

Hydrogen and halogen rearrangements in imidazoles: Hydrogen, fluorine, chlorine and bromine shifts

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Dedicated to the great chemists Alan R. Katritzky and Charles W. Rees

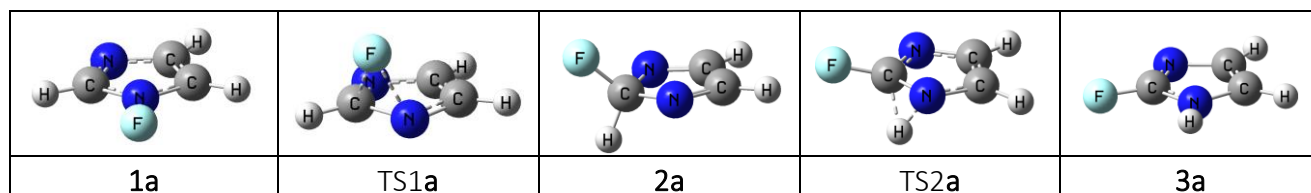
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Abstract

The structures and energetics of the minima and the transition states corresponding to the migration of hydrogen and halogen atoms (F, Cl, Br) in imidazole and in cyclopentadiene rings have been calculated using the composite method Gaussian-4 (G4), a quantum chemical method for the calculation of energies of molecular species containing first-row, second-row, and third row main group atoms. The heats of formation obtained from the G4 values were found to be reliable by comparing them with the NIST Chemistry WebBook values of cyclopentadiene, imidazole and related compounds. The new G4 values thus obtained have been discussed using correlation analyses. In summary, this work was carried out because there is no clear evidence for intramolecular halogen migrations in azoles.

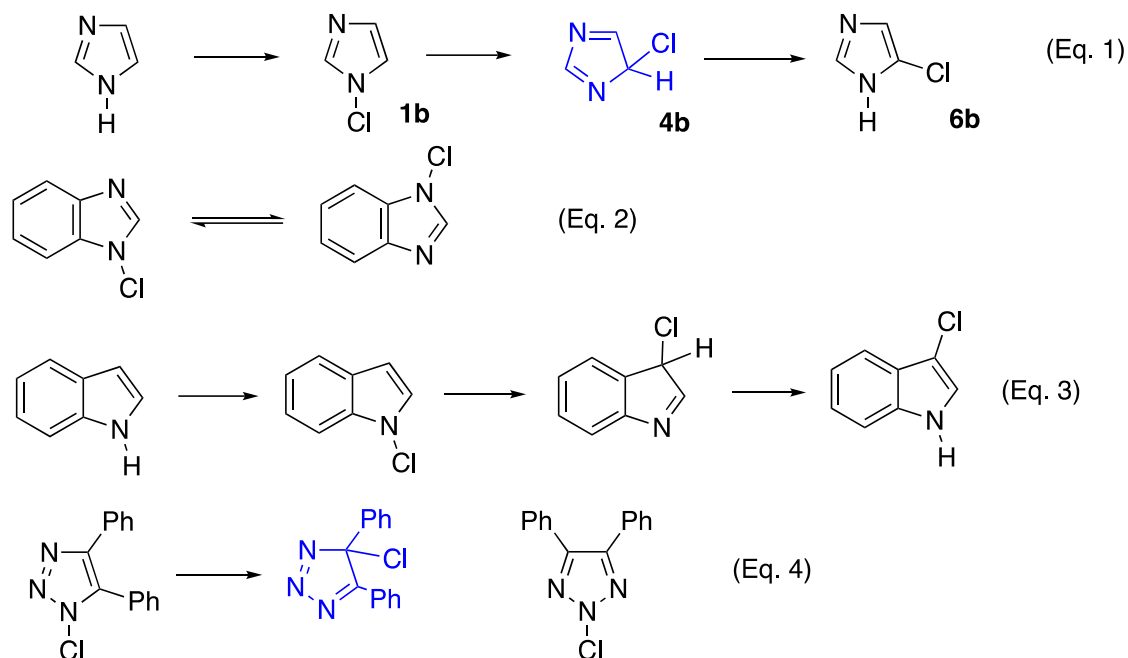


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Introduction

The *N*-halogen derivatives of azoles, from pyrrole to pentazole, and of benzazoles, from indole to benzotriazole, have been often postulated in the mechanism of C-halogenation of azoles by diverse halogenating agents as well as in the related halotropy (halogen migration) processes.

This migration of halogen atoms occurs in five-membered heterocyclic compounds from *N*-X to C-X through non-aromatic C-halogen compounds (Scheme 1).



Scheme 1. Chlorotropies in azoles (for the numbering of molecules of Eq. 1 see Scheme 2).

It has been proposed that chlorination of imidazole starts by *N*-chlorination giving rise to 1-chloro-1*H*-imidazole **1b**, followed by an *N*- to C-chlorotropy to afford 4-chloro-4*H*-imidazole **4b** and a subsequent prototropy to yield 5-chloro-1*H*-imidazole **5b** (or its 4-chloro-1*H*-imidazole tautomer **6b**).¹ But since the non-aromatic tautomer, in blue, was not isolated and the isomerization **1b** to **5b** never attempted, the mechanism of Eq. 1 should be considered unproven.²

