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Application of Self-Organizing Maps in Chemistry. The Case of Phenyl Cations

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1. Introduction

We have recently become interested in the application of Self-Organizing Maps (SOM) during a computational study on phenyl cations. As data accumulated, we realized that the analysis and interpretation of results, particularly when many variables were involved, could lead to a cognitive overload. In fact, it is for this reason that SOM found applications in chemistry in several problems, where the classification of large databases was not immediate, or the identification of the most characterizing properties of each class not obvious, since the a priori subdivision of the observed (complex) behaviour in more simple properties was not possible, as it is often the case.

The applications of SOM in chemistry are at present limited in number, but sufficient for indicating the potential of the method. The most important application is probably in the Quantitative Structure Activity Relationship (QSAR). The QSAR is a statistical method used in drug discovery where a correlation between biological activity (including desirable effects chemicals therapeutic undesirable side effects) and of (drugs/toxicants/environmental pollutants) with descriptors representative of molecular structure and/or properties is searched. Drug design has often the need to process enormous amounts of data, in which complex relationships have to be studied and modelled and is thus advantageously confronted by using SOM (Bienfait, 1994; Gramatica, 2007).

However, applications are really varied, including for example the analysis of complex mixtures such as raw oil spills (Fernàndez-Varela et al., 2010), the interpretation of spectra (Dow et al., 2004; Villman et al., 2008), studies of molecular conformation (Hyvönen et al., 2001), as well as the stucture of polymers (Llyod et al., 2008) or crystals (Willighagen et al., 2008), proteonomics (Herrero & Dopazo, 2002) and many others.

Closer to the topic of the present study, the SOM methods has been applied for recognizing the chemical properties of molecules, e.g. for assigning a degree of aromaticity (Alonso & Herradin, 2008), or more generally for predicting the chemical reactivity and its selectivity (Chen & Gasteiger, 1997; Noeske et al., 2006). As a matter of fact, phenyl cations had been all by unknown to chemists up to a decade ago, when it was discovered that electron-donating substituted phenyl halides, sulfonates and phosphates smoothly undergo heterolytic cleavage forming such intermediates in the triplet state, and that in this multiplicity these react efficiently with π , not with n, nucleophiles (Fagnoni & Albini, 2005). The synthetic potential of such intermediates seemed valuable, but the scope of both generation and

reaction required extensive work. Thus it was of interest to carry out computational studies and to apply the SOM method to the data case in order to recognize and predict the structural and chemical properties.

We used self-organizing maps, as developed by Kohonen (Kohonen, 2001; Wehrens et al., 2007). This is an unsupervised neural network that preserves on a two dimensional plane topological relations. We introduced as many as possible optimized geometric parameters and searched for structure similarities. Indeed a visually effective result was obtained through a Sammon map, which clearly separated triplet and singlet cations and helped to rationalize the different substituent effect on the two species.

In the following, the approach used will be illustrated and new examples will be discussed.

2. Description of the problem

Density Functional Theory (DFT) is a computational approach that has shown to be able to determine accurately energy differences, geometries and spectroscopic data of chemical compounds. The method is particularly useful if applied to transient species, such as excited states or reaction intermediates, for which a direct observation could be difficult.

During the last years, in our laboratories a reaction of photoarylation was studied (see Scheme 1).



Scheme 1. Photoinduced arylation

This process is particularly interesting since such arylations can otherwise be obtained only under catalysis by transition metals, a highly versatile method that suffers however of some limitations, in particular related to the catalysts themselves, often delicate, expensive and polluting. Substituting light for heavy metal catalysis makes the reaction more compatible with the principles of green chemistry, i.e. a photoinduced reaction is more ecosustainable (Fagnoni & Albini, 2005).

We have demonstrated that the active chemical intermediate is the aryl cation, and more particularly the triplet spin state. Such an intermediate is highly reactive (it is a carbocation), but is nevertheless characterized by a high selectivity towards suitable traps. The other spin state, the singlet, is on the contrary completely unselective and reacts at diffusion controlled rate practically with everything. As a result, when generated in solution it typically reacts with the solvent.

The computational approach via DFT has been used often for cations and in the present case a first gratifying result was that the computed UV spectrum of the triplet cation was in

accordance with the experimentally determined spectrum of the intermediate, as obtained by flash photolysis (Manet et al., 2008).

From preliminary studies, it is known that the geometry of singlet and triplet phenyl cations differs significantly. In fact, the triplet phenyl cations have a more regular hexagonal geometry with respect to the singlet phenyl cation.



The introduction of substituents in such high-energy intermediates may induce important effects on structure and chemistry with respect to the parent cation. However, it is not obvious how this effect will operate. Singlet phenyl cations have a $\pi^6 n^0$ structure, that is the positive charge is localized at the divalent carbon and lies in the plane of the molecule. Therefore, mesomeric effects should not operate. On the other hand, triplets have a $\pi^5 n^1$, that is a diradicalic character, one radical site at the divalent carbon, one delocalized over the aromatic ring, which has thus a radical cation character. In this case, mesomeric effects may be significant. For simplicity, we considered monosubstituted derivatives, with the group in the three positions, ortho, meta and para, as indicated in the formulae below, where Y stands for an atom or a group of atoms.



