical changes in which there is retention of the number of bonds of a given formal type, but with a change in their relation to one another". In isodesmic reactions, reactants and products have the same number of electron pairs (George et al., 1976). In a thermochemical sense, it can be used to quantify the stability of reactive intermediates (Rose and Williams, 2002). By hypothetical reaction, the effect of a particular structural feature could get and the best way to cancel out errors in computations (Matthias et al., 2006). Homodesmotic reactions are a subclass of isodesmic reactions where reactants and products share even larger similarity (Grimme et al., 2007). Various definitions have been given for this class in the past and the most consistent one (Wheeler et al., 2009).

The object of this study is to theoretically study the effect of adding substitution on phthalane at para position to find the relative stabilization energy ( $E_{RS}$ ) according to isodesmic reactions by comparing the energies (which equals  $\Delta H$ ) of the difference adding groups.

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## COMPUTATIONAL DETAILS

All structures, were optimized in the gas phase using parameterized model number 3 (PM3) (Stewart, 1998), a semi-empirical method for the quantum calculation of molecular electronic structure in computational chemistry (Stewart, 2004), implemented in the HyperChem8.0 package (Hypercube, 2007). Adding substituted and conjugate acids flowing in the order as shown in Figure 1 and Table 1.

The heat of formation and total energy was found, calculation of  $E_{RS}$  was by calculating the differences in heats of formation close to difference in binding energies (which we often use just for the sake of convenience); however, in this case, we follow the practice of most chemistry journal authors (El-Nahas and Clark, 1995).

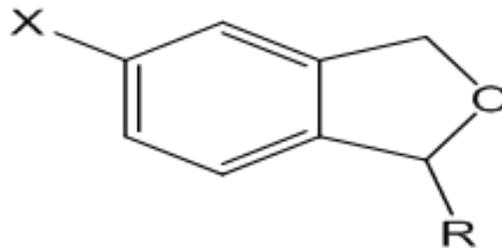
## RESULTS AND DISCUSSION

The study of acid catalyzed hydrolysis of an acetal related to a 4-substituted phthalane and the effect different 4-substituents might have on the rate of hydrolysis. We tested the conclusion by investigating the stabilities of similar carbocations using a computational chemistry tool called an isodesmic equation, as shown in Figure 2. The rates of these reactions were measured experimentally by Rose and Williams (2002).

The objective of this study is to computationally determine the effect of different groups X on the formation of the carbocations. It is difficult to just compare the energies of the different carbocations, because the groups X differ. The difference in energy between the aforementioned reaction for X= H and X = another group, as shown in Figure 3. This is called the "Relative Stabilization Energy", which equals  $\Delta H$  for the following reaction.

Figure 3 is an isodesmic reaction, defined as a chemical reaction in which the type of chemical bonds broken in the reactant is the same as the type of bonds formed in the reaction product. This is often used to calculate substituent effects. From Table 2, after calculation of  $E_{RS}$ , it shows for primary carbocation when substituted group (R) is hydrogen (H) at compounds (1 to 12), and the  $E_{RS}$  increases at the sequence of  $4 < 3 < 6 < 2 < 7 < 5 < 8 < 1 < 10 < 11 < 9 < 12$ .

Negative value of  $E_{RS}$  less than zero ( $E_{RS} < 0$ ) refers to the substituted group which will increase the ability to form the carbocation more than when the substituted group is hydrogen. At compound 4, when the substituted group is ( $\text{NH}_2$ ), there will be increased stability of carbocation in very big amount according to  $E_{RS}$  less than zero ( $E_{RS} < 0$ ). This will increase the stability of an intermediate carbocation formation, and will increase reaction speed. This is because the amino group has the highest stabilization by  $\pi$ -electron donation. Also, for compound 12 when the substituted group is ( $\text{NO}_2$ ), the  $E_{RS}$  has the highest amount and that will lead to difficulties of an intermediate carbocation formation. This is because nitro group is most destabilizing because of its strong  $\sigma$ - and  $\pi$ -accepting nature, thereby leading to decrease in the stability of an intermediate carbocation