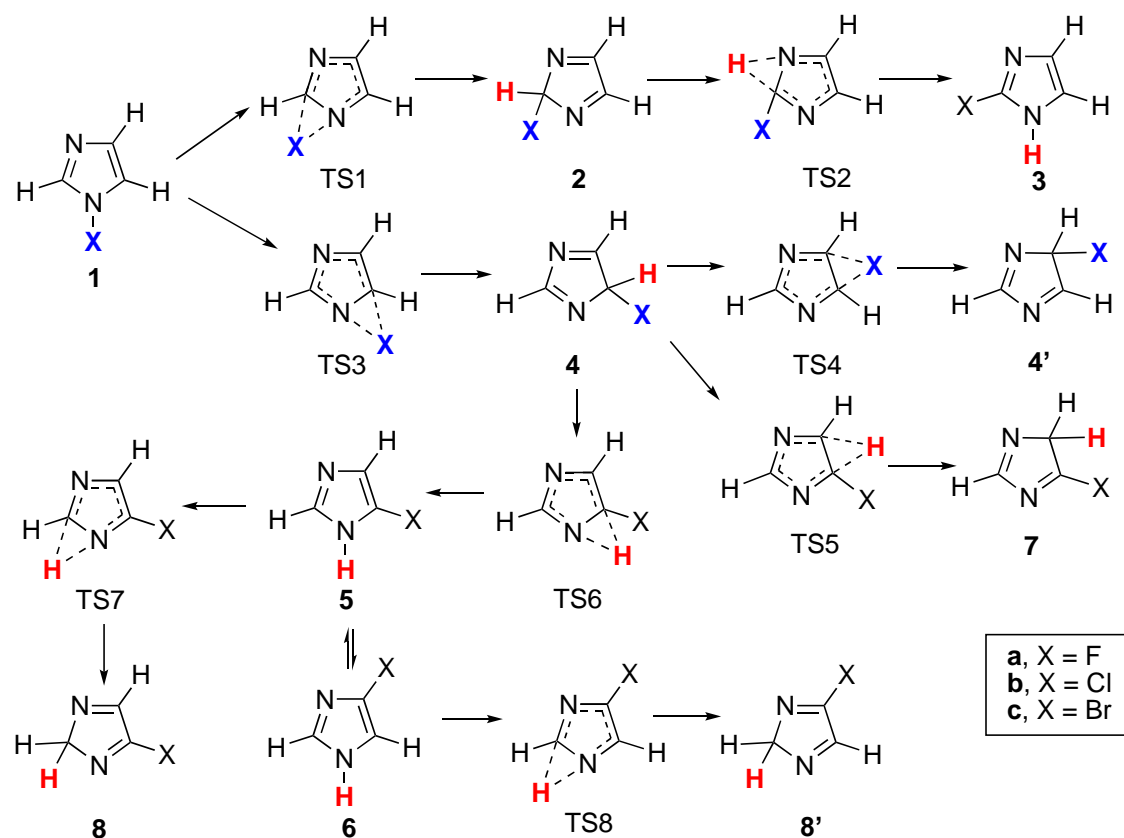
The chlorine migration of 1-chloro-1*H*-benzimidazole, Eq. 2, needs the presence of the parent NH-benzimidazole to occur, therefore it is not an intramolecular 1,3-chlorotropy.³

The 1-chloro-1*H*-indole to 3-chloro-1*H*-indole rearrangement involves 3-chloro-3*H*-indole and the transformation of 3*H*- into 1*H*-indole has been experimentally studied (Eq. 3).^{4,5} Nevertheless, the mechanism has been considered unlikely.⁶

The last example involves 1,2,3-triazoles (Eq. 4).⁷ Besides the fact that the non-aromatic isomer, in blue, was not characterized, it was proved afterwards that the structure of the starting compound was not the 1-chloro-1*H*-triazole isomer but the 2-chloro-2*H*-triazole one.⁶

In summary, there is no clear evidence for intramolecular halogen migrations in azoles. For this reason, we have decided to theoretically approach the case of haloimidazoles to shed light on these open questions. Scheme 2 represents the three series of compounds studied in the present work, fluoro **a**, chloro **b** and bromo-1*H*-imidazoles **c**, sometimes accompanied by proton migrations. The intramolecular migration of

hydrogen or halogen atoms in pyrazoles and imidazoles has been postulated in previous works, by ourselves,^{8,9} by Kereselidze,^{10,11} and summarized in a review by Larina.¹²



Scheme 2. The different compounds involved in the present work, minima and TSs. Compounds **4** and **4'** as well as **8** and **8'** are identical being examples of autotropic or degenerate tautomerism. The atoms that migrate in each step are in bold and colored.

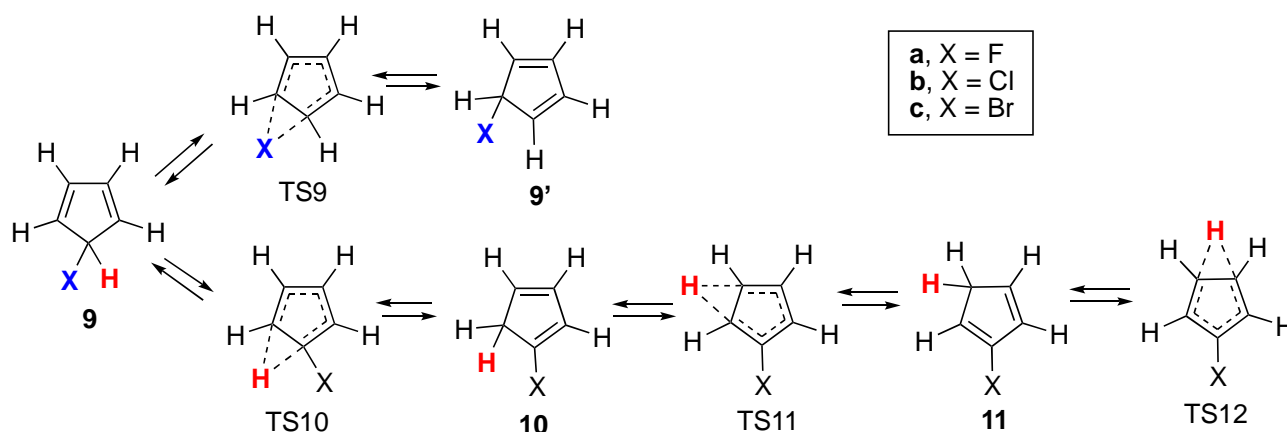
Results and Discussion

We begin by reporting in Table 1 the literature results related to the minima of Scheme 2. All of them correspond to the aromatic structures since there are no experimental data on the CH tautomers. For the theoretical calculations the methods used are given.