3. Data analysis through SOM

The target of the investigation was determining which effect had substituents (and their position) on structure and energy of phenyl cations and how these difference were reflected in the chemical reactivity. Perhaps unexpectedly, in view of the considerations above, the singlet cations had a geometry heavily deformated, with strong dependence on the substituent, despite the fact that these species conserved the intact aromatic sextet. On the

contrary triplets, which had lost the sextet, maintained quite closely the planar hexagonal geometry. The rationalization was not obvious. In order to have a significant results, a sufficiently differentiated choice of substituents had to be considered, avoiding on the other hand to overcome a manageable number. We thus decided to consider eight substituents Y (in the three positions), chosen among those expected to induce large changes due to the electron-donating or –abstracting effect, and to compare their properties with those of the parent cation (Lazzaroni et al, 2008, 2010). The groups, ordered from electron-donating to electron-withrawing were: NH₂, SCH₃, OCH₃, CH₃, Si(CH₃)₃, H, CN and NO₂.

Even in this oversimplified space, these corresponded to a total of 8 (substituents) x 3 (positions) x 2 (spin states) = 48 + 1 structures that were calculated. It was immediately apparent that the comparison by hand of 49 structures in a 3D space was scarcely promising due to the large number of data available. On the other hand, limiting the choice to a few key geometrical parameters was no appealing alternative, due to the lack of objectivity in the choice of such parameters.

This thus appeared as a suitable case for making recourse to unsupervised learning, which can help to find correlations and similarities among large series of data, if a correct input is given.

In the data set, we avoided the use of parameters directly related to the substituent Y, because a trivial categorization factor would be otherwise inserted. Thus, the length of the C-Y bond was not included because it depended on the substituent's nature). For this reason, only parameters related to the carbon skeleton of the aryl cation ring were introduced. In order to describe exhaustively the structure of the six carbon atoms in the space, bond lengths, bond angles and dihedral angles of the phenyl ring were introduced.



Fig. 1. Example of the geometrical data inserted as input

Furthermore, as the divalent carbon (C_1) underwent the most extensive geometrical modifications, all parameters were inserted starting from that carbon, and the shortest path to reach the substituent was adopted. A graphical representation of the choice of parameters and the numbering is given in Figure 1. This choice is essential for the correct application of the SOM.

The complete training set used is given in Table 1.

