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ORIGINAL ARTICLE

The Substituent Effects on Chemical Reactivity and Aromaticity Current of Ritalin Drug

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KEYWORDS

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ABSTRACT: In this study, the effects of four substitutions in two different positions of Methylphenidate (MPH, Ritalin) structure on chemical reactivity indices and aromaticity current of benzene ring were investigated at the density functional theory (DFT) level. The results were interpreted using natural bond orbital (NBO) analysis. The findings indicated that by increasing the participation of the studied substitutions in intramolecular interactions, their effect on the chemical reactivity indices and aromaticity current increased. Therefore, the substituents NO_2 and Cl on the benzene ring, with the highest participation in intramolecular interactions, caused the highest increase in the resonance interactions of the benzene ring. As a result, they increased the values of the Nuclear Independent Chemical Shift (NICS) in the geometric center of the ring. Also, the above substitutions decreased the energy gap between HOMO (highest occupied molecular orbitals) orbitals and LUMO (lowest unoccupied molecular orbitals) and increased chemical reactivity indices. On the other hand, The NBO results represented that electron-withdrawing substituents at positions R_7 and R_9 reduced the accumulation of negative charge on adjacent atoms and the benzene ring.

INTRODUCTION

Methylphenidate (MPH), under the brand name of Ritalin, is a similar compound to amphetamines and stimulates the central nervous system. It is used to treat depression, narcolepsy and the Attention Deficit Hyperactivity Disorder (ADHD) in children [1]. Methylphenidate has two chiral centers and is found in the form of four optical isomers D and L-threo and D and L-erythro. However, Ritalin is marketed as a racemic mixture of the optical isomers D-threomethylphenidate and L-threomethylphenidate [2]. Numerous theoretical and experimental studies have been devoted to investigate crystal structures, MPH conformal analysis and its analogues in solid and soluble states[3–6] and NMR and IR spectroscopy techniques have been used in this field [7,8]. Conformational analysis of neutral and protonated forms of methylphenidate has also been performed by Gilbert et al. using molecular and quantum mechanics methods [9]. Ritalin structure consists of two rings (benzene ring and the hexagonal ring of piperidine), both of which are attached to a carbon atom (C_8) (Figure1). Substitution at different two-ring positions produces a large number of MPH analogues, many of which have been synthesized and studied [10]. Misra et al. studied 80 methylphenidate analogues using quantitative structure-activity relationships (QSAR) to obtain a preliminary model for the binding affinity of those compounds to dopamine carriers [11]. In addition, Gatley et al. investigated the affinities of methylphenidate derivatives with respect to dopamine norepinephrine and serotonin carriers [12]. As mentioned above, the substituent effects in different positions of Ritalin structure on its biological activity have been investigated.

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Many studies have been done on conformational analysis and the investigation of crystallographic structures of MPH and its derivatives. However, the substituent effects at different positions of MPH on effective structural parameters such as aromaticity current of benzene ring and chemical reactivity indices have not been studied so far. In this study, the effects of substituent changes in MPH on the reactivity indices and the benzene aromaticity current were investigated using DFT methods. The results were interpreted using NBO analysis based on molecular structure.

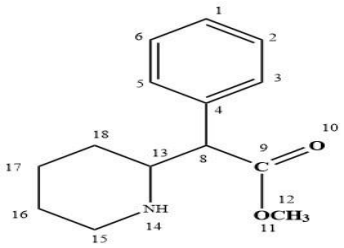


Figure1. The chemical structure of Ritalin and the atomic numbering used in this study.

