A Quantum Chemical Study of "Light-Dependent Herbicides"

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Z. Naturforsch. **48c,** 345–349 (1993); received November 5, 1992

Light-Dependent Herbicides, Protoporphyrinogen Oxidase, Chlorophyll Biosynthesis, Computational Chemistry, Common Structural Feature

Common structural features were investigated for "light-dependent herbicides" (LDHs, also called peroxidizing or photobleaching herbicides). Quantum chemical calculations of 143 herbicidal compounds revealed that LUMO levels of LDHs were similar and strikingly low. Using the LUMO position as an anchor, presumably known structure-activity relationships could be explained. Overall molecular similarity between oxyfluorfen and chlorophthalim was examined by molecular field fitting. The result supported LUMO position correspondence.

Introduction

Several structural types of herbicides such as diphenyl ethers, cyclic imides and pyrazole compounds are effective only in the light but they do not inhibit the photosynthetic system directly. Such types of herbicides have been classified as "light-dependent herbicides (LDHs)" (Fig. 1). These herbicides are also called peroxidizing or photobleaching herbicides. Recently, the target site of LDHs has become clear. The LDHs inhibit protoporphyrinogen oxidase (protox), which is a key enzyme in the chlorophyll biosynthesis pathway. As a result, the intermediate protoporphyrin IX accumulates in plant cells, which is harmful in the light [1]. Structurally diverse LDHs bind to protox in a competitive manner [2]. Therefore LDHs may share a certain common structural feature, which is responsible for the common mode of action. Although any direct measurement for drug-receptor interaction such as X-ray crystallographic analysis is not yet available, the techniques of computational chemistry will be helpful to understand the commonality of structurally diverse compounds [3]. In this study we investigated common structural feature of LDHs by the use of computational chemistry.

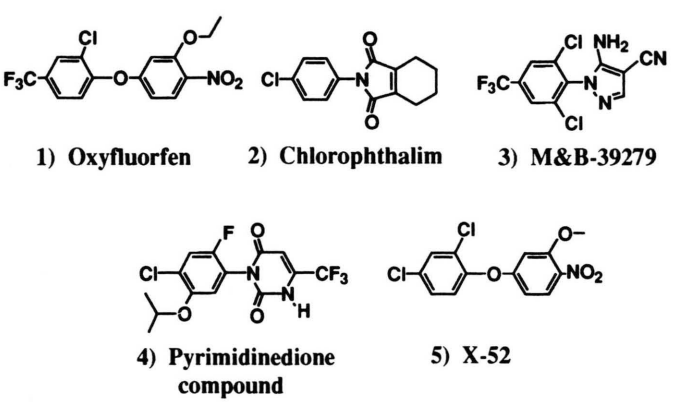

Fig. 1. Chemical structures of "light-dependent herbicides": (**1**) oxyfluorfen, (**2**) chlorophthalim, (**3**) M&B-39279, (**4**) a pyrimidinedione compound, and (**5**) X-52 (chlormethoxynil).

Methods

Three-dimensional structures of herbicides

Chemical structures of 143 herbicidal compounds whose mode of actions were known were taken from several references. These structures

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0939–5075/93/0300–0345 $ 01.30/0

were drawn on a graphical display and initial three-dimensional structures were generated by the algorithm of distance geometry [4]. All of these operations were done by our self-made molecular modelling system (Psyche-3D). The initial three-dimensional structures were then optimized by semiempirical molecular orbital calculation AM1 [5]. All internal coordinates of molecules were optimized during energy minimizations. Program package MOPAC ver. 6 (QCPE # 455) was used in this operation.

Molecular properties

The levels of frontier orbitals (HOMO and LUMO) were calculated by AM1. Hydrophobicities (log P) of compounds were estimated using atomic parameters [6].

Molecular superposition

The similarity between molecular fields of two molecules was estimated using the following equation:

$$\mathbf{Sab} = \sum_{P} \int dv \; E(a, P, x, y, z) \times E(b, P, x, y, z)$$

In above equation, E(a, P, x, y, z) means the interaction energy between a molecular "a" in a certain place and a probe atom "P" at a coordinate (x, y, z). E(a, P, x, y, z) is called the molecular field of "a" and is calculated by Tripos force field [7]. The integration was made for the space outside of the van der Waals surfaces of molecules. Since non-bonding interaction decays quickly when the probing point depart from van der Waals surface, integration within 3 Å from the surfaces is enough to account for molecular field similarity (Fig. 2). The summation for P was taken for positively charged hydrogen ($H^{+0.15}$) and negatively charged oxygen ($O^{-0.3}$). This summation may account for both of hydrogen accepting and donating field of the molecules. If "a" and "b" attract P at the same (x, y, z), both of E(a, P, x, y, z) and E(b, P, x, y, z) become negative and their product becomes positive. Inversely, if "a" and "b" repulse P, both molecular fields become positive and their product becomes positive too. Therefore the more similar the molecular fields are, the larger **Sab** becomes. The best fitting of molecules was achieved by translating and rotating molecule "a" relative to "b" to maximize **Sab.**

