182. Quantum Chemical Investigation of the Structure and Reactivity of Indole Derivatives of Tricarbonylchromium(0)

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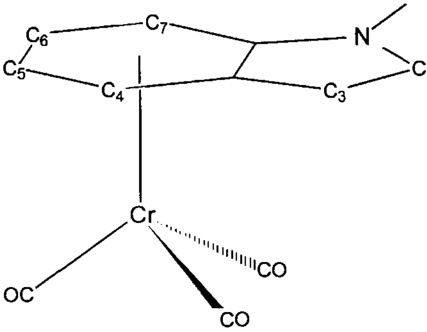
In a theoretical investigation of the structure and reactivity of indole derivatives of tricarbonylchromium(0), we have used two different semi-empirical quantum chemical models derived from the extended *Hückel* molecular-orbital (EHMO) formalism. The first one, based on the atom-superposition and electron-delocalization (ASED) method, is used to optimize the geometry of the systems; it is shown to lead to results in satisfactory agreement with experiment in the case of the complex for which X-ray structural data are available, the average errors being 0.03–0.05 Å for bond distances and 5° for bond angles. The second one consists of a local reactivity index, made of the intermolecular interaction energy between the organometallic substrate and a model reactant. It is seen that this procedure is able to reproduce the experimental trends as to the most reactive regions of the systems investigated towards nucleophilic and electrophilic addition reactions.

Introduction. – The synthesis of substituted indole derivatives has been the subject of a wide range of experimental studies [1], due to the abundance of both natural and synthetic biologically active compounds with an indole skeleton [2]. The different approaches that have been developed to produce functionalized indole derivatives can be roughly classified in two categories: in the first one, the indole nucleus is built up from presubstituted non-indolic products, the starting materials containing either the preformed six-membered or five-membered rings [1a, b]. In the second category, direct substitutions are carried out on the readily available indole ring. However, while several



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methods have been successfully applied to functionalize the pyrrole ring [3], the carbocyclic C(4) and C(7) positions remained difficult to substitute [4]. In recent years, a significant progress in this context has been achieved through the exploration of reaction mechanisms involving indole derivatives complexed to transition metals [5]. It is now well-known both from experimental and theoretical observations that complexation of π-arenes to transition metals significantly enhances their electrophilic reactivity. This has been correlated with the decrease of electron density on the organic ring, due to the strong electron-withdrawing capability of the transition metal. Both *Kozikowski* and *Isobe* [6a], and *Semmelhack et al.* [6b, d] have indeed pointed out that complexation of the carbocyclic ring to the $Cr(CO)_3$ moiety permits substitutions at the C(4) and C(7) sites by reactive C nucleophiles using the addition/oxidation technique. Depending on the nature of the carbanion and on the steric and electronic properties of the substituents on the indole, the preferred site of attack changes between C(4) and C(7). Another route for functionalizing the carbocyclic ring involves nucleophilic substitutions on 4- and 5-chloroindoles complexed by the $RuCp^+$ tripod [7]. More recently, direct functionalization at the C(4) and C(7) site of *N*-protected $[Cr(CO)_3(indole)]$ have been achieved *via* lithiation/electrophilic quench sequence [8].

We have initiated some years ago a project aiming at the development of various molecular modeling tools for organometallic systems [9] [10]. Its main purpose was to have at hand computationally simple models so as to achieve rationalizations, at a qualitative or, at best, semi-quantitative level, of the structure and properties of organometallics within a reasonable amount of computer time. To this end, the model builder is based on the EHMO-ASED (extended *Hückel* molecular-orbital atom-superposition, and electron-delocalization) procedure proposed by *Anderson* and *Hoffmann* [11], and recently reformulated by *Calzaferri et al.* [12]. We have been parametrizing this formalism for organometallic complexes, and the first results obtained for metallocenes and carbonyl compounds are promising [9] [13]. On the other hand, we have developed a reaction potential formalism based on EHMO, called EHPROP, with the purpose to evaluate a semi-empirical reactivity index for organometallics [10]. Applied to a large number of nucleophilic, and electrophilic addition or substitution reaction mechanisms [10] [14–19], this model has been shown to be able to rationalize and generally predict the regioselectivity and energetics of such reactions. It was, therefore, interesting to apply this method to the rationalization of the reactive properties of indole derivatives of $Cr(CO)_3$, in an attempt to better understand their structural features and reactive properties.