Computational details

Geometrical optimizations of Ritalin and its derivatives (compounds 1-5, Figure 2) were performed at B3LYP / 6-311 ++ G (d, p) level of theory [13,14]. The nature of stationary points for the interested structures was determined by calculating the harmonic frequencies at the same level of theory. For minimum state structures, only the real frequency values were accepted. The energy gap values of HOMO and LUMO orbitals (HLG) were obtained using the results of molecular orbitals calculations. The reactivity indices of compounds 1-5 such as chemical hardness (η), electrophilicity (ω) and electronegativity (□) were calculated using the following formulas [15–17]:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

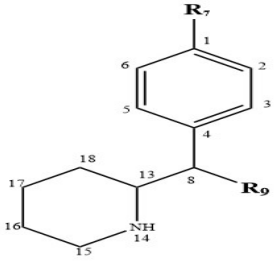
$$\omega = \frac{\mu^2}{2\eta}$$

$$\chi = \frac{-(E_{HOMO} + E_{LUMO})}{2}$$

Also, the negative of the electronegativity was defined as chemical potential (μ) [18] and chemical softness (S) was just the inverse of chemical hardness (S=1 /η).

To investigate the effect of substituent change on aromaticity current of benzene ring and to evaluate the intensity of diamagnetic currents, the Nuclear Independent Chemical Shift (NICS) technique was used on optimized structures of compounds 1-5 at B3LYP / 6-311 ++ G (d, p) level of theory. NICS was defined by Schleyer et al. as the negative value of absolute magnetic shielding computed in centers of rings or 1 Å above the molecular plane [19]. NICS at an empty point in space equals zero and in principle did not require reference molecules and calibrating (homodesmotic) equations for evaluation of aromaticity. Negative values of NICS indicated the shielding presence of induced diatropic ring currents understood as aromaticity at the specific point.

Finally, NBO analysis was performed on the optimized structures at B3LYP / 6-311 ++ G (d, p) level of theory[20,21]. All calculations were performed in the gas phase using Gaussian 09 software [22].



1.R_9=CO_2CH_3, R_7=H, 2.R_9=CHNH, R_7=H

3. R_9=H, R_7=H, 4.R_9=CO_2CH_3, R_7=Cl, 5. R_9=CO_2CH_3, R_7=NO_2

Figure2. The chemical structure of Ritalin and its studied derivatives (compounds 1-5). The investigated substitutions in positions R_7 and

RESULTS AND DISCUSSION

Chemical reactivity indices

The results of chemical reactivity calculations showed that compound 5 had the highest electronegativity, electrophilicity and dipole moment, as well as the lowest chemical hardness among compounds 1-5 (Table 1). With the substituent change in positions R_7 and R_9 of MPH structure, the order of electrophilicity and electronegativity values in the studied compounds was similar and it was 5>4>2>1>3. The order of chemical hardness changes was exactly the opposite of the order mentioned for electrophilicity and electronegativity (Figure3) and it was identical to the order of HLG values. High HLG value means that the molecule was hard. This difference could relate the stability of the molecule to its chemical hardness, meaning that a molecule with a minimum HLG was a more reactive molecule. With the substituent change in compounds 1-5, the order of dipole moment (d) values was 5>4>2>3>1. Therefore, the calculated reactivity indices demonstrated that the electron-withdrawing substituents (NO_2 and Cl**)** on the MPH structure increased its chemical reactivity.

Table 1. The calculated values of HLG (in eV), chemical hardness (η) , chemical softness(S), electronegativity(□) , chemical potential (μ) , electrophilicity and dipole moments (d in Debye) of compounds 1-5 studied at B3LYP/6-311++G(d, p) level of theory.

Compound	HLG	η	S	□	μ	ω	d
	eV						Debye
1	-5.500	2.7511	9.8912	3.3307	-3.3307	2.019	1.1347
2	-5.433	2.7162	10.0180	3.4232	-3.4232	2.155	2.1956
3	-5.511	2.7554	9.8756	3.2186	-3.2186	1.880	1.7165
4	-5.415	2.7048	10.0502	3.5130	-3.5130	2.278	3.4028
5	-3.773	1.8858	14.4248	4.5960	-4.5960	5.597	7.2539