Table 1. Experimental and calculated data on compounds **1**, **3**, **5(6)** of Scheme 1. None TS was ever reported

Compound	CAS RN	Experimental F	Calculated
1a 1-fluoro	77392-76-8	Unknown	G3B3LYP/6-31G* ¹³ B3LYP/6-31+G(d,p) ¹⁴ B3LYP/A'VTZ ¹⁵ G4(MP2) ¹⁶
3a 2-fluoro	57212-34-7	Commercially available + ¹⁷	G3B3LYP/6-31G* ¹³ B3LYP/6-311++G(d,p) ¹⁸
5a, 6a 4(5)-fluoro	30086-17-0	Commercially available + ¹⁹	B3LYP/6-311++G(d,p) ¹⁸
		Cl	
1b 1-chloro	1029353-06-7	Commercially available + ²⁰	B3LYP/6-31+G(d,p) ¹⁴ B3LYP/A'VTZ ¹⁵ B3LYP/6-311++G(d,p) ²¹ G4(MP2) ²² B3LYP/cc-pVTZ ²³
3b 2-chloro	16265-04-6	Commercially available	B3LYP/6-311++G(d,p) ¹⁸
5b, 6b 4(5)-chloro	15965-31-8	Commercially available	B3LYP/6-311++G(d,p) ¹⁸
		Br	
1c 1-bromo	1174132-71-8	Commercially available	M06-2x/6-31+G(d,p)- LanLZDZdp-PP ²⁴
3c 2-bromo	16681-56-4	Commercially available	Not calculated
5c, 6c 4(5)-bromo	2302-25-2	Commercially available	Not calculated

The 1,2-migrations of both X and H atoms of Scheme 2 are 1,5-sigmatropic shifts. The [1,5]-shifts involve the movement of the substituent through five atoms of the π system. This π system can be cyclic, typically that occurring in cyclopentadiene **9**. One of the most sound foundations of the Woodward–Hoffmann rules are the [1,*j*]-sigmatropic migrations.^{25,26,27,28,29,30,31} Amongst these migrations, the [1,5]-sigmatropic rearrangement of cyclopentadiene ($\sigma^2s + \pi^4s$) is particularly relevant to the present work (Scheme 3).

**Scheme 3.** The 1,2-migrations of both X and H atoms in cyclopentadienes **9**, **9'**, **10** and **11**.

Bachrach reported MP2/6-31G* calculations of these shifts for cyclopentadiene (110.5 kJ·mol⁻¹), for 1*H*-pyrrole to 2*H*-pyrrole (186.2 kJ·mol⁻¹) and for 2*H*-pyrrole to 3*H*-pyrrole (110.0 kJ·mol⁻¹).⁴⁰ The barriers to hydrogen and fluorine shifts in 5-fluorocyclopentadiene **9a** were calculated by Fowler *et al.* at the MP2/6-31+G* level: fluorine migration (200.8 kJ·mol⁻¹) and hydrogen migration (119.7 kJ·mol⁻¹);³² see also reference.³³ Minkin *et al.* have reported several theoretical and experimental studies of 1,2-migrations of chlorine and bromine, which they termed circumambulatory rearrangements, in poly-substituted cyclopentadienes.^{34,35,36,37}

These migrations involve *sp*³ and *sp*² C atoms. Applying these rules to pyrroles, from an *sp*² N atom to an *sp*² C atom, is similar to comparing the aromaticity of benzene with that of azoles. Sammes and Katritzky were among the first to report experiments involving [1,5]-sigmatropic hydrogen shifts in pyrroles.^{38,39,40}

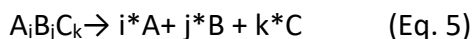
In the case of pyrazole, the shift corresponds to a migration from NH to N. The possibility that the intramolecular migration of hydrogen between the nitrogen atoms of pyrazole could represent another example of [1,5]-sigmatropic reaction has been considered by different authors.^{8,41,42} At the B3LYP/6-31G* + ZPE level the calculated barriers for cyclopentadiene **9** (X = H) and pyrazole are 113.0 and 197.9 kJ·mol⁻¹.⁴³

In short, the following calculated barriers are for H migration *Csp*³ → *Csp*², 110.5, 110.0 and 119.7 (mean value 113.4 kJ·mol⁻¹), *Nsp*³ → *Csp*², 186.2 and for F migration *Csp*³ → *Csp*², 200.8 kJ·mol⁻¹. Therefore, there is a considerable increase in the barrier of 72.8 kJ·mol⁻¹ due to the N effect and 87.4 kJ·mol⁻¹ for the F migration relative to the *Csp*³ → *Csp*² H migration.

In view of these results, we decided to explore the profile of Scheme 2 and Scheme 3 with the Gaussian-4 (G4) composite method, which is considered very convenient for thermodynamic calculations.⁴⁴ As detailed in the Experimental Section, the outcome is that G4 provides energetic values for different thermodynamic properties with an average absolute deviation of 3.5 kJ·mol⁻¹.⁴⁴ Our calculations correspond to gas phase because most experimental data are from NIST and therefore are gas phase values. Besides, computational efficiency and acceptable accuracy are supplementary reasons for carrying the calculations in these conditions. The geometries and enthalpies of the stationary points are gathered in Table S1 of the Supplementary Material.

