ON THE REDUCTION OF 4-OXO-4H-BENZOPYRAN-3-CARBALDEHYDES : GLOBAL AND LOCAL ELECTROPHILICITY PATTERNS‡

Ramiro Araya-Maturana[1]*, *Jorge Heredia-Moya*[1],
Carlos A. Escobar[2] *and Patricia Pérez*[2]*

[1]Departamento de Química Orgánica y Fisicoquímica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago 1, Chile.
[2]Departamento de Ciencias Químicas, Facultad de Ecología y Recursos Naturales, Universidad Andrés Bello, Santiago, Chile. E-mail : raraya@ciq.uchile.cl

ABSTRACT

The theoretical global and local electrophilicity patterns of substituted and chelated 4-oxo-4H-benzopyran-3-carbaldehydes (formylchromones) have been evaluated using the electrophilicity index proposed by Parr et al [J. Am. Chem. Soc. 1999, 121, 1922]. The complexation of formylchromones with aluminum predicts a strong electrophilic character of these compounds against nucleophiles. Local response at the active sites may also be assessed in terms of a global contribution described by the global electrophilicity, and a local contribution described by the variations in electrophilic Fukui function at those sites. The highest local electrophilicity is found at the formyl group of the chelated formylchromones, in spite of that, the highest positive charge is located on the pyrone carbonyl group. This result is consistent with the experimental observed reactivity displayed by 4-oxo-4H-benzopyran-3-carbaldehydes in the presence of 2-propanol and alumina.

INTRODUCTION

The remarkable biological properties,[1-8] proton affinities,[9] optical properties and the degree of aromaticity[10] of the 4-oxo-4H-benzopyranes (chromones) have attracted considerable attention from both experimental and theoretical point of views. A facile route to obtain the 3- formyl substituted chromones (4-oxo-4H-benzopyran-3-carbaldehydes) from the o-hydroxyacetophenones is the Vilsmeier-Haack reaction.[11,12] These kind of products can be used to obtain 3-substituted chromones, obtained by selective reduction of the aldehydic carbonyl group of the 3-formylchromones by 2-propanol on dried woelm alumina[13] or in a recent improvement of this methodology employing 2-propanol on basic alumina.[14] Others attempts oriented to selectively reduce one of the three electrophilic centers at the formyl chromones have been singularly unsuccessful in providing an adequate chemoselectivity between the pyrone carbonyl, formyl and ethylenic C-2 position (Figure 1, positions marked as C_a, C_b and C_c, respectively).

Attempts to address this purpose have been reported using different methods with variable yields. The first of them, described thirty years ago,[11a] used $NaBH_4$ and $AlCl_3$ with about a 10% yield. However, different authors have claimed that certain two substituted chromones undergoes reduction of both aldehyde carbonyl and α,β-ethylenic group using sodium borohydride-aluminum chloride, as well as, sodium borohydride, DIBAL-H in tetrahydrofuran, and, sodium cyanoborohydride in the presence of acid. These are inert to Meerwein-Pondorf-Verley homogeneous conditions using aluminum isopropoxide.[13]

Although a plausible mechanism that explain the carbonyl reduction with 2-propanol and alumina has been proposed by Posner,[13] there has been no clear explanation of the chemoselectivity and the absence of reaction with aluminum isopropoxide in homogeneous conditions.

This work describes the results of a theoretical study about the global and local electrophilicity in 3-formylchromones. For this purpose, three 3-formylchromones having reduction data available in the literature were selected, namely, the 4-oxo-4H-benzopyran-3-carbaldehyde 1, and two additional derivatives with a oxygenated substituent in the aromatic ring: 5-hydroxy-4-oxo-4H-benzopyran-3-carbaldehyde 2 and 6-metoxy-4-oxo-4H-benzopyran-3-carbaldehyde 3. Besides, these three chromone derivatives were exposed to the interaction with aluminum chloride to form hypothetical chelated formyl chromone derivatives that served as simple models to study the variation of the electrophilic properties of the three different centers of the formyl chromones in a environment resembling that in the alumina cavities. Also, with zinc chloride to compare the effect of the metal. Since, $ZnBr_2$ has been employed to chelate β-ketosulfoxides to allow the stereoselective obtention of β–hydroxysulfoxides. [15]