The main purpose of the present work is first to apply the EHMO-ASED model to evaluate the structural parameters of $[Cr(CO)_3(\eta^6\text{-}N\text{-methylindole})]$ (**1**), $[Cr(\eta^6\text{-benzofuran})(CO)_3]$ (**2**), and the adduct of **1** with 1,3-dithiane (**3**). The capacity of the model to predict accurate geometries for these systems will be tested by comparing the results obtained for **1** with X-ray crystal-structure data. Then, in an attempt to rationalize the reactivity of **1** and **2** towards nucleophilic attack and of **3** towards electrophilic addition, the corresponding reaction potentials will be calculated using the EHPROP local reactivity index.

Computational Details. – The EHMO-ASED model is based on the introduction of *i*) a distance-dependent *Wolfsberg-Helmholz* formula to evaluate the off-diagonal matrix elements $H_{\mu\nu}$ for metal–ligand and ligand–metal–ligand interactions:

$$H_{\mu\nu} = 1/2\,K_{\mathrm{AB}}(H_{\mu\mu} + H_{\nu\nu})\,S_{\mu\nu}$$
$$\text{with } K_{\mathrm{AB}} = 1 + \kappa e^{-\delta(R_{\mathrm{AB}} - (R_{\mathrm{covA}} + R_{\mathrm{covB}}))}$$

where A and B are the atoms to which to orbitals μ and ν belong; κ and δ are positive empirical parameters, R_{AB} the distance between the atoms A and B, R_{covA} and R_{covB} their covalent radii; *ii*) an approximate two-body repulsive electrostatic energy term [9]. The geometry-optimization part of the calculation is carried out using a powerful sequential quadratic procedure [20].

The EHPROP model makes use of a local reactivity index based on the interaction energy E_{int} between the organometallic substrate S and an incoming electrophilic or nucleophilic reactant R located in $\mathbf{r}$. This energy is expressed as:

$$E_{\mathrm{int}}(\mathbf{r}) = E_{\mathrm{es}}(\mathbf{r}) + E_{\mathrm{ct}}(\mathbf{r}) + E_{\mathrm{ex}}(\mathbf{r})$$

where $\mathrm{E}_{\mathrm{es}}(\mathbf{r})$, $\mathrm{E}_{\mathrm{ct}}(\mathbf{r})$, and $\mathrm{E}_{\mathrm{ex}}(\mathbf{r})$ are the electrostatic, charge-transfer, and exchange-repulsion components, respectively. Both E_{es} and E_{ct} are evaluated in the framework of the extended *Hückel* quantum-chemical formalism, using the electrostatic potential and the supermolecule approach, respectively, whereas E_{ex} is approximated using a parametrized potential of *Buckingham* type [10]. Negative (positive) values of E_{int} correspond to attractive (repulsive) interactions between S and R. The minima of E_{int} may be, therefore, considered as the most reactive sites of S towards attack by R. To have a model that is computationally expedient, we make use of spherically symmetric model reactants: a proton with a virtual 1s orbital for an electrophile, and an H^- ion with a fully occupied 1s orbital for a nucleophile. The E_{int} reactivity index is then displayed as three-dimensional solid models of isoenergy surfaces by means of molecular-graphics techniques.