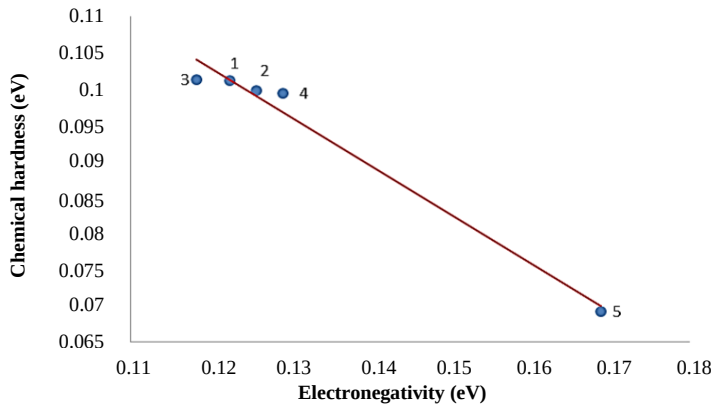


Figure 3. Chemical hardness values as a function of electronegativity values in compounds 1-5.

NICS results

In this study, the NICS technique at B3LYP / 6-311 ++ G (d, p) level of theory was used to evaluate the aromaticity current in the benzene ring and the intensity of the ring diamagnetic currents in MPH and its derivatives. In all compounds 1-5, the sets of points located below and above the geometric center of the ring were used. Their locations correspond to distances from -5 to +5 Å relative to the geometric center of the benzene ring with 0.5 Å steps. The NICS diagrams of compounds 1-5 were almost symmetrical along the molecule plane. Therefore, only the NICS values above the plane were presented in Figure 4. The numerical values of NICS and Figure 4 confirmed that all analogues were aromatic, and all of them exhibited a certain decrease of NICS value from the point located in the geometric center of the ring to 1 Å above or below it. The results indicated that the minima

of NICS values were located at the distance of 0.5–1.0 Å below and above the plane. This result was consistent with the presence of delocalized π-electrons current above and below the molecule planes as expected for aromatic compounds. The maximum diatropic current was observed at the 0.5-1.0 Å above the geometric center of five analogues. The NICS 0 Å values in the ring center NICS (0) were affected by sigma bonds. However, the NICS values up to 1 Å from the geometric center and above ring NICS (1) were affected more by π bonds. The strongest aromaticity quality was observed in the geometric center of the benzene ring in compound 5 and compound 2 had the least aromaticity. The order of NICS (0) values in compounds 1-5 was 5>4>1>3>2. However, this order was at NICS (0.5) as 4>5>3>1>2 and at NICS (1) at the 1 Å above the plane was 1>3>4>5>2. Therefore, the results showed that the electron-withdrawing substituents (NO_2 and Cl**)** increased diatropic currents and enhanced aromatic quality in the geometric center of ring benzene. At NICS (0.5), substituent Cl had the greatest effect on aromaticity quality, which indicated its effect on the π-electrons clouds of the benzene ring. As the distance from the center of the ring increased, the effect of electron-withdrawing substituents (NO_2 and Cl**)** on the aromaticity of benzene ring decreased.

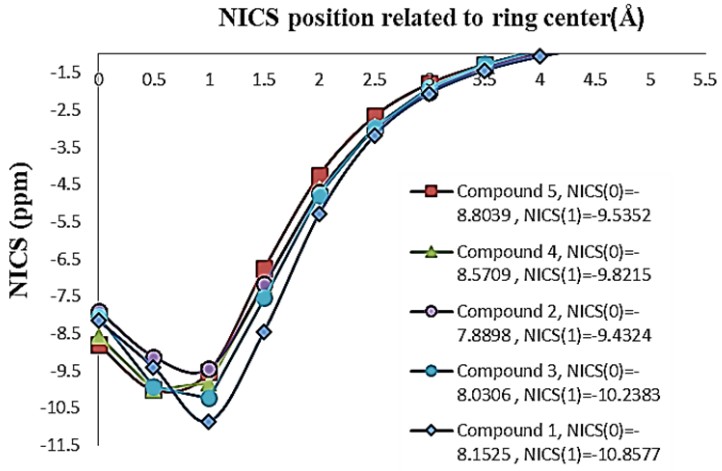


Figure 4. Aromaticity of compounds 1-5 estimated as a function of NICS (negative value of absolute magnetic shielding) versus distance from ring geometric center. NICS (0) and NICS (1) denoted values estimated at ring geometric center and 1 Å above, respectively.