**Figure 1.** Adding substituted and conjugate acid to phthalane.

**Table 1.** Adding substituted and conjugate acid to phthalane.

Compound	X	R
Original compound	H	H
1	F	H
2	OH	H
3	OCH <sub>3</sub>	H
4	NH <sub>2</sub>	H
5	CH <sub>3</sub>	H
6	C <sub>6</sub> H <sub>5</sub>	H
7	CH=CH <sub>2</sub>	H
8	C≡CH	H
9	CN	H
10	CHO	H
11	COOH	H
12	NO <sub>2</sub>	H
13	F	CH <sub>3</sub>
14	OH	CH <sub>3</sub>
15	OCH <sub>3</sub>	CH <sub>3</sub>
16	NH <sub>2</sub>	CH <sub>3</sub>
17	CH <sub>3</sub>	CH <sub>3</sub>
18	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
19	CH=CH <sub>2</sub>	CH <sub>3</sub>
20	C≡CH	CH <sub>3</sub>
21	CN	CH <sub>3</sub>
22	CHO	CH <sub>3</sub>
23	COOH	CH <sub>3</sub>
24	NO <sub>2</sub>	CH <sub>3</sub>

formation. When substituted group (R) is methyl (CH<sub>3</sub>) at compounds (13 to 24), it will form secondary carbocation, and  $E_{RS}$  will increase at the sequence of  $16 < 15 < 18 < 14 < 19 < 17 < 20 < 13 < 22 < 23 < 21 < 24$ . Also, at the same substituents at compound 16 when substituted group is NH<sub>2</sub>, the lower amount of  $E_{RS}$  is less than zero ( $E_{RS} < 0$ ), and at compound 24 when the substituted group is NO<sub>2</sub>,  $E_{RS}$  is in the highest amount. This methyl group increases all the amount of  $E_{RS}$  more than how hydrogen do, by decreasing the stability of an intermediate carbocation formation and will lead to decrease

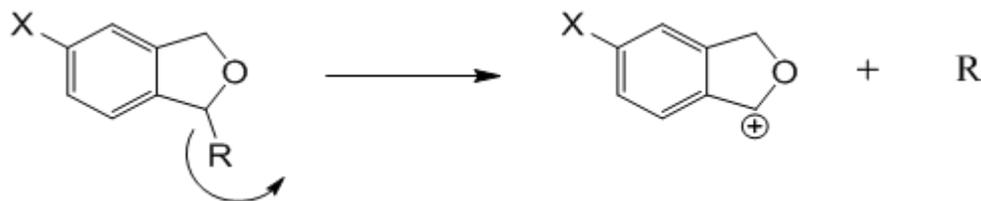


Figure 2. Acid catalyzed hydrolysis of an acetal.

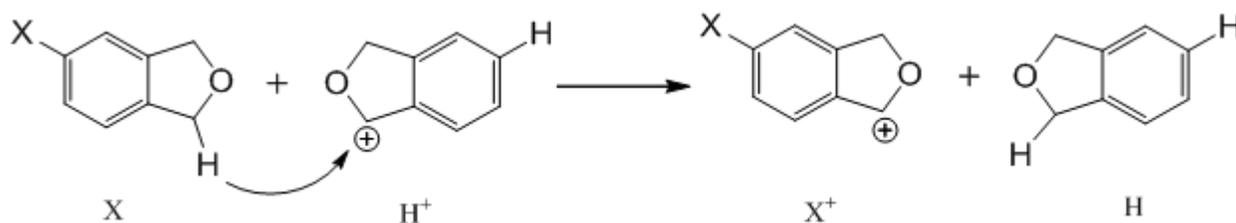


Figure 3. Formation of the carbocation.

Table 2. Theoretical value of calculated relative stabilization energy (ERS) (kcal/mol).