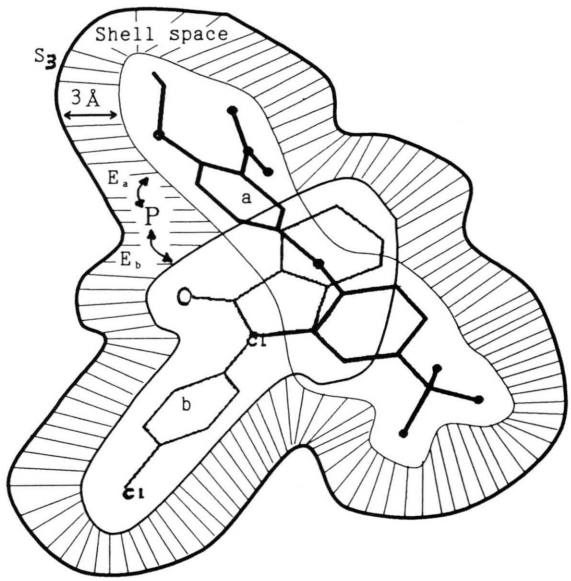


Fig. 2. Method to calculate the molecular field and its similarity. S3: the surface which is 3 Å away from van der Waals surfaces; Ea: molecular field of molecule "a" (thick lines, oxyfluorfen) estimated by a probe atom P; Eb: defined similarly as Ea, molecule "b" is chlorophthalim, thin lines. Integration of Eqn. (1) was made over the hatched space indicated.

Results and Discussion

To compare molecular properties in several different types of herbicides, HOMO and LUMO levels as well as hydrophobicities were calculated for 143 herbicidal compounds, which contain 32 LDHs, 18 acetolactate synthase (ALS) inhibitors, 54 photosynthetic system II inhibitors, 10 fatty acid synthesis inhibitors, 4 gibberellin synthesis inhibitors, 18 auxin agonists, 5 auxin antagonists and 2 cytokinin agonists. The chemical structures of the above compounds, reported in several references, were stored in our self-made data base. Average and standard deviation of HOMO, LUMO and log P values for each group of herbicides are summarized in Table I. Both HOMO and LUMO of ALS inhibitors are very low. But many of ALS inhibitors have acidic protons which dissociate at physiological pH and these compounds exist as anionic forms in biological systems. Therefore such low HOMO and LUMO can not play an important role in drug action. Besides of that, LUMO levels of LDHs are strikingly low. Since differences in average LUMO

Table I. Molecular properties of herbicides. Levels of the frontier orbitals were calculated by the AM 1 method. Hydrophobicities were estimated using atomic parameters [6].

Compounds	*n*	HOMO/ev	LUMO/ev	log P
Acetolactate synthase	18	−10.11 ± 0.22	−1.99 ± 0.28	1.18 ± 1.25
Photosystem II	54	−9.23 ± 0.12	−0.16 ± 0.34	2.06 ± 1.18
Fatty acid synthesis	10	−9.28 ± 0.04	−0.42 ± 0.08	4.21 ± 0.21
Light-dependent	32	−9.56 ± 0.28	−1.15 ± 0.32	3.83 ± 0.96
Gibberellin synthesis	4	−9.57 ± 0.01	−0.35 ± 0.06	3.85 ± 0.35
Auxin	18	−9.07 ± 0.26	−0.34 ± 0.19	2.40 ± 0.53
Anti-auxin	5	−9.73 ± 0.05	−0.54 ± 0.08	3.35 ± 1.17
Cytokinin	2	−8.87 ± 0.20	−0.34 ± 0.07	1.83 ± 0.06

level between LDHs and other groups are by far larger than the standard deviation within each group, this feature is statistically significant. On the other hand, there are no differences in HOMO level and log P of LDHs from other herbicides. Therefore we can guess that LUMO participates in drug action of LDHs.