Heats of formation ($\Delta_f H^\circ$)

The heats of formation $\Delta_f H^\circ_{\text{gas}}$ values have been calculated using the atomization method (Eq. 5) and the experimental values of the atomic heat of formation for the different atoms considered here (C, N, H, F, Cl and Br) applying (Eq. 6). The atomic $\Delta_f H^\circ_{\text{gas}}$ values used have been obtained from the NIST database⁴⁵ and are gathered in Table S2 of the Supplementary Material.



$$\Delta_f H^\circ_{\text{gas}} (A_i B_j C_k) = i^* \Delta_f H^\circ_{\text{gas-exp.}} (A) + j^* \Delta_f H^\circ_{\text{gas-exp.}} (B) + k^* \Delta_f H^\circ_{\text{gas-exp.}} (C) - \Delta H^\circ (\text{reaction Eq. 5}) \quad (\text{Eq. 6})$$

To test the robustness of our calculations we have calculated at the G4 level, the series of compounds with H, N, C, F, Cl and Br reported in Table 2, for which the experimental $\Delta_f H^\circ_{\text{gas}}$ values are found in the NIST database.⁴⁵ In all cases, we have chosen NIST most recent values.

Table 2. Test set ($\Delta_f H^\circ$, $\text{kJ}\cdot\text{mol}^{-1}$)

Compound	$\Delta_f H^\circ$ gas-exp.	$\Delta_f H^\circ$ gas-calc.	Error
Cyclopentadiene 9	139. ^a	137.0	2.0
Imidazole	129.5 ^b	131.4	1.9
1-CH ₃ -4-F-C ₆ H ₄	-147.5	-142.0	5.5
C ₆ H ₅ Cl	54.42	52.4	-2.0
CH ₃ F	-234.30 ^c	-235.4	-1.1
CH ₃ Cl	-83.68 ^d	-81.1	2.6
CH ₃ Br	-34.3	-34.8	-0.5

^a Two values available: 139. and 133.4 $\text{kJ}\cdot\text{mol}^{-1}$. ^b Several values between 128.0 and 139.3 $\text{kJ}\cdot\text{mol}^{-1}$.

^c Two values available, -247.0 and -234.30 $\text{kJ}\cdot\text{mol}^{-1}$. ^d Several values available between -81.9 and -85.9 $\text{kJ}\cdot\text{mol}^{-1}$. ^e Three values available between -34.3 and -38 $\text{kJ}\cdot\text{mol}^{-1}$.

The agreement between the experimental and calculated results of Table 2, justifies our confidence in the calculated values for compounds **1-8** of this work, gathered in Table 3.

Table 3. Predicted $\Delta_f H^\circ$ gas-calc. values in $\text{kJ}\cdot\text{mol}^{-1}$

Compound	X = F	X = Cl	X = Br
1	170.0	230.8	257.9
2	17.1	184.9	230.6
3	-58.2	107.6	158.8
4	29.7	186.3	229.5
5	-35.7	114.1	162.5
6	-55.8	106.3	156.6
7	-10.4	160.1	212.2
8	-9.8	161.5	213.5

The negative value of some of the fluorine derivatives is a common observation due to the small bond dissociation energy of the F₂ molecule,⁴⁶ for instance $\Delta_f H^\circ$ gas (C₆H₆) = 82.9 $\text{kJ}\cdot\text{mol}^{-1}$ and $\Delta_f H^\circ$ gas (C₆F₆) = -1015 $\text{kJ}\cdot\text{mol}^{-1}$.⁴⁵

The case of cyclopentadienes **9**, **9'**, **10** and **11**

The energetic values of the three cyclopentadienes and the four transition states TS (see Scheme 3) are represented in Figure 1, and refer to the starting compounds **9a**, **9b** and **9c**. The G4 barriers for cyclopentadiene itself are $\Delta H = 110.2$ and $\Delta G = 110.0$ $\text{kJ}\cdot\text{mol}^{-1}$, very close to the value reported by Bachrach⁴⁰ which, in turn, is very close to Roth's experimental value (101.7 $\text{kJ}\cdot\text{mol}^{-1}$).⁴⁷ Okajima and Imafuku reported values of $\Delta G^\ddagger = 116.2$ $\text{kJ}\cdot\text{mol}^{-1}$ and $\Delta G^\ddagger_{298} = 107.9$ $\text{kJ}\cdot\text{mol}^{-1}$.⁴⁸ The values of ΔH and ΔG calculated with the G4 method in the compounds studied here are almost perfectly proportional (Eq. 7), for this reason only ΔH values will be discussed.

$$\Delta G = (0.95 \pm 0.08) + (1.004 \pm 0.001) \Delta H, n = 85, R^2 = 0.99998 \quad (\text{Eq. 7})$$