Results and Discussion. – In a previous study, we have already carried out a full geometry optimization of **1** [13]. However, the κ, δ parameters employed to describe the interactions within the *N*-methylindole ligand were given standard values, which led to rather poor bond distances for the pyrrole part of the ligand. In an attempt to improve these results, a new set of κ, δ parameters has been determined for pyrrole and introduced in the calculations. *Fig. 1* presents the EHMO-ASED optimized geometry of **1** as obtained using this new parametrization. As previously noted, the metal–ligand distances are rather well reproduced, the average discrepancies with experimental data being 0.068 and 0.026 Å for metal–cycle and metal–CO bonds, respectively [9] [13]. The bond angles for the $\mathrm{Cr(CO)_3}$ tripod are also in good agreement with experiment [21], the average error on ring–Cr–CO angles being equal to 5.3°. It should be noted that, as observed in the crystallographic structure, the $\mathrm{Cr(CO)_3}$ tripod adopts in our calculation a staggered conformation, the optimized $\mathrm{X_1{-}X_2{-}Cr{-}CO^*}$ bond angle being in very good agreement with experiment (*cf. Fig. 1*). Concerning the *N*-methylindole ligand, it appears that the introduction of the new parameters leads to a small overall improvement of 0.010 Å in the bond distances of the organic ring, as compared to our previous calculation [13], due to a better prediction of the geometry of the pyrrole ring, whereas the results obtained for the carbocyclic ring are slightly worse. However, in view of the relatively small average error for all the optimized distances (0.037 Å), we may expect our EHMO-ASED model to give reasonable structures and related organometallics. We have, therefore, decided to carry out the same calculation on **2**, for which no crystallographic study has been reported. The result of the geometry optimization is presented in *Fig. 2*. As expected from the strong similarity of **1** and **2**, the metal–ligand bond distances and bond angles are approximately the same for both structures. However, it should be noted that the most significant change is concerned with the conformation of the tripod (*cf. Figs. 1* and *2*). The $Cr(CO)_3$ fragment is rotated in such a way in **2** that one of the Cr–C(O) bonds is closer to C(4) as compared with **1**. At a first sight, we may attribute this difference to a steric hindrance due to the presence of the Me group in **1**. However, an additional calculation carried out on the $[Cr(CO)_3(\eta^6\text{-indole})]$ complex leads to the same conformation of the tripod as the one found in **1**, and we might, therefore, preferably attribute this change in the conformation of $Cr(CO)_3$ to an electronic effect.

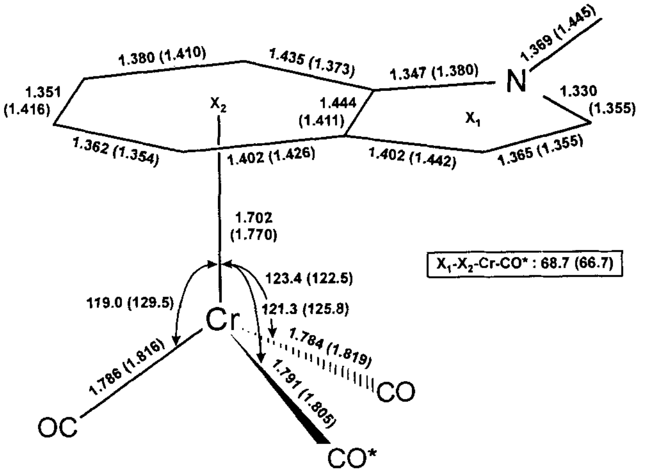

Fig. 1. *Optimized structure of* $[Cr(CO)_3(\eta^6\text{-N-methylindole})]$ (**1**). Bond distances are given in Å, bond angles in degrees, experimental data in parentheses.

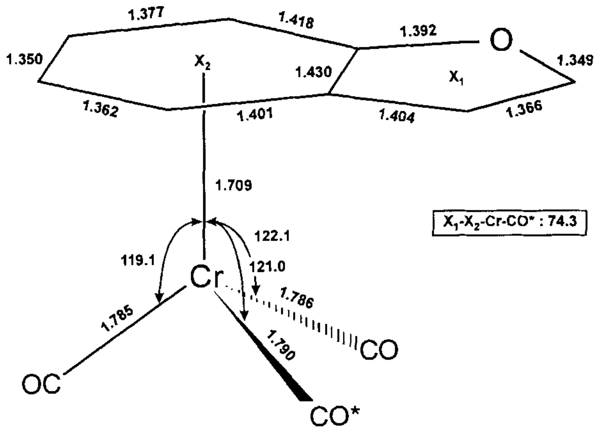

Fig. 2. *Optimized structure of the* $[Cr(\eta^6\text{-benzofuran})(CO)_3]$ (**2**). Bond distances are given in Å, bond angles in degrees.