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	giốt	Ame	e 1 M	1.397	1.378	1.440	1.440	1.379	1.397	126.790	116.760	119.400	120.890	119.400	116.760	0.005	0.000
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International constraints of SOMs was SOMPAK (Kohomen, 1997). International constraints of SOMs was SOMPAK (Kohomen, 1997). International constraints of the first step and 3 for the first step an		iec iec	d ar F	1 4 3 0	1 434	1.400	1 4 3 1	1 413	1.360	125 360	117 480	118.380	121.110	121.080	115 980	0.000	0.000
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$ \begin{array}{c} 1.380 & 1.446 & 1.377 & 1.412 & 1.39 & 1.363 & 136.630 & 109.140 & 118.870 & 121.970 & 122.480 & 106.030 & 9.451 & 1.721 \\ 1.440 & 1.420 & 1.380 & 1.446 & 1.404 & 1.367 & 127.440 & 115.00 & 119.640 & 121.550 & 120.860 & 115.020 & 0.023 & 0.012 \\ 1.326 & 1.450 & 1.392 & 1.397 & 1.428 & 1.331 & 148.870 & 100.000 & 124.390 & 129.980 & 119.990 & 105.440 & 0.007 & 0.003 \\ 1.346 & 1.423 & 1.330 & 1.440 & 1.403 & 1.328 & 124.870 & 101.500 & 124.390 & 129.980 & 119.990 & 105.440 & 0.007 & 0.000 \\ 1.343 & 1.444 & 1.391 & 1.395 & 1.438 & 1.322 & 147.150 & 103.310 & 122.250 & 121.90 & 121.530 & 104.470 & 0.006 & 0.004 \\ 1.343 & 1.444 & 1.391 & 1.395 & 1.438 & 1.322 & 147.150 & 103.310 & 122.250 & 121.90 & 121.530 & 104.470 & 0.006 & 0.004 \\ 1.344 & 1.345 & 1.427 & 1.435 & 1.381 & 1.425 & 124.52 & 13.082 & 119.344 & 120.823 & 119.844 & 116.286 & 0.000 & 0.000 \\ 1.338 & 1.410 & 1.409 & 1.415 & 1.405 & 1.341 & 1.382.72 & 107.636 & 120.990 & 119.909 & 121.511 & 107.313 & 10.663 & 1.08 \\ 1.330 & 1.427 & 1.395 & 1.395 & 1.381 & 1.405 & 127.151 & 116.098 & 117.690 & 124.691 & 119.640 & 176.601 & 160.99 & 0.036 & 0.044 \\ 1.344 & 1.344 & 1.344 & 1.343 & 1.348 & 1.318 & 1.545 & 104.524 & 123.580 & 118.087 & 129.424 & 124.82 & 0.003 & 0.000 \\ 1.344 & 1.345 & 1.422 & 1.329 & 1.349 & 127.66 & 115.915 & 120.390 & 118.607 & 129.40 & 15.910 & 2.941 & 7.298 \\ 1.345 & 1.442 & 1.429 & 1.379 & 1.405 & 1.387 & 126.541 & 115.580 & 120.425 & 120.350 & 103.695 & 0.003 \\ 1.318 & 1.457 & 1.417 & 1.377 & 1.439 & 1.321 & 143.067 & 107.079 & 119.179 & 122.18 & 20.000 & 0.018 \\ 1.348 & 1.425 & 1.341 & 1.399 & 1.342 & 1.344 & 1.344 & 1.347 & 127.96 & 113.267 & 123.263 & 119.831 & 118.966 & 177.312 & 0.000 & 0.018 \\ 1.344 & 1.345 & 1.442 & 1.321 & 143.067 & 107.079 & 119.179 & 122.18 & 10.420 & 0.017 & 0.008 \\ 1.348 & 1.410 & 1.345 & 1.421 & 1.337 & 1.426 & 1.325 & 115.655 & 120.430 & 107.115 & 3.925 & 1.714 \\ 1.343 & 1.442 & 1.391 & 1.349 & 1.426 & 1.324 & 10.1405 & 123.260 & 119.643 & 121.666 & 121.334 & 116.551 & 120.666 & 121.334 & 116.551 &$	Cu	he ⊻i	irs es	1 422	1 4 4 1	1 373	1 423	1 4 1 7	1 360	125 300	117 000	119 020	121 300	121 030	116 350	0.000	0.000
tity of Technology. 1440 1420 1380 1446 1404 1367 127.440 115500 119.640 121.550 120.860 115.020 0.023 0.012 1326 1440 1423 1320 1440 1410 1365 125.660 117.780 118.240 121.410 121.620 115.270 0.000 0.000 1343 1444 1391 1395 1438 1322 147.150 103.10 122.250 121.200 121.530 104.470 0.006 0.004 1343 1.444 1.391 1.395 1.438 1.322 147.150 103.10 122.250 121.200 121.510 104.470 0.006 0.004 1348 1.435 1.427 1.435 1.425 1.381 1.425 126.822 116.882 119.344 120.823 119.844 116.286 0.000 0.000 1348 1.410 1.409 14.15 1.405 13.41 138.272 107.636 120.980 119.909 121.511 107.313 10.663 1.108 1.338 1.440 1.409 14.15 1.405 1.341 138.272 107.636 120.980 119.909 121.511 107.313 10.663 1.080 1.338 1.410 1.409 14.15 1.305 1.394 127.066 115.095 120.425 120.350 136.965 0.084 0.049 1.330 1.427 1.330 14.27 1.330 14.27 1.330 14.84 15 10.695 120.350 120.425 120.350 136.965 0.084 0.049 1.330 1.427 1.395 1.395 1.427 1.330 148.485 103.695 120.425 120.350 136.965 0.084 0.049 1.330 1.427 1.395 1.395 1.427 1.330 148.45 103.695 120.425 120.350 136.965 0.084 0.049 1.330 1.427 1.330 14.22 1.429 1.376 1.344 1.430 1.437 1.437 1.376 1.394 127.066 115.910 120.450 115.910 2.341 7.294 1.591 1.340 1.209 0.115 10 0.294 1.591 0.396 0.084 0.049 1.336 1.427 1.430 1.393 1.438 1.418 145.545 104.524 123.598 118.007 10.040 115.910 2.341 7.294 1.2359 1.18.00 0.000 cycles starting with an initial lengther bond lengths (unit 1.338 1.425 1.429 1.337 1.440 1.403 1.437 1.439 1.322 1.447 127.366 113.267 123.263 119.640 117.195 0.000 0.013 1.338 1.348 1.341 1.457 1.417 1.377 1.439 1.324 1.417 1.327 1.421 1.4306 10.010 0.122.18 120.401 107.115 3.922 1.714 1.333 1.448 1.381 1.386 1.420 1.421 1.332 1.425 1.325 1.4507 10.010 118.001 122.269 118.907 10.241 11.520 120.261 11.549 1.012 1.012 1.212.81 11.541 1.555 1.550 1.	lat	th n p		1.380	1.446	1.377	1.412	1.429	1.336	136.630	109.140	118.870	121.970	122,490	106.030	9.451	1.721