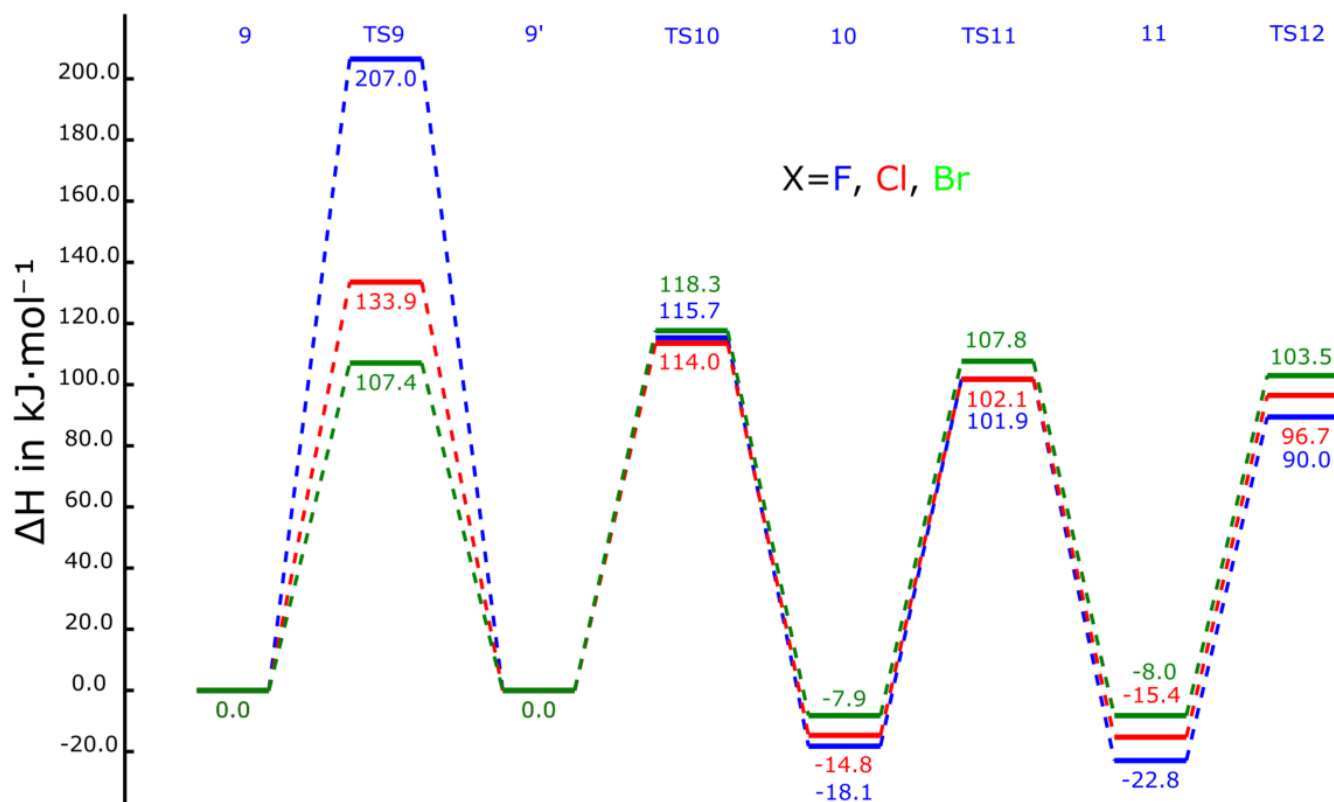


Figure 1. Cyclopentadienes.

The profile of Figure 1 shows that all the minima as well as the H migrations have similar energies; the halogen migration of Br is surprisingly the same, that of Cl increases clearly and that of F is almost twice.

The values for TS9a and TS10a (207.0 and 115.7) are close to those reported by Fowler, 200.8 and 119.7 $\text{kJ}\cdot\text{mol}^{-1}$.³² The stability of the three minima decreases in the order **11** > **10** > **9**, that is, the further the CH_2 part of the molecule is from the X atom.

There is proportionality between the enthalpies of the three halogen atoms if the minima and the transition states, TS, are treated separately. So, for the three minima, **9**, **10** and **11**:

$$\text{Br} = (0.38 \pm 0.03) \text{F}, R^2 = 0.988 \quad (\text{Eq. 8})$$

$$\text{Cl} = (0.73 \pm 0.05) \text{F}, R^2 = 0.991 \quad (\text{Eq. 9})$$

$$\text{Br} = (0.53 \pm 0.01) \text{Cl}, R^2 = 1.000 \quad (\text{Eq. 10})$$

For the four TS, TS9 to TS12:

$$\text{Br} = (0.75 \pm 0.16) \text{F}, R^2 = 0.883 \quad (\text{Eq. 11})$$

$$\text{Cl} = (0.80 \pm 0.11) \text{F}, R^2 = 0.951 \quad (\text{Eq. 12})$$

$$\text{Br} = (0.95 \pm 0.07) \text{Cl}, R^2 = 0.985 \quad (\text{Eq. 13})$$

Regarding the TS, it is TS9 that deviates systematically, since it corresponds to an X migration. But, if it is eliminated, we obtain:

$$\text{Br} = (1.07 \pm 0.04) \text{ F}, R^2 = 0.998 \quad (\text{Eq. 14})$$

$$\text{Cl} = (1.01 \pm 0.03) \text{ F}, R^2 = 0.999 \quad (\text{Eq. 15})$$

$$\text{Br} = (1.05 \pm 0.01) \text{ Cl}, R^2 = 1.000 \quad (\text{Eq. 16})$$

These last values indicate that the enthalpies increase in the order $\text{F} < \text{Cl} < \text{Br}$ but only moderately, since the slopes are not far from 1.

The C-X interatomic distances in the minima and TS are different depending on the nature of the carbon atom (sp^2 or sp^3) and on whether they are minima or TS. Thus, the average interatomic C-H distances are 1.08/1.10/1.31 Å for the $\text{C}(sp^2)\text{-H}$, $\text{C}(sp^3)\text{-H}$, and C-H(TS), respectively. Likewise for the C-F bonds are 1.32/1.38/1.85, for the C-Cl ones 1.73/1.82/2.27 and for the C-Br contacts 1.88/1.99/2.42. Linear correlations ($R^2 = 0.97$, $n = 4$) show that the TS interatomic distances are 34% longer on average than those of $\text{C}(sp^3)\text{-X}$ and 22% longer than those of $\text{C}(sp^2)\text{-X}$.

Analysis of the electron densities of the stationary points shows unique bonding paths for each X atom (X= H, F, Cl and Br) in the minima, while in the TS, those atoms involved in the transformation are involved in two C-X bonds. The values of the electron densities ρ_{BCP} at the bond critical points, BCP, of the C-X bonds, decrease as the intermolecular distance increases. A more detailed analysis will be carried out at the end of the discussion section using the data for the cyclopentadienes and imidazoles together.