NBO analysis

NBO analysis results of MPH and its analogues at the computational level of B3LYP / 6-311 ++ G (d, p) were reported in Tables 2 and 3. The results indicated that the nitrogen of piperidine ring (N_{14}) in compound 2 had the highest value of negative charge and C_9 nuclei in compound 1 (Ritalin) had the highest value of positive charge among the studied atoms. NO_2 oxygens in compound 5 also had the lowest negative charge values among the oxygen atoms in the investigated structures. The findings represented that the substituent change in positions R_7 and R_9 had the greatest effect on the values of atomic charges C_1 and C_8 nuclei (range of atomic charge changes was 0.28e and 0.5e for nuclei C_1 and C_8, respectively). The order of the values of the negative charges on atoms C_1 and C_8 in the studied compounds was 3>2>1>4>5 and 3>5>1>4>2, respectively. As observed, the electron-withdrawing substituents at positions R_7 and R_9 reduced the negative charge on adjacent atoms, especially C_1. The order of negative charge values on the benzene ring was identical to the observed order of charge values on the C_1 atom. Interestingly, both C_1 and C_8 nuclei had the highest negative charge in compound 3, which was free of any electron-withdrawing substituents at positions R_7 and R_9. The order of the negative charge values on C_9 and N_{14} atoms was 1>4>5>2 and 2>3>5>4>1, respectively. However, the least effect of substituent changing was observed in the negative charge values of O_{10} and O_{11} nuclei and the order of the negative charge values on them was the same; it was 1>4>5. The NBO analysis also stated that the lone-pairs electrons of oxygens (LPOs) in compounds 1-5 were affected more in intramolecular

interactions than LP Ns (lone- pair electrons of nitrogens) and LP Cls (lone-pairs electrons of chlorine) and had higher resonance energy (E (2)). The highest value of resonance interactions was related to LP $O_7 \rightarrow \sigma^*$ or π^* interactions of substituent NO_2 in compound 5 (the total interaction energy of LPOs in substituent NO_2 was 240.45 kcal/mol). The point to consider in the intramolecular interactions of NO_2 and Cl substations was that all the LPOs interactions of NO_2 group were with the sigma bonds of the molecule and the benzene ring. However, the LP Cls interactions of compound 4 were with sigma bonds and also the π-electron system of the benzene ring. The NBO results obtained were in agreement with the NICS values in the geometric center of the ring NICS (0) up to one angstrom above the ring. The order of interaction energy values related to BD (1) C - C $\rightarrow \sigma^*$ or π^* and BD (2) C - C $\rightarrow \sigma^*$ or π^* interactions in the benzene ring by substituent changing was 5>4>1>2>3. The above order was exactly the opposite of the observed order for the electrical charge of the carbon atoms of the benzene ring and very close to NICS (0) (Figure 5). On the other hand, the findings showed that the substituent change in positions R_7 and R_9 had the greatest effect on the LP N_{14} interaction energy of the piperidine ring. The range of change in resonance energy associated with the LP $N_{14} \rightarrow \sigma^*$ or π^* interactions by substituent change was 1.85 kcal/mol. The order of resonance energy values related to the interactions of LP O_{10} and LP O_{11} was almost the same and was the opposite of the order of their negative charge values. From the whole results, it could be stated that with increasing the participation of LPOs in the intramolecular interactions of the studied compounds, the negative charge on them decreased. Meanwhile, the chemical reactivity increased and the aromaticity of the benzene ring in its geometric center was enhanced.

Table 2. Calculated values of natural atomic charges (in atomic unit (e)) and total resonance energy (∑E (2) in kcal/mol) values related to LP $\rightarrow\sigma^*$ or π^* interactions of nitrogen, oxygen and chlorine lone- pairs electrons of compounds 1-5 at B3LYP/6-311++G** level of theory.