Model Equations

Recently, it has been reported the useful of the global electrophilicity index, ω, proposed by Parr et al.[16] to classify the global electrophilicity of a series of important reagents involved in important organic reactions.[17-19] The electrophilicity concept is based on a second order model for the energy changes describing the charge transfer between the electrophile and the environment. It is described in terms of the electronic chemical potential, μ , and the chemical hardness, η, as: [16]

$$1) \qquad \omega = \frac{\mu^2}{2\eta}.$$

While the electronic chemical potential μ describes the charge transfer pattern of the system in its ground state geometry, the chemical hardness η describes the resistance to the change.[20] The electronic chemical potential μ, and chemical hardness η values may be approached by the one electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO, ε_H and ε_L , respectively, using the following expressions $\approx \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta \approx \varepsilon_L - \varepsilon_H$.[20]

[20] The last expression for the chemical hardness, without the known (1/2) factor, was introduced by Parr et al. from the ground-state parabola

model of the total energy to obtain approximate expressions for the ω index. [16,20]

Local electrophilicity index ω(r) in terms of the electrophilic Fukui function and local (regional) softness has been recently proposed.[21,22] Using the inverse relationship between chemical hardness and the global softness $S = 1/\eta$, [20] Eq (1) may be rewritten as:

$$\omega = \frac{\mu^2}{2\eta} = \frac{\mu^2}{2}S = \frac{\mu^2}{2}\sum_k s_k^+ = \sum_k \omega_k \; ; \qquad (2)$$

from which we may define a semi-local, or regional electrophilicity condensed to atom k given by:

$$\omega_k = \frac{\mu^2}{2} s_k^+ \qquad (3)$$

In deriving Eq (3), we have used the additivity rule for the global softness, namely, $S = \sum_k s_k^+$, [20] where describes the condensed local softness for a nucleophilic attack on the system.[20] Note that within the present model, the maximum electrophilicity within a molecule will be located at the softest electrophilic site of the system, described by s_k^+ index (i.e the highest value for an nucleophilic attack). (see reference 20 for details). If we further use the exact relationship between condensed local softness and condensed electrophilic Fukui function, namely, $s_k^+ = f_k^+ S$,[20]

[20] then the local electrophilicity power given in Eq (3) may also be expressed as:

$$\omega_k = \frac{\mu^2}{2} s_k^+ = \frac{\mu^2 S}{2} f_k^+ = \omega f_k^+ \; ; \qquad (4)$$

thereby showing that the maximum electrophilicity in a molecule will be developed at the site where the condensed Fukui function for a nucleophilic attack f_k^+

displays its maximum value, i.e. at the active site of the electrophile.

Computational details

Full geometry optimization for a series of substituted and chelated 4-oxo-4H-benzopyran-3-carbaldehydes have been performed at the B3LYP/6-31G(d) level of theory, using the GAUSSIAN98 package of programs.[23] The global electrophilic character was evaluated using Eq (1). The electronic chemical potential μ, and the chemical hardness η, were evaluated using the frontier molecular orbital model described above. Numerous works in the literature have used the frontier molecular orbital approximation to obtain the magnitude of the chemical potential and chemical hardness [24]. Condensed electrophilic Fukui functions f_k^+ were obtained from single point calculations at the optimized structures in their ground states, by a method described elsewhere.[25] This method evaluates the condensed Fukui function for electrophilic and nucleophilic attacks as the electron density of the molecular orbital involved in the reaction. The condensed electrophilic Fukui function is obtained from the frontier molecular orbital coefficients and the overlap matrix. With these values at hand, the local electrophilicity (ω_k) are obtained from Eq (4).