Shapes and locations of LUMO of 4 representative LDHs are shown in Fig. 3. It is evident that the LUMO of oxyfluorfen (# 1) is not located at the phenyl ring substituted with a nitro group, but on the other ring. The LUMO of chlorophthalim (# 2) is located at the cyclic imide moiety. If we match the LUMO containing rings (L-rings), presumably known structure-activity relationships can be explained. Non-planar substituents such as CF_3 and $-CH_2CH_2CH_2CH_2-$ often exist at *para*-like positions of L-rings. Functional groups which contain a lone electron pair such as chlorine and carbonyl oxygen often appear at *ortho*-like position of L-ring. The pyrimidinedione compound # 4 can be assumed as a hybrid of a diphenyl ether type and cyclic imide type, because its L-ring looks like that of oxyfluorfen and the other ring looks like that of chlorophthalim. This compound suggests that the chlorine at *ortho* position of the L-ring in diphenyl ethers correspond to carbonyl oxygens of cyclic imides. The large substituents never appear at *meta* positions of the L-ring without losing its activity. On the other hand somewhat larger groups can be introduced at *meta* position of the other ring. Moreover there are some bioisosterisms in this position (Fig. 4). There are diphenyl ethers and cyclic imides which have

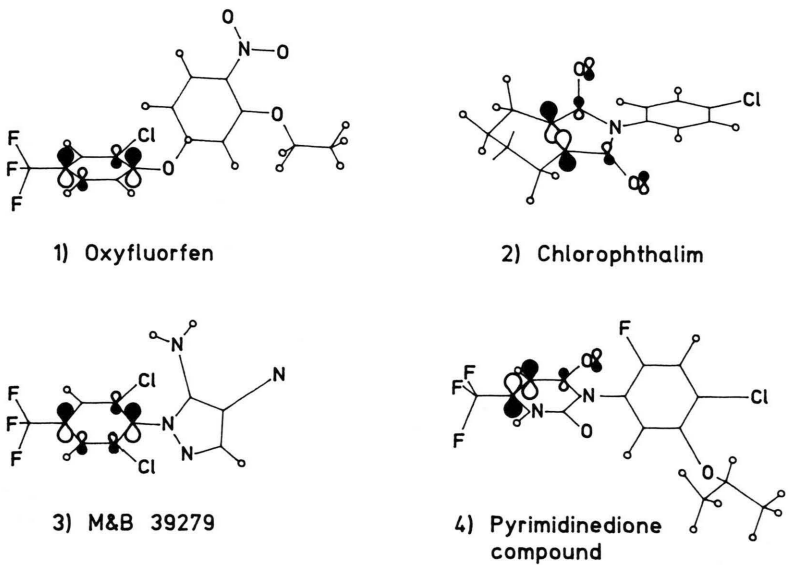


Fig. 3. Graphical representation of LUMOs of 4 herbicides: (**1**) oxyfluorfen (−1.262 eV), (**2**) chlorophthalim (−1.226 eV), (**3**) M&B-39279 (−1.467 eV), and (**4**) a pyrimidinedione compound (−1.305 eV). Oxygen is indicated by a capital O. The tiny open circles at the formulas represent hydrogen atoms (−o). Sizes of the lobes of the π-orbitals (open, positive; closed, negative) are approximately proportional to the atomic coefficients of the LUMO orbital.

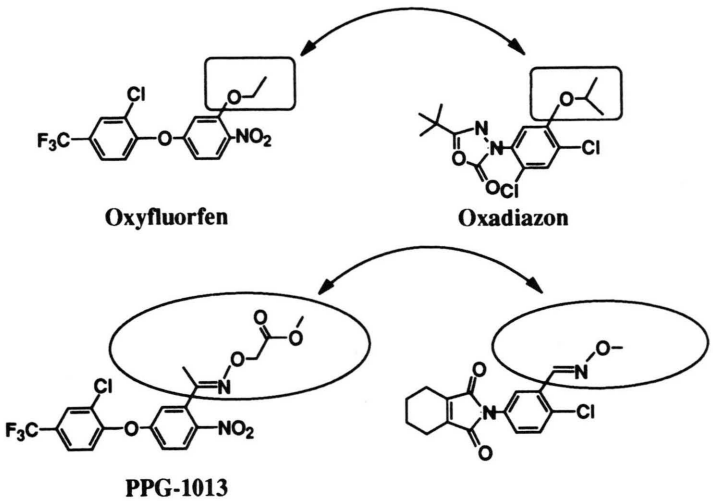


Fig. 4. Bioisosterism for the *meta* position.

alkoxy or oxime group at this position. In contrast to chlorophthalim, the LUMO of the pyrazole compound # 3 is not located at the nitrogen-containing ring but at the phenyl ring. Therefore it is plausible that substitution at *meta* position with a large group had never resulted in active compounds. These explanations can be applied only if the L-rings correspond to each other.