We have seen in this first part that our EHMO-ASED model is able to give a reasonable structure for **1**. This suggests that this procedure may be used as a model builder for organometallics so as to have at hand initial geometries for reactivity investigations. Therefore, in the second part, we will apply the EHPROP formalism in order to model the reactivity of these compounds. *Fig. 3* displays the isoenergy surfaces of the E_{int} reactivity index calculated for nucleophilic attack of **1**. It is seen that the global minimum corresponding to an E_{int} value of −23.5 kcal/mol is located on the '*exo*'-face of the ligand, in a position close to C(7). On the other hand, examination of the values of the components of E_{int} at this minimum reveals that the major contribution arises from E_{es} (−27.2 kcal/mol), whereas the E_{ct} and E_{ex} energies are rather small, +3.1 kcal/mol and +0.6 kcal/mol, respectively. This positive value of the E_{ct} contribution suggests that 4-electron interactions between the HOMO of R and the occupied levels of S are predominant. For higher (*i.e.* less negative) values of the reactivity index, the isovalue surfaces significantly extend in the direction of the carbocyclic ring. This result is in global agreement with the experimental observations of *Semmelhack et al.* [6c]. Using various nucleophiles and *N*-protecting groups, these authors report indeed that the selectivity of the attack may be modulated between the C(4) or C(7) site (*i.e.* on the carbocyclic ring). To evaluate the sensitivity of our results upon substrate geometry, we have performed a similar calculation using the crystallographic structure of **1**, and no clear difference emerges between the position of the isoenergy surfaces. On the other hand, we have also evaluated the regioselectivity of a nucleophilic attack on the uncoordinated *N*-methylindole molecule, using the same EHPROP model. We have then found the most favorable site of attack to lie at a much lower energy (−10.1 kcal/mol), and to be located on the H-atoms of the Me group. This result emphasizes the dramatic change in selectivity due the complexation of the *N*-methylindole to the $Cr(CO)_3$ fragment. Moreover, it may also explain the fact that our global minimum is shifted out of the center of the carbocyclic ring, in the direction of the *N*-methyl moiety. To investigate the influence of the nature of the uncoordinated cycle of the bicyclic ligand on the reactivity of these systems, we have performed a similar study for [Cr(η^6-benzofuran)$(CO)_3$] (**2**). In this case, the global minimum of E_{int} is also located on the '*exo*'-face of the carbocyclic ring, but practically above its center, *i.e.*, no clear selectivity is predicted (*cf. Fig. 4*). Experimentally, however, it is known that nucleophiles add to **2** at the C(4) position [6c].

We note that the above considerations concerning regioselectivity of nucleophilic addition are restricted to irreversible reactions. In [Cr(arene)$(CO)_3$] complexes, this is the case only if reactive carbanions are employed, low reaction temperatures are maintained, and a polar medium (THF/HMPA) is used [22]. Furthermore, we assume in our model that the geometry of the substrate is kept frozen during the approach of the reactant (*i.e.*, we do not attempt at calculating a reaction path), and it can be anticipated that the regioselectivity of processes involving substantial distortions of the partners may be difficult to rationalize. Indeed, previous results have shown that such reaction potentials, based on the undistorted fragment approximation, are appropriate in cases where regioselectivity is mostly dictated by initial product selection occurring well in advance of the transition state and mainly due to long-range favorable interactions [10] [23]. However, the E_{int} reactivity index provides generally a qualitative account of selectivity preferences for long-to-intermediate-range S−R distances.

Let us turn to the reactivity of the anionic cyclohexadienyl complex **3** towards electrophilic addition. This intermediate, which has not been crystallographically characterized, results from the nucleophilic addition of 1,3-dithiane to **1**. In a first step, a geometry optimization has been carried out for **3** using EHMO-ASED. A new set of κ, δ parameters has been derived from an '*exo*'-substituted [$Cr(CO)_3(\eta^5$-cyclohexadienyl)] anion [24], in order to take account of the interactions between C(7) and the dienyl. An eclipsed conformation of the tripod has been chosen, as suggested by X-ray structural investigations on related adducts [24–26]. *Fig. 5* presents some isoenergy surfaces of E_{int} calculated for electrophilic attack of **1**. It is seen that the surfaces corresponding to the lowest E_{int} values are clearly located around metal atom, in a region which extends from below Cr-atom to a *trans*-position with respect to C(7). This indicates that an incoming electrophile should bind to the metal atom. While this reaction has not yet been studied with the anionic complex **3**, recent investigations performed on adducts of similar anionic [$Cr(\eta^5$-cyclohexadienyl)L_2L'] (L = CO, PF_3; L' = CO, PF_3, $P(OMe)_3$) systems show that the electrophilic attack takes place indeed at the metal center [18] [27–29].