Compound	Heat of formation for H (R=H, X=H)	Heat of formation for H <sup>+</sup> (R=H, X=H)	Heat of formation for X	Heat of formation for X <sup>+</sup>	$E_{RS} = \Delta H(X) - \Delta H(H)$
1	-13.338	177.659	-56.805	137.25	3.058
2	-13.338	177.659	-58.403	127.864	-4.73
3	-13.338	177.659	-51.323	133.567	-6.107
4	-13.338	177.659	-15.557	163.434	-12.006
5	-13.338	177.659	-22.701	165.579	-2.717
6	-13.338	177.659	10.775	196.561	-5.211
7	-13.338	177.659	2.327	189.72	-3.604
8	-13.338	177.659	37.885	226.849	-2.033
9	-13.338	177.659	22.042	220.317	7.278
10	-13.338	177.659	-47.245	148.919	5.167
11	-13.338	177.659	-102.726	94.287	6.016
12	-13.338	177.659	-21.711	183.937	14.651
13	-19.153	163.798	-62.648	123.383	3.08
14	-19.153	163.798	-64.246	114.673	-4.032
15	-19.153	163.798	-57.163	120.495	-5.293
16	-19.153	163.798	-21.389	151.214	-10.348
17	-19.153	163.798	-28.54	152.01	-2.401
18	-19.153	163.798	4.961	183.477	-4.435
19	-19.153	163.798	-3.482	176.399	-3.07
20	-19.153	163.798	32.071	213.384	-1.638
21	-19.153	163.798	16.207	206.208	7.05
22	-19.153	163.798	-53.058	134.802	4.909
23	-19.153	163.798	-108.542	80.118	5.709
24	-19.153	163.798	-27.541	169.247	13.837

reaction speed, except when the substitutes are CHO, COOH and NO<sub>2</sub> and will increase  $E_{RS}$  as compared to when the substituted group (R) is hydrogen (H). The

effect for substituents on  $E_{RS}$  at phthalane will follow the same order for primary and secondary carbocation.

We can classify substituents into four categories: (1)

lone pair electron donors (F, OH, OCH<sub>3</sub> and NH<sub>2</sub>, (2) conjugated systems (C<sub>6</sub>H<sub>5</sub>, CH=CH<sub>2</sub> and C≡CH), (3) hyperconjugative groups (CH<sub>3</sub>) and (4) σ- and π-acceptors (CN, CHO, COOH and NO<sub>2</sub>). If we look to F, OH, OCH<sub>3</sub> and NH<sub>2</sub> as lone pair electron donors, despite of their σ-withdrawing nature, F, OH, OCH<sub>3</sub> and NH<sub>2</sub> will give large amount of  $E_{RS}$ , with the amino group being the most effective. The stability of these carbocations decrease with increasing substituent electro negativities.

For conjugated systems (C<sub>6</sub>H<sub>5</sub>, CH=CH<sub>2</sub> and C≡CH), these groups have double bonds which can resonate with the adjacent cation center. The  $E_{RS}$  order is C<sub>6</sub>H<sub>5</sub> < CH=CH<sub>2</sub> < C≡CH in line with the ability of these substituents to donate their π-electrons. As a hyperconjugative group, methyl group shows a moderate effect on  $E_{RS}$  due to its π-electron donation through hyperconjugation, while σ- and π-acceptors, (CN, CHO and COOH) shows significant π-interaction between these groups and the vacant p orbital at the cation center. The  $E_{RS}$  order CN > COOH > CHO indicating the degree of π-contribution. The strongest electron-withdrawing group, NO<sub>2</sub>, give the most destabilized carbocations as the highest  $E_{RS}$  in the whole series.

In all compounds, the ability of reaction increases with the increase of stability for an intermediate carbocation formation when  $E_{RS} < 0$  and the ability of reaction decreases with decrease of stability for an intermediate carbocation formation when  $E_{RS} > 0$ .

## Conclusions

In this study,  $E_{RS}$  of phthalane oxidations and effect of substituents on the original compound has been calculated to investigate the stabilities of similar carbocations by using computational chemistry called an isodesmic equation. For primary and secondary carbocations, the effect for substituents on  $E_{RS}$  at phthalane will follow the same order. The amino group will increase the stability of carbocation in very big amount according to the  $E_{RS}$  (that is, less than zero), and the nitro group is the most destabilizing.

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