$ \begin{array}{c} 1.326 & 1.450 & 1.392 & 1.397 & 1.426 & 1.333 & 148.870 & 100.360 & 124.390 & 129.980 & 119.960 & 105.440 & 0.007 & 0.003 \\ 1.436 & 1.423 & 1.380 & 1.440 & 1.410 & 1.363 & 125.680 & 117.780 & 118.240 & 121.410 & 121.620 & 115.270 & 0.000 & 0.000 \\ 1.436 & 1.423 & 1.380 & 1.440 & 1.410 & 1.383 & 122.680 & 117.780 & 118.240 & 121.410 & 121.620 & 115.270 & 0.000 & 0.000 \\ 1.343 & 1.444 & 1.391 & 1.395 & 1.438 & 1.322 & 147.150 & 103.310 & 122.250 & 121.290 & 121.531 & 104.470 & 0.006 & 0.041 \\ 1.343 & 1.444 & 1.391 & 1.395 & 1.438 & 1.382 & 147.150 & 103.310 & 120.250 & 121.290 & 119.909 & 121.511 & 107.313 & 10.663 & 1.008 \\ 1.394 & 1.385 & 1.427 & 1.435 & 1.385 & 1.405 & 1.341 & 13822 & 177.653 & 120.990 & 119.909 & 121.511 & 107.313 & 10.663 & 1.008 \\ 1.394 & 1.338 & 1.440 & 1.049 & 1.445 & 1.331 & 1.405 & 127.815 & 116.098 & 117.660 & 124.699 & 117.660 & 116.99 & 0.139 & 0.766 \\ 1.333 & 1.427 & 1.395 & 1.427 & 1.395 & 1.427 & 1.330 & 148.485 & 103.695 & 120.425 & 120.350 & 0.2046 & 0.049 \\ 1.394 & 1.376 & 1.431 & 1.390 & 1.339 & 1.428 & 1.330 & 148.485 & 103.695 & 120.425 & 120.350 & 0.148.402 & 0.003 & 0.000 \\ 1.354 & 1.422 & 1.429 & 1.376 & 1.331 & 14.565 & 106.524 & 123.596 & 118.607 & 120.422 & 104.523 & 0.000 & 0.000 \\ 1.354 & 1.422 & 1.429 & 1.376 & 1.387 & 126.914 & 115.380 & 120.422 & 104.523 & 0.000 & 0.000 \\ 1.354 & 1.422 & 1.429 & 1.379 & 1.405 & 1.387 & 126.914 & 115.380 & 120.421 & 107.115 & 3.292 & 1.714 \\ 1.383 & 1.385 & 1.440 & 1.403 & 1.392 & 1.417 & 127.66 & 113.267 & 123.263 & 119.813 & 118.976 & 117.312 & 0.000 & 0.018 \\ 1.364 & 1.404 & 1.457 & 1.392 & 1.387 & 1.466 & 103.16 & 124.208 & 119.624 & 121.662 & 104.393 & 0.017 & 0.008 \\ 1.332 & 1.428 & 1.394 & 1.394 & 1.396 & 1.420 & 1.333 & 1.4806 & 100.216 & 123.268 & 123.258 & 119.813 & 118.976 & 117.312 & 0.000 & 0.003 \\ 1.338 & 1.410 & 1.378 & 1.408 & 1.420 & 1.333 & 1.426 & 13.264 & 119.104 & 118.505 & 20.666 & 121.334 & 116.751 & 0.259 & 0.377 \\ 1.333 & 1.448 & 1.391 & 1.396 & 1.420 & 1.333 & 1.420 & 1.333 & 1.440 & 1.389 & 1.371 $	it io	ne 1(of	1.440	1.420	1.380	1.446	1.404	1.367	127.440	115.500	119.640	121.550	120.860	115.020	0.023	0.012
of SOMs was SOMPAK (Kohonen, 1997), 1438 1.423 1.380 1.440 1.410 1.363 125.680 117.780 118.240 121.410 121.620 15.270 0.000 0.000 1.343 1.444 1.391 1.395 1.438 1.322 147.150 103.310 122.250 121.290 121.530 104.470 0.006 0.000 1.343 1.444 1.391 1.395 1.438 1.322 147.150 103.310 122.250 121.290 121.530 104.470 0.006 0.000 1.343 1.444 1.391 1.395 1.435 1.435 1.435 1.435 1.435 1.436 1.431 132.272 107.636 120.900 119.909 121.511 107.313 10.663 1.009 0.139 0.076 1.330 1.427 1.395 1.395 1.427 1.301 148.45 103.695 120.350 120.425 120.350 10.642.469 17.660 116.990 0.139 0.076 1.330 1.427 1.395 1.437 1.391 1.437 1.391 1477	ns /	100 In	th gree of	1.326	1.450	1.392	1.397	1.426	1.333	148.870	100.360	124.390	120.980	119.960	105.440	0.007	0.003
FSOMs was SOMPAK (Kohonen, 1997), for the first step and 3 for the fir	f	D ed	e l	1.436	1.423	1.380	1.440	1.410	1.363	125.680	117.780	118.240	121.410	121.620	115.270	0.000	0.000
$ \begin{array}{c} \text{Drology.} \\ \text{OMS was SOMPAK} (Kohonen, 1997), \\ \text{Vith} 10000 cycles starting with alp lengths (units 138, 1427, 1438, 1440, 1389, 1422, 1436, 1339, 126,822, 116,882, 119,344, 120,823, 119,844, 116,286, 0,000$	le fe	cyo l w	of (1.343	1.444	1.391	1.395	1.438	1.322	147.150	103.310	122.250	121.290	121.530	104.470	0.006	0.004
	F Ö	vit	en si	1.394	1.385	1.427	1.435	1.385	1.389	126.822	116.882	119.344	120.823	119.844	116.286	0.000	0.000
S was SOMPAK (Kohonen, 1997), 1997), 1455 1.381 1.425	nc M	ag h is	iyl x c	1.338	1.410	1.409	1.415	1.405	1.341	138.272	107.636	120.980	119.909	121.511	107.313	10.663	1.108
	s v lo	10 10	c the ol	1.405	1.381	1.425	1.425	1.381	1.405	127.815	116.098	117.660	124.669	117.660	116.099	0.139	0.076
$ \begin{array}{c} 1.394 \\ 1.316 \\ 1.444 \\ 1.390 \\ 1.356 \\ 1.422 \\ 1.429 \\ 1.351 \\ 1.444 \\ 1.390 \\ 1.391 $	SN NS	0 <u>1</u> 0	te t	1.330	1.427	1.395	1.395	1.427	1.330	148.485	103.695	120.350	120.425	120.350	103.695	0.084	0.049