RESULTS AND DISCUSSION

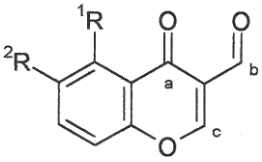
Table 1 summarizes the global properties of the series of substituted and chelated formylchromones (see Figure 1). The values of electronic chemical potential, chemical hardness and electrophilicity show little variations with the substituent at aromatic ring (see compounds 1-3). However, the complexation with aluminum in compounds 4-6 generates a decreasing of both HOMO and LUMO energies, the chemical potential becomes twice more negative than unchelated chromones, and chelated formylchromones (compounds 4-9) are softer than unchelated chromones. It may be seen, from Table 1, that in the absence of the Lewis acid (LA) catalyst, the electrophilicity of the isolated compounds 1-3 fall in the range of moderate electrophiles (i.e. compounds with global electrophilicity values around 2.0 eV). Coordination of compounds 1-3 to the LA catalyst $AlCl_2^+$ dramatically increases the global electrophilicity in compounds 4-6 to values close to 12.0 eV (i.e. within the range of benzhydryl super electrophile cations.[22]). On the other hand, coordination of compounds 1-3 to the LA catalyst $ZnCl_2$ brings the electrophilicity of compounds 7-9 to the range of strong electrophiles similar to that present in DA cycloaddition reactions.[17] The presence of both metals in formylchromones generates an enhancement in the global reactivity predicting a higher reactivity for the aluminum complexes against nucleophiles. This result is not surprising in view of the presence of a net positive charge in aluminum chelated compounds 4-6. For instance, it has been shown that the enhanced electrophilicity of HF respect to the F_2 is mainly due to the presence of an electron deficiency at the H site in HF compared to the electronegativity of F in F_2, thus HF is locally more electrophilic than F_2.[26] This aspect is relevant in the sense that the electrophilicity concept is more likely related to local rather than global aspects. However, the local electrophilicity concept is not trivially related to the site where the electron deficiency is expected from a simple population analysis. While the presence of the hole is expected to be located at the Al site, it is not obvious that the more electrophilic site will always coincide with this site. This argument is reinforced by the Mulliken population analysis (see Table 2, last column) showing that the net atomic charges do not predict the electrophilic sites experimentally established [13,14] : the reduction by hydride is only at the formyl carbon C_b in the presence of alumina and 2-propanol, indicating the orbitally controlled nature of these reactions. Note that according to the HSAB rule, soft reactions (involving the soft nucleophile H^-) should be mainly orbital controlled [27].

Table 1. HOMO and LUMO energy values in atomic units (a..u.), global electrophilicity values (ω), electronic chemical potential (μ) and chemical hardness (η) values for a series of formylchromones (see the text for details).

Compound	HOMO	LUMO	μ (a.u.)	η (a.u.)	ω (eV)
1	-0.2384	-0.0696	-0.1540	0.1689	1.91
2	-0.2368	-0.0746	-0.1557	0.1622	2.03
3	-0.2340	-0.0696	-0.1518	0.1644	1.91
4	-0.4202	-0.2764	-0.3483	0.1438	11.48
5	-0.3981	-0.2689	-0.3335	0.1292	11.72
6	-0.3825	-0.2673	-0.3249	0.1152	12.47
7	-0.2421	-0.1245	-0.1833	0.1176	3.89
8	-0.2362	-0.1169	-0.1766	0.1193	3.56
9	-0.2372	-0.1185	-0.1778	0.1187	3.63

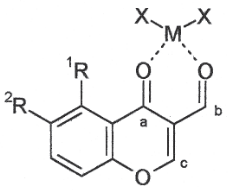
Fig.1. Compounds cited in this work. Sub index a,b,c placed close to the carbon atoms in the heterocyclic and formyl moieties, will be used to inform the calculated properties at these atoms.

Substituted 4-oxo-4H-benzopyran-3-carbaldehydes.



Compound N°	^{1}R	^{2}R
1	H	H
2	OH	H
3	H	OCH_3

Chelated 4-oxo-4H-benzopyran-3-carbaldehydes.