The case of imidazoles 1-8: minima

Table 4. Minima structures of Scheme 2, all values in $\text{kJ}\cdot\text{mol}^{-1}$ regarding compound **1**. They are obtained by subtracting the values of Table 3 from the value of compound **1** (obviously, it results 0 for compound **1**)

Compound	a, X = F	b, X = Cl	c, X = Br
1	0.0	0.0	0.0
2	-152.9	-45.9	-27.3
3	-228.2	-123.2	-99.1
4 (4')	-140.3	-44.5	-28.4
5	-205.7	-116.7	-95.4
6	-225.8	-124.5	-101.3
7	-180.4	-70.7	-45.7
8 (8')	-179.8	-69.3	-44.4

The stability of the systems decreases in the order (**3** or **6**) > **5** > **7** > **8** for $\text{C}sp^2\text{-X}$, (**2** or **4**) $\text{C}sp^3\text{-X}$ and **1** for N-X. It seems reasonable to suppose that these enthalpies are related to bond dissociation energies (BDE) of the three types of bonds, using as models $\text{C}_2\text{H}_3\text{X}$, $\text{C}_2\text{H}_5\text{F}$ and H_2NX .⁴⁹

Using mean values for Csp^2-X and Csp^3-X and considering the three possible situations, Csp^2-X , Csp^3-X and $N-X$ (Table S3 of the Supplementary Material) we obtain Eq. 17:

$$\Delta H = (188 \pm 25) + (0.70 \pm 0.08) \text{ BDE} - (57 \pm 16) Csp^2 + (28 \pm 18) Csp^3, n = 8, R^2 = 0.975 \quad (\text{Eq. 17})$$

Searching again for relationship between the values of the three columns (**a**, X= F/ **b**, X= Cl/ **c**, X= Br) of Table 4, we obtained Eqs. 18-23:

$$\text{Br} = (18.7 \pm 19.6) + (0.45 \pm 0.11) \text{ F}, n = 8, R^2 = 0.735 \quad (\text{Eq. 18})$$

$$\text{Cl} = (17.2 \pm 17.5) + (0.56 \pm 0.10) \text{ F}, n = 8, R^2 = 0.842 \quad (\text{Eq. 19})$$

$$\text{Br} = (8.4 \pm 4.1) + (0.86 \pm 0.05) \text{ Cl}, n = 8, R^2 = 0.981 \quad (\text{Eq. 20})$$

Since the intercepts are different the best is to remove compound **1**:

$$\text{Br} = (116 \pm 25) + (0.95 \pm 0.13) \text{ F}, n = 7, R^2 = 0.915 \quad (\text{Eq. 21})$$

$$\text{Cl} = (107 \pm 20) + (1.02 \pm 0.10) \text{ F}, n = 7, R^2 = 0.952 \quad (\text{Eq. 22})$$

$$\text{Br} = (18 \pm 3) + (0.95 \pm 0.04) \text{ Cl}, n = 7, R^2 = 0.993 \quad (\text{Eq. 23})$$

Note that the slopes of Eqs 21 to 23 are not far from 1 meaning that the effect of the halogen appears mainly on the intercept.

The case of imidazoles 1-8: transitions states

We will now examine the transition states TS, linking the minima of Table 4 and represented in Scheme 2. Table 5 contains all the minima and TSs values.

In this case we have included as independent variables i) the group X that migrates (X = 1 for any halogen (TS1, TS3, TS4), X = 0 for H); ii) the barrier from aromatic to non-aromatic (ANA = 1) and from non-aromatic to non-aromatic (NANA to indicate the leaving and ending atoms, NANA = 0, only TS4 and TS5).

$$\text{Br} = (0.78 \pm 0.07) \text{ F} - (50 \pm 9) \text{ X} + (40 \pm 11) \text{ NANA}, n = 8, R^2 = 0.997 \quad (\text{Eq. 24})$$

$$\text{Cl} = (0.87 \pm 0.09) \text{ F} - (30 \pm 11) \text{ X} + (26 \pm 14) \text{ NANA}, n = 8, R^2 = 0.995 \quad (\text{Eq. 25})$$

$$\text{Br} = (0.89 \pm 0.05) \text{ Cl} - (21 \pm 6) \text{ X} + (19 \pm 9) \text{ NANA}, n = 8, R^2 = 0.998 \quad (\text{Eq. 26})$$

The most interesting information from Eqs. 24–26 is the X coefficient that relative to F (0) is $-50 \text{ kJ}\cdot\text{mol}^{-1}$ for Br and $-30 \text{ kJ}\cdot\text{mol}^{-1}$ for Cl, and approximately linear with their atomic number F, 0/9; Cl, 30/17; Br, 50/35 see Eq. 27. Note that the difference between 50 and 30 is close to 21, the slope of Eq. 26.

$$\text{X coefficient} = (1.42 \pm 0.25) \text{ atomic number}, n = 3, R^2 = 0.94 \quad (\text{Eq. 27})$$

Table 5. Stationary points of haloimidazoles. Energy barriers of Scheme 2, all values in $\text{kJ}\cdot\text{mol}^{-1}$ with respect to the compound on the left side of the arrow in Scheme 2; for instance, TS2 that links **2** to **3** is referred to compound **2**

Relative to 1	a , X = F	b , X = Cl	c , X = Br
TS1	147.6	137.4	116.1
TS2	-10.2	91.9	113.2
TS3	216.9	181.9	153.6
TS4	24.2	55.9	48.9
TS5	-42.3	55.8	78.7
TS6	5.4	95.4	116.2
TS7	-20.1	77.6	101.8
TS8	-37.0	70.5	96.5
Preceding minima ^a	a , X = F	b , X = Cl	c , X = Br
1	0.0	0.0	0.0
2	-152.9	-45.9	-27.3
1	0.0	0.0	0.0
4	-140.3	-44.5	-28.3
4	-140.3	-44.5	-28.3
4	-140.3	-44.5	-28.3
5	-205.7	-116.7	-95.4
6	-225.8	-124.5	-101.3
Barrier	a , X = F	b , X = Cl	c , X = Br
TS1	147.6	137.4	116.1
TS2	142.8	137.8	140.5
TS3	216.9	181.9	153.6
TS4	164.5	100.5	77.2
TS5	97.5	100.4	77.2
TS6	145.6	139.9	143.2
TS7	185.5	194.3	195.7
TS8	188.8	195.0	196.2

^a Minima situated on the left side of the arrow in Scheme 2.

The other interesting property of the above equations is the NANA term. To discuss this property together with that of cyclopentadiene, we have selected the barriers from non-aromatic to non-aromatic isomers, also present in cyclopentadiene (Scheme 3), and build up Table 6.

