The availability of simple analytical formulae for expressing the intermolecular interaction energies and/or the intramolecular conformational energies is essential for a number of applications. A possible way for deriving and/or improving such formulae consists in using the quantum theory of intermolecular interactions, and more specifically its perturbation–theory version[1]. In this framework, the interaction energy between two molecules may be expressed as a series of terms: 1st order, electrostatic and exchange (short-range repulsion) terms; 2nd order, induction and dispersion terms (2nd order exchange and higher-order terms are usually neglected). Then each term is expressed through some simplified expression, the essential idea being to introduce a sum of local contributions, namely elementary interactions between sites (atoms and/or bonds), expressed in terms of suitable molecular properties[2,3]. Thus, the electrostatic term is obtained as a sum of interactions between molecular charge distributions represented by sets of multipoles (charges, dipoles, quadrupoles) located at the atoms and the middles of the bonds. The (long-range) induction terms are obtained from the electric fields created by these same multipoles and from bond and/or atom polarizabilities. The (long-range) dispersion term is expressed as a sum of atom–atom terms $-(C_6/R^6 + C_8/R^8 + C_{10}/R^{10})$ and the short-range repulsion term as a sum of atom–atom or bond–bond terms (with exponential dependence with respect to interatomic distances). Recently an explicit charge-transfer term (corresponding to the short-range behaviour of the induction energy) has been introduced: it involves atom–atom terms with *nonisotropic* behaviour, i.e. with a dependence upon the orientation of the bonds pertaining to the atoms under consideration. The elaboration of simplified formulae (such as those used in molecular mechanics) from basic quantum theory, for the intramolecular (conformational) energy, and more precisely its dependence upon the torsional angles (with bond lengths and valence angles kept fixed) is much less advanced that it is for intermolecular interactions. It is tempting to use formulae of the intermolecular type for evaluating intramolecular interaction terms between nonbonded atoms, and we did so in our recently proposed procedure SIBFA (Sum of Interactions Between Fragments computed *ab initio*)[4]. Noticeably, the evaluation of the short-range repulsion is refined by introducing, besides the genuine chemical bonds, fictitious bonds associated with the lone-pairs. The results obtained so far are encouraging.

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Computer graphics applications of electron deformation densities and electrostatic potentials in coordination chemistry

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Computer programs have been developed in order to display on a raster scan device electron deformation densities (EDD) and electrostatic potentials (EP), both as 2D colour-filled contour maps and as coloured 3D solid models. In the latter case, we represent isovalue surfaces obtained from a triangulation algorithm based on the connection of contours lying in successive planes are given. The combined use of these molecular properties calculated by the multiple scattering Xα quantum chemical model and such graphics is expected to be of value in rationalizing and interpreting the reactivity of coordination and organometallic compounds. Indeed, several important reaction mechanisms of inorganic chemistry, such as ligand substitution or rearrangement, proceed generally by nucleophilic (or electrophilic) attack and may therefore be described in first approximation by simple arguments based on the EDD or EP of model compounds. As an example the case of $[Cr(O_2)_4]^{3-}$, $[Mo(O_2)_4]^{2-}$ and $[Nb(O_2)_4]^{3-}$ complexes are discussed in an attempt to understand the differences in metal–ligand bonding and chemical behaviour exhibited by parent metal dioxygen complexes. Investigations by the authors, which reveal that the main features of EDD and EP maps are strongly correlated, provide a simple interpretation of the unique catalytic properties of Mo(VI) dioxygen complexes for the epoxidation of alkenes.