Source for the first step and 3 for the for a description with alpha 1.318 1.444 1.390 1.393 1.438 1.318 145.545 104.524 123.598 118.084 123.422 104.828 0.003 0.000 0.001 1.354 1.422 1.429 1.379 1.405 1.387 126.914 115.380 120.221 120.651 119.640 117.195 0.005 0.003 1.318 1.457 1.417 1.377 1.439 1.321 143.067 107.079 119.179 122.218 120.420 107.115 3.925 1.714 1.383 1.385 1.440 1.403 1.392 1.417 127.366 113.267 123.263 119.813 118.976 117.312 0.000 0.018 1.323 1.425 1.391 1.399 1.428 1.334 146.584 103.116 124.085 119.624 121.662 104.930 0.017 0.008 1.323 1.425 1.310 1.448 1.393 1.392 1.416 1.331 148.014 100.910 123.280 122.595 117.920 07.281 0.132 0.103 1.310 1.448 1.393 1.392 1.416 1.331 148.014 100.910 123.280 122.595 117.920 07.281 0.132 0.001 0.001 1.398 1.410 1.378 1.408 1.402 1.363 123.640 119.104 118.505 120.666 121.334 116.751 0.259 0.237 1.333 1.448 1.381 1.396 1.426 1.325 145.077 104.011 121.794 120.732 105.748 3.741 0.189 1.417 1.389 1.389 1.440 1.395 1.379 124.639 120.282 116.617 121.912 121.236 115.269 2.046 1.824 1.403 1.411 1.381 1.440 1.395 1.379 124.639 120.282 116.617 121.912 121.236 115.269 2.046 1.824 1.403 1.411 1.381 1.440 1.389 1.371 128.776 114.430 120.001 121.667 120.542 114.585 0.164 0.103 1.294 1.452 1.387 1.395 1.420 1.333 149.011 102.573 121.807 121.460 120.847 104.301 0.004 0.000	<u>ک</u> '	₩ 0 10	on hii	1.394	1.376	1.434	1.434	1.376	1.394	127.066	115.915	120.936	118.807	120.940	115.910	2.941	7.298
$\begin{array}{llllllllllllllllllllllllllllllllllll$	S	: tl	bu bu	1.315	1.444	1.390	1.393	1.438	1.318	145.545	104.524	123.598	118.084	123.422	104.828	0.003	0.000
$\begin{array}{c} \text{IPAK} (\text{Kohonen, 1997}), \\ \text{text for a description} \\ text for a descript$	M	n cle	ee di	1.354	1.422	1.429	1.379	1.405	1.387	126.914	115.380	120.221	120.651	119.640	117.195	0.005	0.003
AK (Kohonen, 1997), 1383 1.385 1.440 1.403 1.392 1.417 127.366 113.267 123.263 119.813 118.976 117.312 0.000 0.018 1.383 1.385 1.440 1.403 1.392 1.417 127.366 113.267 123.263 119.813 118.976 117.312 0.000 $0.0181.323$ 1.425 1.391 1.399 1.428 1.334 146.584 103.116 124.085 119.624 121.662 104.930 0.017 $0.0081.364$ 1.404 1.457 1.392 1.387 1.416 127.245 116.565 117.542 123.395 118.320 116.932 0.000 $0.0031.310$ 1.448 1.393 1.392 1.416 1.331 148.014 100.910 123.280 122.595 117.920 107.281 0.132 $0.1031.398$ 1.410 1.378 1.408 1.402 1.363 123.640 119.104 118.505 120.666 121.334 116.751 0.259 $0.2371.333$ 1.448 1.381 1.396 1.426 1.325 145.077 104.011 121.794 120.732 105.748 3.741 $0.1891.417$ 1.389 1.398 1.440 1.395 1.379 124.639 120.282 116.617 121.912 121.236 115.269 2.046 $1.8241.403$ 1.411 1.381 1.440 1.389 1.371 128.776 114.430 120.001 121.667 120.542 114.585 0.164 $0.1031.294$ 1.452 1.387 1.395 1.420 1.333 149.011 102.573 121.807 121.460 120.847 104.301 0.004 0.000	P	fi: Si an	e b	1.318	1.457	1.417	1.377	1.439	1.321	143.067	107.079	119.179	122.218	120.420	107.115	3.925	1.714
K (Kohonen, 1997), K (kohonen,	A	sta rst	ext ed or	1.383	1.385	1.440	1.403	1.392	1.417	127.366	113.267	123.263	119.813	118.976	117.312	0.000	0.018
$ \begin{array}{c} \text{(Kohonen, 1997)} \\ \text{(Kohonen, 1997)}, \end{array} \begin{array}{c} \text{(Kohonen, 1997)} \\ \text{(Kohonen, 1997)} \\ \text{(Kohonen, 1997)} \\ (Koho$	X	urt it	nd ral	1.323	1.425	1.391	1.399	1.428	1.334	146.584	103.116	124.085	119.624	121.662	104.930	0.017	0.008
$\begin{array}{c} \text{Opp} \\ \text{Opp} \\ \text{Opp} \\ \text{Hearning} \\ Hearning$	(K	ia] in	le or	1.364	1.404	1.457	1.392	1.387	1.416	127.245	116.565	117.542	123.395	118.320	116.932	0.000	0.003
$\begin{array}{c} \begin{array}{c} \text{form} \\ \text{h} \\ h$	oh		ng	1.310	1.448	1.393	1.392	1.416	1.331	148.014	100.910	123.280	122.595	117.920	107.281	0.132	0.103
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	lOI	wi n		1.398	1.410	1.378	1.408	1.402	1.363	123.640	119.104	118.505	120.666	121.334	116.751	0.259	0.237
$ \begin{array}{c} n \\ 1997 \\ n \\ $	าย	d fr	s SCI	1.333	1.448	1.381	1.396	1.426	1.325	145.077	104.011	121.794	121.794	120.732	105.748	3.741	0.189
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	n,	$\frac{3}{6}$ al in	rip (u	1.417	1.389	1.398	1.440	1.395	1.379	124.639	120.282	116.617	121.912	121.236	115.269	2.046	1.824
Y E E E Y I 1.294 1.452 1.395 1.420 1.333 149.011 102.573 121.807 121.460 120.847 104.301 0.004 0.000	19	or pr	nit nit	1.403	1.411	1.381	1.440	1.389	1.371	128.776	114.430	120.001	121.667	120.542	114.585	0.164	0.103
	97	na rat	s ¹	1.294	1.452	1.387	1.395	1.420	1.333	149.011	102.573	121.807	121.460	120.847	104.301	0.004	0.000
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A first trial with a rectangular 2x2 grid was carried out in order to verify the correctness of the input data; indeed, the database was correctly divided into two classes, the first one containing only singlets and the second one only triplets.