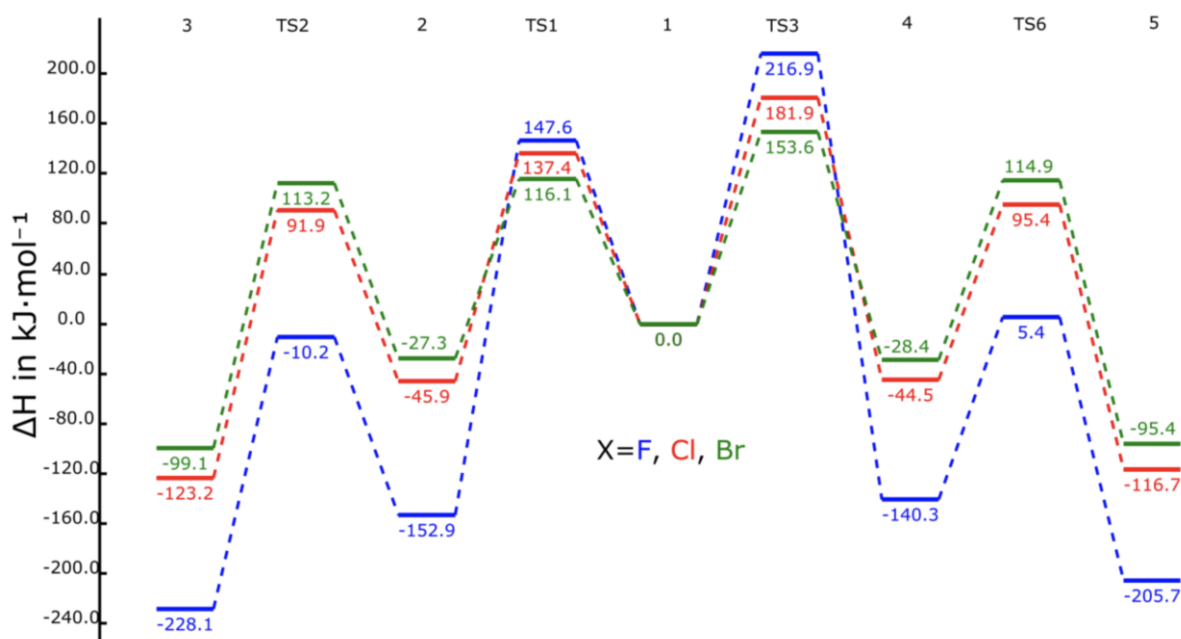
Table 6. NANA barriers of non-aromatic to non-aromatic isomers (Figure 1 and Table 5)

Compound	TS	Atom	F	Cl	Br	Mean
Cyclopentadienes	9	X	207.0	133.9	107.4	
	10	H	115.7	114.0	118.3	
	11	H	101.9	102.1	107.8	
	12	H	90.0	96.7	103.9	
	10, 11, 12	Mean H	102.5	104.3	110.0	105.6
Imidazoles	4	X	164.5	100.5	77.2	
	5	H	97.9	100.4	105.1	101.1

An examination of the data of Table 7 leads to the following conclusions: i) barriers to the proton transfer are similar; ii) the halogen atom transfer barriers are 1.33 ± 0.06 times higher in cyclopentadienes than in imidazoles.

The bond distances obtained in the stationary point of the haloimidazoles show a similar pattern to those of the cyclopentadienes with $C(sp^3)-X > C(sp^2)-X$. The N-X bond is similar to the $C(sp^3)-X$ for X = F while for X = Cl and Br it is shorter than the $C(sp^2)-X$ one. Interestingly, in the TS of halogen transfer where a N and C atoms are involved the N-X bond is shorter than the C-X one in average 0.15 \AA , independently of X.

The molecular graph of the minima shows a single bond path between the halogen or the hydrogens and the ring atoms. Meanwhile, in TS, the atom being transferred, X or H, shows a two bond path connecting the ring atoms involved in the reaction.

**Figure 2.** Haloimidazoles.

The profile of Figure 2 corresponds to a part of Table 5 and Scheme 2; the part concerning the 5/6 tautomerism has been excluded since the proton transfer from 5 to 6, and vice-versa, occurs through a mechanism involving solvent molecules.⁹ The N-halo derivatives are much higher in energy than all the other isomers, prototropic and halotropic, including the non-aromatic ones 2 and 4. The TS1 barrier is lower than

the TS3 barrier (69.3, 44.5 and 37.5 kJ·mol⁻¹ for F, Cl and Br, respectively) making the transfer to 2-halo-2*H*-imidazole **2** favored over the transfer to 4-halo-4*H*-imidazole **4** (Scheme 2). The gain in aromatization from **2** to 2-halo-1*H*-imidazole **3** and from **4** to 5-halo-1*H*-imidazole **5** is 75.2 and 66.4 kJ·mol⁻¹, respectively. This is in contradiction with the results of Scheme 1 where a **1b** to **5b** (X = Cl) migration through **4b** has been postulated. Thus, our calculations do not support the mechanism described in reference 5.

In what concerns the tautomerism of 4-halo-4*H*-imidazole **6**/5-halo-1*H*-imidazole **5**, from the data of Table 5, always the 4-halo is more stable than the 5-halo by -20.1 kJ·mol⁻¹ for the F, -7.8 kJ·mol⁻¹ for the Cl and -5.9 kJ·mol⁻¹ for the Br. This is to be expected for the electronic properties of these substituents, see for instance Eq. 28.

$$\Delta H^\circ = -(25.0 \pm 1.5) + (79.3 \pm 7.8) \sigma_p,^{50} n = 3, R^2 = 0.990 \quad (\text{Eq. 28})$$

Although the only experimental data were determined in solution and are -5.4 kJ·mol⁻¹ for Cl and 0.2 kJ·mol⁻¹ for Br,⁵¹ the tendency is the same. There is a calculation of the tautomerism of 4(5)-fluoro-1*H*-histidine [5(4)-methyl-1*H*-imidazole] in the gas phase that favors the 4-fluoro-5-methyl tautomer by 20 kJ·mol⁻¹ in average (the methyl substituent has very little effect on tautomerism).⁵²