Compound N°	^{1}R	^{2}R	X-M-X
4	H	H	Cl-Al-Cl
5	OH	H	Cl-Al-Cl
6	H	OCH_3	Cl-Al-Cl
7	H	H	Cl-Zn-Cl
8	OH	H	Cl-Zn-Cl
9	H	OCH_3	Cl-Zn-Cl

The presence of a LA catalyst may be viewed as a chemical substitution by electron deficient (i.e electron withdrawing (EW)) groups. Such a complexation may produce electrophilic activating/deactivating effects in different sites of the substrate.[21,22] For instance, chemical substitution on ethylenes by EW groups usually activates position beta for a nucleophilic attack.[28] Local electrophilicity embodies both the global electrophilicity of molecules and the local counterpart represented by the condensed electrophilic Fukui function, which acts as a distribution function for this property (see Eq (4)). Values of local electrophilicity and condensed electrophilic Fukui functions are also summarized in Table 2. It may be seen that in unchelated chromones 1-3, the electrophilic site is predicted at C_c, thereby emphasizing the role of the LA catalyst to determine the regioselectivity of the reaction. The theoretical local electrophilicity pattern is in agreement with the experimental data [13,14] for compounds 4-6 where the $AlCl_2^+$ LA catalyst has been incorporated. Note that incorporation of the neutral $ZnCl_2$ LA catalyst predicts a similar but enhanced quimioselectivity compared to unchelated formylchromones (the highest local electrophilicity value is predicted at the C_c site for compounds 7-9), indicating the importance of the metal nature on the electrophilic properties of the formylchromone complexes. These results show that the use of $AlCl_2^+$ LA catalyst as a model of alumina and the theoretical model for the local electrophilicity index [21,22] correctly reproduce the observed selectivity towards the reduction reaction at the carbonyl C_b carbon atom. These are consistent with the experimental data,[13,14] where the reduction reaction of these compounds in the presence of alumina and 2-propanol was reported to mainly occur at he C_b site. Note that in general, the most electrophilic site of formylchromones in the presence of $AlCl_2^+$ LA catalyst coincides with the softest site in the molecule.

Table 2. Condensed electrophilic Fukui function (f_k^+), local electrophilicity (ω_k), condensed local electrophilic softness (s_k^+) and Mulliken electronic population for a series of formylchromones (see the text for details).

Compound	Site	f_k^+	ω_k(eV)	s_k^+ (a.u.)$^{-1}$	Atomic Charge (Mulliken)
1	C_a	0.1050	0.20	0.6217	0.3948
	C_b	0.0532	0.10	0.3151	0.1999
	C_c	0.3562	0.68	2.1085	0.0641
2	C_a	0.1166	0.24	0.7182	0.4167
	C_b	0.0633	0.13	0.3901	0.1997
	C_c	0.3963	0.80	2.4414	0.0695
3	C_a	0.1540	0.29	0.9364	0.3861
	C_b	0.0051	0.01	0.0309	0.1987
	C_c	0.2154	0.41	1.3094	0.0642
4	C_a	0.0264	0.30	0.1840	0.4933
	C_b	0.3803	4.37	2.6466	0.2609
	C_c	0.2345	2.69	1.6320	0.1513
5	C_a	0.0134	0.16	0.1037	0.5115
	C_b	0.3622	4.24	2.8031	0.2550
	C_c	0.2677	3.14	2.0718	0.1499
6	C_a	0.0483	0.60	0.4195	0.4922
	C_b	0.3921	4.89	3.4033	0.2576
	C_c	0.1901	2.37	1.6500	0.1447
7	C_a	0.0353	0.14	0.3004	0.4797
	C_b	0.1753	0.68	1.4898	0.2518
	C_c	0.4113	1.60	3.4960	0.0993
8	C_a	0.0222	0.08	0.1860	0.4949
	C_b	0.1898	0.68	1.5903	0.2452
	C_c	0.4040	1.44	3.3856	0.0958
9	C_a	0.1009	0.37	0.8505	0.4811
	C_b	0.0854	0.31	0.7202	0.2508
	C_c	0.4003	1.45	3.3746	0.0980

Concluding remarks

Our model based on the global electrophilicity index defined by Parr et al. correctly accounts for the experimental electrophilicity for a series of substituted and chelated formylchromones. The global and local properties may be then used to explain and to predict the most probable kinetic products in an electrophile-hydride interaction. The most reactive site in these compounds is predicted to be the formyl group in the presence of $AlCl_2^+$ as a LA catalyst as a model of alumina. These reactions are predicted to be mostly orbitally controlled rather than charge controlled.

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