A more advanced level of information could be obtained by increasing the size of the map. The program used allowed the creation of two different lattice arrangements of neurons: rectangular and hexagonal. After some experimenting, we found convenient to adopt the rectangular lattice.

The calculated rectangular 5x5 map containing all the phenyl cation intermediates is reported below (Table 2). The numbering in the table is referred to the substituent position, as indicated in Figure 2, while the spin state is specified by the capital letter superscripts S for singlets and T for triplets. The formula of the substituent Y is placed after the number and H is used for the unsubstituted (parent) phenyl cation.



Fig. 2. Substituent numbering used in Table 2

The differences in geometry of singlet and triplet phenyl cations is well apparent, with the two classes lying in different positions in the table.

In this 5x5 map, 17 cathegories were represented, each one of them corresponding to an active neuron.

By analyzing the position of the entries in the table, some generalizations could be made; for example, when considering the singlets, substituents such as CN, NO₂, Si(CH₃)₃ and CH₃ were all grouped in the bottom left corner, close to the parent cation.

A chemical meaning can be immediately associated with this result. Thus, all of the substituents above are known to be electron-withdrawing or almost electron-neutral groups. The presence of an empty sp² orbital at C₁ in the place of a σ bond makes little difference for

the intact π^6 system with which the substituents mainly interact, resulting in a moderate effect on the geometry of the phenyl cation.