Electron density analysis

A total of 22 C-halogen bond critical points, BCP, for each halogen are identified in the characterized stationary points. The value of ρ_{BCP} for each C-halogen bond decreases as the interatomic distance increases, as can be observed in Figure 3, following an exponential relationship in good agreement with the similar relationship in other bonds.^{53,54,55}

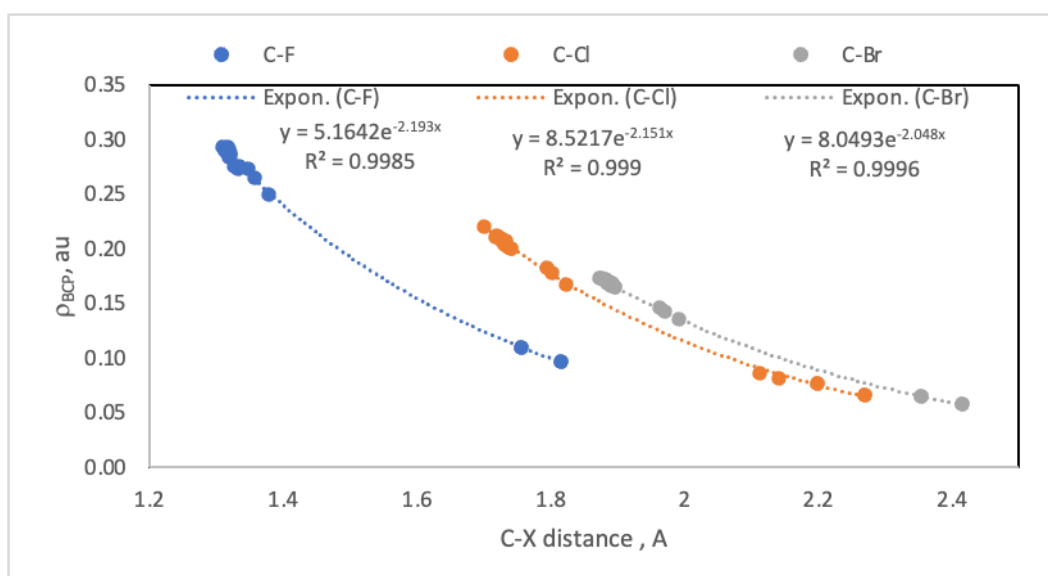


Figure 3. Evolution of ρ_{BCP} (au) with the interatomic distances (Å). The fitted exponential relationships are indicated.

The values of $\nabla^2\rho_{\text{BCP}}$ are negative except for the longest C-X interactions. In contrast, the total energy density at the BCPs, H_{BCP} , for all the C-X bonds is negative as expected for a partial covalent character of the

interactions even for the longest distances.⁵⁶ The values of H_{BCP} also show excellent exponential relationship with the intermolecular distances (Figure S1 of the Supplementary Material)

Conclusions

Heats of formation $\Delta_f H^\circ$ for cyclopentadienes and haloimidazoles ($X = F, Cl$ and Br) have been obtained from the enthalpies calculated with the composite G4 method. The robustness of our approach was verified by comparing, with satisfactory results, the $\Delta_f H^\circ_{gas}$ calculated with the G4 method with the experimental values for a set of compounds related to those studied here.

The difference between cyclopentadienes, where halogen jumping occurs, and imidazoles where it does not take place, is due to the existence of aromatic tautomers in imidazoles.

In halocyclopentadienes there are several isomers depending on the position of the halogen with regard to the double bonds. Two kinds of barriers have been found, one corresponding to the migration of the halogen atom, halotropy, and three others to the prototropy (mean values). The barriers (Figure 1) are very different in the case of fluorine ($F, 207.0$ vs. 102.5 $\text{kJ}\cdot\text{mol}^{-1}$) but almost identical in the case of bromine ($Br, 107.4$ vs. 107.9 $\text{kJ}\cdot\text{mol}^{-1}$), the case of chlorine being intermediate ($Cl, 133.9$ vs. 104.3 $\text{kJ}\cdot\text{mol}^{-1}$).

In haloimidazoles the transition states are dependent both on the nature of the halogen, F, Cl and Br , being proportional to their atomic number, and on the nature of the atoms involved in the migration, C or N and sp^3 or sp^2 .

Graphical profiles have been used to obtain a quick overview of the processes involved in the cyclopentadienes and imidazoles cases.

In summary, the conclusions derived from this study on haloimidazoles should be applicable to other azoles and benzazoles.

Experimental Section

Computational Details. The Gaussian-4 (G4) theory has been used to calculate the thermodynamic stability of the compounds included in this study. In this methodology, the final energies are calculated by combining contributions obtained using Møller–Plesset perturbation theory up to the fourth order, MP4, and CCSD(T) coupled cluster theory. To these MP4 and CCSD(T) energy contributions, an estimation of the Hartree-Fock energy limit (HFlimit) together with two high-level empirical corrections are added, in order to ensure that the final energies are accurate up to a CCSD(T,full)/G3LargeXP + HFlimit level. The outcome is that G4 provides energetic values for different thermodynamic properties with an average absolute deviation of 3.5 $\text{kJ}\cdot\text{mol}^{-1}$.⁴⁴

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Supplementary Material

Optimized geometries of the stationary points (Å), Enthalpy (au) and number of imaginary frequencies obtained with the G4 method (Table S1); Experimental values of the atomic heat of formation, ΔH_f° gas, used in this article (Table S2); Average ΔH for compounds **1-8** and bond dissociation energies, BDE, of model compounds (kJ mol⁻¹, Table S3); Evolution of -H_{B_{CP}} (au) with the interatomic distances (Å). The fitted exponential relationships are indicated (Figure S1).

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