Overall molecular similarity was investigated by molecular field fitting. In this technique, nonbonding interaction between a molecule and a probe atom located at a certain place is calculated theoretically. Scanning the position of the probe atom, a "molecular field" of that molecule is obtained, which virtually represents a negative image of the molecule. Similarity between two molecular fields is estimated by the similarity index **Sab** as published by Carbo [8]. By means of maximizing **Sab,** the best fitting in terms of molecular field is achieved. Oxyfluorfen and chlorophthalim were superimposed in several orientations. Then **Sab** was maximized. The best fitting is shown in Fig. 5. This result supported the hypothesis given above. LUMOs of both compounds occupied almost same place (LUMO) and so did the *meta* position of the other ring.

The role of LUMO in drug action is not clear yet. Generally, LUMO can participate in red-ox reactions, charge-transfer interaction or electrostatic interaction with the receptor. Of these possibilities, the first can be discarded because LDHs

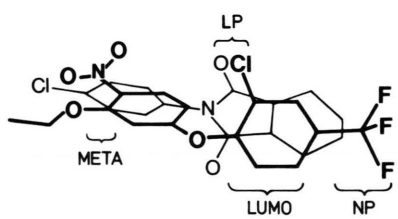
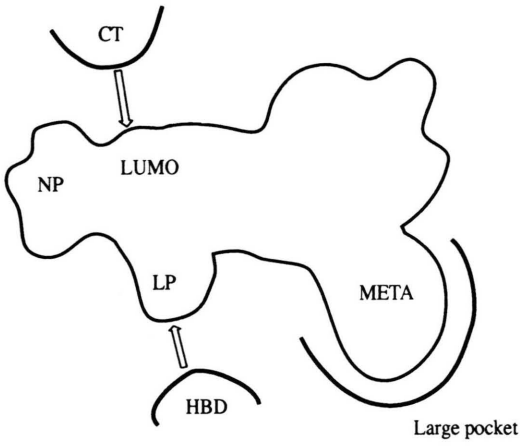


Fig. 5. Result of molecular field fitting for oxyfluorfen (formula drawn with a thick line) and chlorophthalim (thin line). LUMO: the region where LUMOs exist in both cases for oxyfluorfen and chlorophthalim; LP: the functional groups which contain lone pairs; NP: nonplanar moieties; META: the *meta* position on the other ring. At this position the bioisosterism as indicated in Fig. 4 can be found.

inhibit protox in a competitive manner and will bind to protox weakly. Therefore the second and third type of interaction is feasible. Theoretical studies on molecular interactions proved that charge transfer and electrostatic interactions often work simultaneously [9]. Accordingly, we can suggest that mixed charge transfer and electrostatic interactions act in drug receptor binding. Anyway, since protox is a red-ox enzyme, it is likely that this enzyme has electrically polar functional groups near the reaction site and that LDHs bind to them by electrical force.

The present work suggests that LUMO and several sterical features are common in LDHs. Overall molecular field was similar when these features



corresponded. These features may be responsible for the identical drug action of protox inhibition (Fig. 6).

Fig. 6. "Receptor" mapping of protoporphyrinogen oxidase: CT, charge transfer or some other electronic interactions to LUMO; HBD, hydrogen donation to LP; LP, the functional groups which contain lone pairs (see also Fig. 5).

[1] M. Matringe, J. M. Camadro, P. Labbe, and R. Scalla, Biochem. J. **260,** 231 (1989); J. M. Camadro, M. Matringe, R. Scalla, and P. Labbe, Biochem. J. **277,** 17 (1991).
[2] R. Varsano, M. Matringe, N. Magnin, R. Mornet, and R. Scalla, FEBS Lett. **272,** 106 (1990).
[3] L. Barino, Computer & Chemistry **5,** 85 (1981); Y. Takahashi, T. Akagi, and S. Sasaki, Tetrahedron Comput. Method. **3,** 27 (1990); R. P. Sheridan, R. Nilakantan, J. S. Dixon, and R. Venkataraghavan, J. Med. Chem. **29,** 899 (1986).
[4] G. M. Crippen, in: Distance Geometry and Conformational Calculations (D. Bawden, ed.), Chemometrics Research Studies Series, **Vol. 1,** Research Studies Press (Wiley), New York 1981.
[5] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. Stewart, J. Am. Chem. Soc. **107,** 3902 (1985).
[6] V. N. Viswanadhan, A. P. Ghose, G. R. Revankar, and R. K. Robins, J. Chem. Inf. Sci. **29,** 163 (1989).
[7] M. Clark, R. D. Cramer III, and N. V. Opdenbosch, J. Comput. Chem. **10,** 982 (1989).
[8] R. Carbo, L. Leyda, and M. Arnau, Int. J. Quant. Chem. **17,** 1185 (1980).
[9] H. Umeyama and K. Morokuma, J. Am. Soc. Chem. **98,** 7208 (1976); H. Umeyama, S. Yamabe, and K. Morokuma, J. Am. Soc. Chem. **99,** 330 (1977).