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A new approach of drug design based on the determination of a minimum set of common parameters in terms of molecular surface electrostatic potentials for compounds with the same therapeutic activities: case of neuroactive agents

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It has been shown[1,2] that molecular electrostatic potentials can be considered as a reactivity index in terms of quantum mechanics. The main idea is that the recognition step can be described in a fixed nuclei modelization and is essentially determined by two factors: the molecular surfaces and the molecular electrostatic potentials on these surfaces. These entities must form complementary pairs, if their interaction is to lead to the formation of a stable or a metastable complex. The structures of the drug receptors are rarely known, while lots of molecules with the same therapeutic activity are perfectly defined. This common activity indicates that these drugs probably act on the same biological receptors; from the concept previously defined, these molecules must present some identical parameters characteristic of the molecular electrostatic potential. The determination[4] and the analysis of such parameters on tricyclic neuroleptic and antidepressant drugs (41

molecules or molecular conformations were treated) allowed for the first time the *a priori* differentiation of their therapeutic properties and led to the classification of psychotomic or sedative agents in the family of antidepressants. It is now possible from existing diagrams to predict the activity of new tricyclic compounds. The molecular electrostatic potential is computed using a monopole approximation[3] on the Van der Waals surface.

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Karma: a knowledge-based system for receptor mapping

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A combination of molecular modelling and quantitative structure–activity relationships (QSAR) is a powerful tool in the design of ligands and inhibitors, and provides a means to better understand ligand–receptor interactions[1,2]. This approach is most successful where the 3D structure of the receptor site is known. Karma (Kee assisted receptor mapping analysis) is an interactive computer-assisted rule-based drug design tool that utilizes real-time interactive 3D colour computer graphics (Silicon Graphics IRIS 2400T) with numerical computations (DEC VAX 8600) and symbolic manipulation techniques (Symbolics 3600 Lisp Machine) using the expert system software tool Kee (Knowledge engineering environment). Karma incorporates Qsar, conformational analysis (distance geometry and energy minimization), and graphics to generate a theoretical receptor site surface model[3]. Three-dimensional structures are input for the conformational analysis programs. Selected structures or distance matrices contain the geometric relations of the input structures and are used to generate the preliminary receptor surface model. An outline of the surface is obtained by the intersection of spheres, while details of the surface are generated using bicubic patches with the outline as the basis set. Bicubic patches form a continuous surface which may be reshaped interactively and have local density variations. The multiple visual cues of colour, texture and intensity represent simultaneously a number of receptor properties such as shape (i.e., cleft or hole), volume, hydrophilicity and hydrophobicity, and effectively summarize large amounts of numerical data. The deductions made by the KEE inference engine are based on Qsar equations, physicochemical parameters, kinetic data, and structural chemistry. Upon completion of the deduction phase, the characterized receptor model is displayed. The user may then manipulate and modify the model to test hypotheses and generate new rules. Modified models may be resubmitted to the inference engine to make additional deductions and detect inconsistencies. An integral part of Karma is user interation. By combining Karma's knowledge base with the knowledge and insight of the expert user, a more refined model may be built than permitted by either the user's or Karma's knowledge alone.

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Structural aspects of antigen–antibody recognition

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The antigenicity of a protein resides in discrete areas or epitopes of the molecule's surface that are specifically recognized by the binding sites or paratopes of antibody molecules. Although it is commonly assumed that paratopes always take the form of a pocket, there is evidence that shapes complementary between epitopes and paratopes can also take other forms. Exposed or protruding regions at the protein surface often correspond to antigenic sites which may consist of a series of overlapping epitopes that are distinguishable with appropriate monoclonal antibodies. Linear peptide fragments of a protein that binds to antibodies raised against the whole molecule are usually considered to represent continuous epitopes. However, it is possible that such peptides are antigenically active because they contain a short stretch of residues corresponding to a subregion of a larger discontinuous epitope. Discontinuous epitopes are made up of residues distant from each other in the sequence but brought together by the folding of the chain, and they may be more numerous in globular proteins than continuous epitopes. The following approaches have been used to delineate epitopes: 1) cross-reactivity studies between protein fragments and antibodies to the native protein; 2) cross-reactivity studies between native protein and antipeptide antibodies; 3) cross-reactivity studies among homologous proteins; 4) crystallographic study of antigen–antibody complexes. The approximate location of a limited number of epitopes has been established for only a dozen proteins of known tertiary structure. Attempts to correlate certain structural features of proteins with their antigenicity have been concerned mainly with continuous epitopes. Parameters that have