Compound=1	**C_1**	**C_8**	**C_9**	**O_{10}**	**O_{11}**	**N_{10}**	**N_{14}**
Charge	-0.2067	-0.3256	0.8344	-0.6163	-0.5484	-	-0.6896
∑E(2) LP(1) → σ* or π*	-	-	-	3.61	10.48	-	21.01
∑E(2) LP(2) → σ* or π*	-	-	-	50.49	56.02	-	-
Compound=2							
Charge	-0.2084	-0.2978	0.1702	-	-	-0.6168	-0.7046
∑E(2) LP(1) N → σ* or π*	-	-	-	-	-	13.01	19.89
Compound=3							
Charge	-0.2121	-0.3914	-	-	-	-	-0.6933
∑E(2) LP(1) N → σ* or π*	-	-	-	-	-	-	19.57
Compound=4							
Charge	-0.0376	-0.3243	0.8336	-0.6155	-0.5478	-	-0.6901
∑E(2) LP(1) → σ* or π*	-	-	-	3.62	10.47	-	21.15
∑E(2) LP(2) → σ* or π*	-	-	-	50.3	56.58	-	-
Compound=5							
Charge	0.0651	-0.3302	0.8318	-0.6115	-0.547٦	-	-0.6907
∑E(2) LP(1) → σ* or π*	-	-	-	3.63	10.51	-	21.42
∑E(2) LP(2) → σ* or π*	-	-	-	51.00	56.74	-	-

Table 3. Calculated values of natural atomic charges (in atomic unit (e)) and interaction energy (E (2) in kcal/mol) values related to LP $\rightarrow\sigma^*$ or π^* interactions of oxygen and chlorine lone- pairs electrons of compounds 4 and 5 at B3LYP/6-311++G** level of theory.

Compound	Type	Charge	Intra-molecular Interactions	E(2)
4	**Cl_7**	-0.0059		
	LP(1)Cl_7		LP(1) $Cl_7 \rightarrow$ BD*(1) C_1 - C_2	1.63
			LP(1) $Cl_7 \rightarrow$ BD*(1) C_1 - C_6	1.63
	LP(2)Cl_7		LP(2) $Cl_7 \rightarrow$ BD*(1) C_1 - C_2	4.09
			LP(2) $Cl_7 \rightarrow$ BD*(1) C_1 - C_6	4.07
	LP(3)Cl_7		LP(3) $Cl_7 \rightarrow$ BD*(2) C_1 - C_6	12.05
5				
	N_7	0.4851		
	O_{7-1}	-0.3821		
	LP(1) O_{7-1}		LP(1) $O_{7-1} \rightarrow$ BD*(1) C_1 - N_7	4.20
			LP(1) $O_{7-1} \rightarrow$ BD*(1) N_7 - O_{7-2}	2.34
	LP(2) O_{7-1}		LP(2) $O_{7-1} \rightarrow$ BD*(1) C_1 - C_2	0.68
			LP(2) $O_{7-1} \rightarrow$ BD*(1) C_1 - N_7	12.07
			LP(2) $O_{7-1} \rightarrow$ BD*(1) C_5 - C_6	0.53
			LP(2) $O_{7-1} \rightarrow$ BD*(1) N_7 - O_{7-2}	18.99
	O_{7-2}	-0.3833		
	LP(1) O_{7-2}		LP(1) $O_{7-2} \rightarrow$ BD*(1) C_1 - N_7	4.20
			LP(1) $O_{7-2} \rightarrow$ BD*(1) N_7 - O_{7-1}	2.33
	LP(2) O_{7-2}		LP(2) $O_{7-2} \rightarrow$ BD*(1) C_1 - C_6	0.68
			LP(2) $O_{7-2} \rightarrow$ BD*(1) C_1 - N_7	12.05
			LP(2) $O_{7-2} \rightarrow$ BD*(1) $C_۲$ – $C_۲$	0.54
			LP(2) $O_{7-2} \rightarrow$ BD*(1) N_7 - O_{7-1}	18.95
	LP(3) O_{7-2}		LP(3) $O_{7-2} \rightarrow$ BD*(1) N_7 - O_{7-1}	162.82