On the other hand, cations bearing electron-donating substituents are found in the left part of the table, but their distribution is more spread across the table, with an effect that varies with the position in a different way for each substituent. The substituents with a strong mesomeric effect, such as amino, methoxy and thiomethoxy group cluster at the upper left corner. Clearly, the electron-rich π system does interact with the empty σ orbital, and both the nature and the position of ring substituents are important in determining the final geometric parameters.

As for the triplets, these are grouped in three big classes in the rightmost column. Each of them containing (mainly) cations bearing the substituent in the same position, regardless of their-donating or -withdrawing character. Apparently, with triplets the effect of the position of the substituent overcame the electronic effect in causing a deformation of the phenyl cation.

4-OCH ₃ s				4-Si(CH ₃) ₃ ^T
4-NH ₂ s				
2-NH ₂ s				
4-SCH ₃ s				
	2-SCH ₃ s	3-NH ₂ s 3-SCH ₃ s		3-NO ₂ ^T
2-OCH ₃ s	3-OCH ₃ s		$2-CH_3^T$	4-CH ₃ ^T
				3-OCH ₃ ^T
				$3-NH_2^T$
				3-CN ^T
				$3-SCH_3^T$
2-CH ₃ s		2-Si(CH ₃) ₃ ^T	$4-OCH_3^T$	$4-NH_2^T$
3-Si(CH ₃) ₃ s			$4-CN^{T}$	$4-SCH_3^T$
			HT	
			$3-CH_3^T$	
			$4-NO_2^T$	
4-CN ^s	4-CH ₃ s		3-Si(CH ₃) ₃ ^T	2-OCH ₃ ^T
2-CN ^s	3-CH₃ ^s			$2-NH_2^T$
Hs	3-CN ^s			2-CN ^T
$4-NO_2^S$	4-Si(CH ₃) ₃ s			$2-SCH_3^T$
3-NO ₂ s				$2-NO_2^T$
2-Si(CH ₃) ₃ s				

	Table 2.5	5x5 SOM ma	p obtained	for the com	plete set of	calculated	phenyl	cations
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Another useful information is given by the quantization of the error regarding each of the entries of the map. The quantization error is inversely proportional to the matching of each entry line (in our case each phenyl cation) within the assigned class.

Figure 3 shows the pictorial representation of the quantization errors for the 5x5 calculated map; each one of the grid intercepts has a corresponding element in Table 2. Circles with small areas are related to small quantization errors. As can be seen in the figure, a small number of neurons corresponds to classes having most of the best-matching entries. These neurons define a sharp-defined class, i.e. the entries located by this neuron are most similar among them. Considering those of the 'sharp' classes that contain more than one entry, it is found that these corresponds to the four classes evidenced in Table 2, one for the singlets with bearing no electron-donating substituent, three for the triplets with the substituent in each of the three position (that is the classes at positions 1;5, 4;4, 5;3 and 5;5).

Although the distribution in a table does give useful information about any alikeness, a more quantitative representation of class similarities in a calculated map is the projection of neurons through the Sammon's map (see Figure 4).

The label assigned to each point is that of the first entry in the class identified with that neuron. A look at Figure 4 makes it apparent that all of the triplets (squares) lie within a much smaller area with respect to that occupied by singlets (circles). Thus, even if the number of classes belonging to triplets is similar to that of singlets, the former ones are subject to a smaller geometric variation.

Concerning singlets, the map shows how they are rather scattered on the Sammon's projection. The parent phenyl cation is located at coordinates -18, -10. Electron-donating substituents appear to cause a deformation that increases when passing from substituents in position 2 to the same in position 4.



Fig. 3. Quantization error for the calculated 5x5 SOM. The area of the circle is proportional to the quantization error for that entry. Please note that overlap between circles is diminished because a random value was added to the position of the center



Fig. 4. Sammon's projection for the 5x5 map showed in table 1. Axes are in arbitral units

The above observation affords indications for assessing the effect of substituents on the geometry of phenyl cations. However, arriving at recognizing the key geometrical parameters for each class requires a different approach. This is possible by having recourse to the analysis of 'activation planes'. During the SOM optimization a plane of activation is created for each input variable. In our case we have three groups of six variables each, viz. bond lengths, bond angles and dihedral angles.

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$\begin{array}{cccc} \cdot & \bullet \cdot & \circ & \bullet \cdot \\ \hline \bullet & \bullet & \bullet & \bullet \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{array}$				
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Fig. 5. Activation planes for each element of the grid



Fig. 6. Geometries of carbon rings for the phenyl cations 4-OCH₃^S and 4-CN^S, top and side view

In Figure 5 these values are shown as circles having an area proportional to the weight of the corresponding input. For every element of Table 2 three lines (bond length, angle, dihedral angle) containing six circles each are a representation of the importance of the input data. As it can be seen in the figure, even table elements (and thus neurons) having no class members have nonzero values. In this picture, is also apparent the meaning of the word neighbourhood in this context (and thus the importance of rectangular or hexagonal grid): neurons in close contact have similar activation weights.