Conclusions. – The present results suggest that the EHMO-ASED method might be used in a first step as an approximate model builder for organometallics, its main limitation being due to the fact that it requires an adequate parametrization derived from test compounds with similar ligands. Indeed, when comparing the geometrical parameters of **1** with X-ray structural data, average error bars amount to 0.03–0.05 Å for bond distances and to 5° for bond angles. The structures so obtained can subsequently be used for an evaluation of the trends in the regioselectivity exhibited by these compounds towards nucleophilic and electrophilic attack, using the EHPROP formalism. In particular, we have shown that the regioselectivity of nucleophilic addition to compounds such as **1** and **2** can be reasonably described using the geometries predicted by EHMO-ASED and a local reactivity index generated from additional EH calculations. A similar conclusion may be drawn for the electrophilic attack on the adduct of **1** with 1,3-dithiane, which indicates that the model is able to reproduce the experimental trends as to reactive properties of these systems. However, a quantitatively accurate and reliable description of the reactivity of these compounds towards nucleophiles and electrophiles would undoubtedly require performing calculations of the corresponding minimum-energy reaction paths using more sophisticated quantum-chemical methods.

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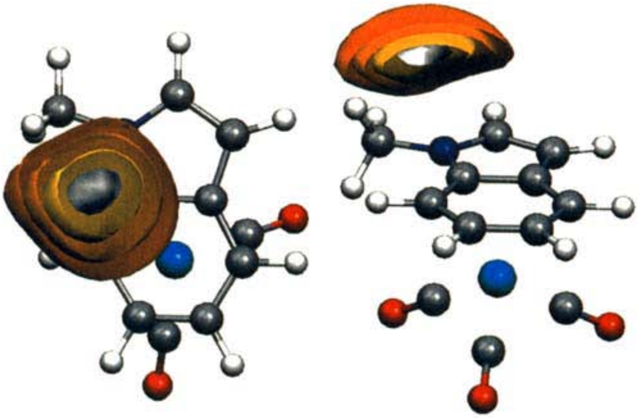

Fig. 3. *Top view* (left) *and front view* (right) *of the optimized structure of* $[\mathit{Cr(CO)_3}(\eta^6\text{-N-}\mathit{methylindole})]$ (**1**) *represented together with solid models of* E_{int} *isovalue surfaces calculated for nucleophilic attack* (at −23, −22, −21, −20 kcal/mol)

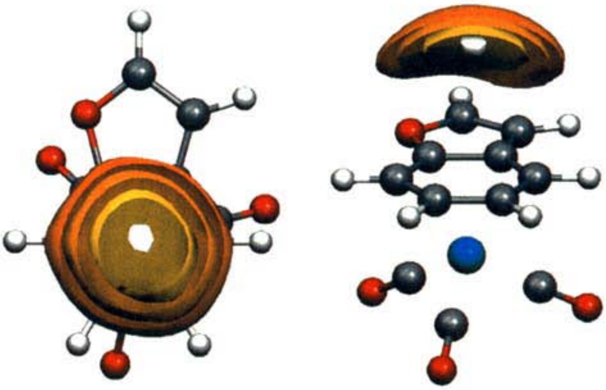

Fig. 4. *Top view* (left) *and front view* (right) *of the optimized structure of* $[\mathit{Cr}(\eta^3\text{-}\mathit{benzofuran})\text{-}(\mathit{CO})_3]$ (**2**) *represented together with solid models of* E_{int} *isovalue surfaces calculated for nucleophilic attack* (at −24, −23, −22, −21 kcal/mol)

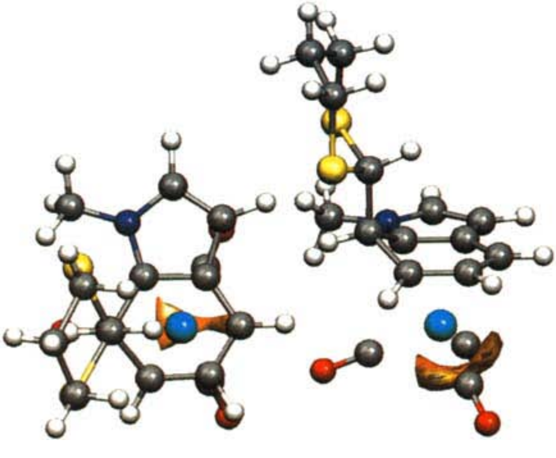

Fig. 5. *Top view* (left) *and front view* (right) *of the optimized structure of the adduct of* $[\mathit{Cr(CO)_3}\text{-}(\eta^6\text{-N-}\mathit{methylindole})]$ (**1**) *with 1,3-dithiane* (**3**), *represented together with solid models of* E_{int} *isovalue surfaces calculated for electrophilic attack* (at −275, −270, −265, −260 kcal/mol)

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