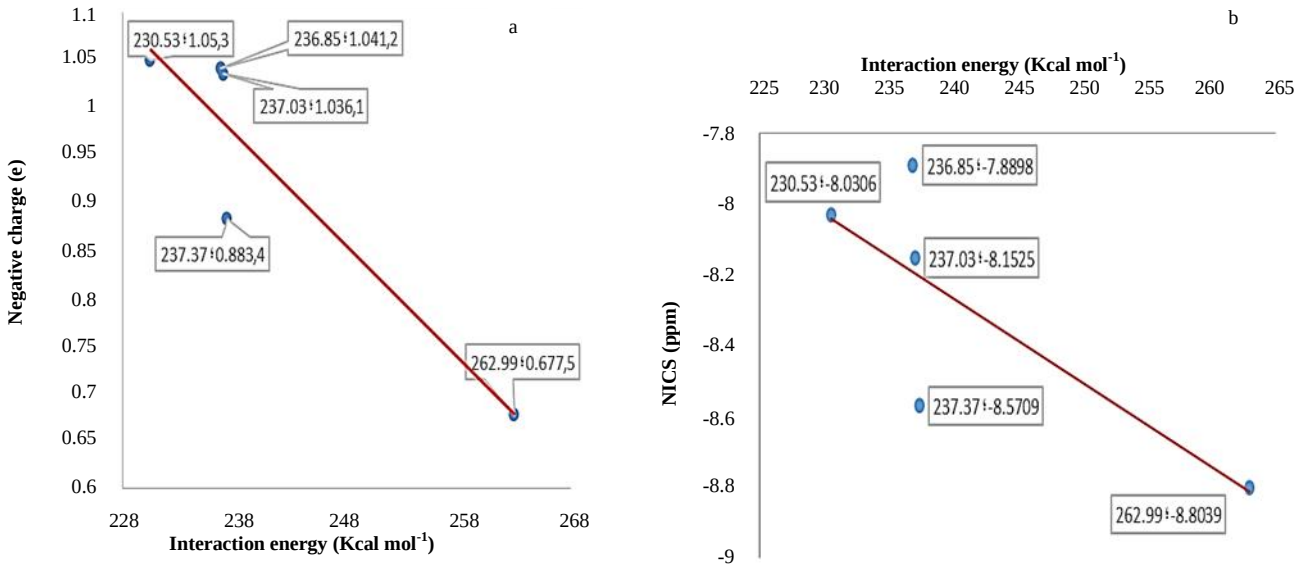


Figure 5. a) Negative charge values of the benzene ring as a function of the interaction energy of benzene ring atoms and **b)** NICS values of the benzene ring as a function of the interaction energy of benzene ring atoms in compounds 1-5.

CONCLUSIONS

Investigation of the substituent effects is one of the important research aspects in the chemistry of medicinal compounds. In this study, it was attempted to show the role of substituent change at two different MPH positions on structural parameters, chemical reactivity and aromaticity current. The results represented a good and reasonable relation between structural parameters such as intramolecular interactions and atomic charges with chemical reactivity and aromaticity current in Ritalin and its derivatives. The findings indicated that with increasing participation of the studied substitutions in intramolecular interactions, their effect on reactivity indices and NICS has increased. Therefore, substituents NO_2 and Cl on the benzene ring, with the highest participation in intramolecular interactions, caused the highest increase in the resonance interactions of the benzene ring. As a result, they increased diatropic currents, enhanced aromaticity in the geometric center of benzene ring NICS (0.0), and increased chemical reactivity. Lone-pair electrons of Chlorine (LP Cls) also had the highest interaction with benzene backbone system compared to other substitutions, which increased diatropic currents and enhanced aromaticity at NICS values (0.5). The NBO results showed that electron-withdrawing substituents at positions R_7 and R_9 reduced the accumulation of negative charge on adjacent atoms and benzene ring carbons.

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Conflict of interests

The authors declare that they have no conflict of interest.

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