Let us consider the leftmost column of grid shown in Figure 5. It is apparent that when proceeding from the top to the bottom of the figure, the classification algorithm changes from one characterized by a high weight of the dihedral angles to one characterized by a high weight for specific bond lengths (second and fifth bond) and bond angles (1,2,4,5).

Notice that only few of these characteristics are visible by observing the actual geometries (see Figure 6).

In fact, only the dihedral angle differences are immediately appreciated in the side view, while the variation of bond lengths are better visible by looking at the corresponding rows in Table 2. The largest effect among the out-of-plane variations is the lengthening of bonds 2 and 5 for the CN-substituted derivative. This effect could be reasonably assigned to the stabilization of the radical site by the CN substituent. Correspondingly, the methoxy group stabilizes the charge by the resonance electron donation (see the formulae in Figure 7).



Fig. 7. Contribution of the electronic effect to the stabilization of singlet phenyl cations

In the same line, it may be asked which are the geometrical key parameter for the three distinct classes of triplets located at 4;4, 5;3 and 5;5. Figure 5 tell us that the dihedral angles do not contribute significantly (third row of six circles). In fact, all of these structures lie almost perfectly in a plane.

For these phenyl cations, the structures can be roughly represented as indicated in Figure 8, where the dashed double bond is slightly shorter with respect to other bonds. Since this effect, which is due to the electronic stabilization by the substituent, is quite small, almost no effect is visible observing the 3D structures (also in this case, a close scrutiny of the data in Table 2 reveals the effect, however).

Summing up, the various analyses carried out in this work allow a better understanding of the structure of phenyl cations and the effect of substituents on it. This is much more complex than that obtained by one- or two-parameters linear relationships (Lazzaroni et al., 2008, 2010) and not easily framed in the usual mesomeric/inductive effects. On the other hand, patterns are recognized and may have some predictive effect for further substituents

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or for suggesting new chemistry (notice, as an example, the diradicalic nature of triplets, depending only from the position of the substituent, for which is not known at the moment any corresponding reaction.



Fig. 8. Schematic structures for 2-, 3- and 4- substituted triplet phenyl cations

Finally, the important question of the relation between energy and geometry in these cations can be confronted. For this aim it is convenient to introduce a isodesmic chemical equation in which a hypothetical reaction is considered. One of these reactions has to be assumed as the reference zero, and in this case the unsubstituted phenyl cation was chosen. The isodesmic reaction considered is thus that shown in Figure 9.



Fig. 9. Isodesmic reaction for the determination of the substituted phenyl cations stability

The calculation of the free energy (ΔG) of this reaction gives a direct information about the stabilization induced by substituent Y. If the free energy is negative for the reaction considered from the left side to the right side, as indicated in the equation the substituted phenyl cation is less stable than the parent cation. If, on the other hand, the reaction has a positive free energy value, the group Y stabilizes the phenyl cation.

If there is a relationship between the geometric classification and the stabilization of the phenyl cation, a pattern should appear by placing in the SOM table the calculated values of free energies. The result is shown in Figure 10, where, for each element of the table, a sphere was drawn having a radius directly proportional to the absolute value of the free energy.

The colour of the sphere indicate the sign of the free energy, blue and red for negative and positive values, respectively. When multiple data are located in the same cell, the sphere is shifted on the right.

As one can see, only a loose correlation between stabilization energy and geometric parameters can be perceived.

4. Conclusion

The geometry and the energy of the singlet and triplet state of a series of substituted phenyl cations have been investigated by DFT methods. The pattern of the effects with reference to the nature of the substituent and to its position has been recognized through the SOM method. The regular hexagon geometry of ring carbons in the triplet state is minimally affected by substituents. The singlet cation is more heavily deformed (cumulene character at the C2-C1-C6 moiety) and is affected to a large extent both by the position and by the nature of the substituent in particular with electron-donating substituents that cause a ring carbon to shift out of plane.



Fig. 10. Stabilization energies of phenyl cations corresponding to the classification in Table 2 (See text)

It was attempted to find a correlation between geometric structure and stabilization energy by the use of this procedure, but this turned out to be weak. We plan to take further advantage of the SOM method for the analysis of the structure and chemical properties of these novel intermediates, phenyl cations.

More generally, we feel that the SOM method should be more largely used for predicting chemical reactivity, both for novel intermediates, as is the case here, and for old ones, where

perhaps it may reveal that the substituent effect is treated in a simplicistic way when using a traditional approach.

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Kohonen Self Organizing Maps (SOM) has found application in practical all fields, especially those which tend to handle high dimensional data. SOM can be used for the clustering of genes in the medical field, the study of multi-media and web based contents and in the transportation industry, just to name a few. Apart from the aforementioned areas this book also covers the study of complex data found in meteorological and remotely sensed images acquired using satellite sensing. Data management and envelopment analysis has also been covered. The application of SOM in mechanical and manufacturing engineering forms another important area of this book. The final section of this book, addresses the design and application of novel variants of SOM algorithms.

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