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Quantum mechanical and QSAR study of some α-arylpropionic acids as anti-inflammatory agents

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Abstract – The optimal structures of a series of α-arylpropionic acids with anti-inflammatory activity are established by using the semi-empirical quantum mechanical procedures, AM1 and AMSOL, in the gas phase and in water solution, respectively. In these calculations, the arylpropionic acids are considered in their neutral and ionized forms. As expected, these compounds exhibit two preferred conformations in which the α-hydrogen atoms of the propionic acid group lies approximately in the plane of the central aryl ring. The deprotonation energies are then determined as the difference between the formation energies of the protonated and deprotonated forms. A Quantitative Structure Activity Relationship (QSAR) study reveals that only the gas phase results compare to some extent favorably with the anti-inflammatory activity. As expected, the smaller the deprotonation energy, the larger the anti-inflammatory activity. Satisfactory relationships between the in vivo activities and deprotonation energies, the HOMO energies and lipophilicities were found. © Elsevier, Paris

QSAR / anti-inflammatory agents / quantum-pharmacology / α-arylpropionic acids

1. Introduction

The substituted α-arylpropionic acids constitute a large family of nonsteroidal anti-inflammatory agents. Different chemical structures have been found to possess different anti-inflammatory activities. In view of the complexity and multitude of biochemical factors involved in inflammatory events, few general correlations of chemical structures and physicochemical properties with biological activities would be expected. Nevertheless, some general features seem to be commonly associated with a large number of active drugs. However, these main features are not sufficient, but they could reflect certain physicochemical requirements for in vivo efficacy [1].

The main structural feature of these compounds may be considered in terms of three basic units: (i) the propionic acid side chain, (ii) the central aryl moiety, and (iii) a hydrophobic terminal residue. The propionic acid side chain has an asymmetric carbon atom, C*, and the anti-inflammatory activity is usually associated with the (*S*)-(+)-isomer [2, 3]. The central aryl moiety is generally an electronegatively substituted phenyl ring, and the hydrophobic residue may be a flexible aliphatic group, a cyclic side chain, or even a rigid condensed cycle. These drugs are poorly soluble in aqueous media and are generally well absorbed and often strongly bound to serum protein [4]. For these drugs there are two or even more affinity hydrophobic binding sites per molecule of serum albumin.

Several anti-inflammatory receptor site models have been proposed. They consist in two non-coplanar hydrophobic regions and a cationic center [5, 6]. Gund et al. suggested a model with different binding sites to prostaglandin synthetase (PG) for several arylpropionic acids, indomethacin and other analogues with anti-inflammatory activity. These binding sites are: (i) a coulombic or hydrogen bonding to the carboxy group; (ii) a hydrophobic binding to the aromatic ring; (iii) an electron-accepting group (binding to the indole nitrogen in indomethacin); and (iv) a hydrophobic groove to bind to another aromatic group [6]. Several quantitative structure–activity relationship (QSAR) studies have been reported, obtaining only partial results [7–10]. Quantum-chemical descriptors have been used frequently, especially in the last years, in QSAR studies, because of the large well-defined physical information content encoded in many theoretical descriptors [11].

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The substituted α-phenylpropionic acids have been studied theoretically and experimentally by us in previous papers [12–14]. In the first paper, the influence of the conformation of the propionic moiety on the activity is analyzed. A comparison between ibuprofen [2-*p*-isobutylphenylpropionic acid], α-methyl-ibuprofen [2-methyl-2-(*p*-isobutylphenyl)propionic acid] and a rigid analogue [5-isopropyl-1-indancarboxylic acid], shows that the conformation, in which the α-hydrogen atom lies in the plane of the phenyl ring, is the most active. In the second and third papers, the deprotonation energy in the gas phase of a series of α-arylpropionic acids is determined theoretically by using the CNDO/2 [13] and AM1 [14] approximations, and correlated with the anti-inflammatory activity. Both methods indicate roughly that the smaller the protonation energy, the larger the anti-inflammatory activity.

In the present paper, a similar but larger series of α-arylpropionic acids is considered in the gas phase and water solution. In the first calculations a more accurate version of the AM1 approach was used [15]. For the second calculations in water solution, the AMSOL approach was employed [16]. The compounds under study in [14] were: ibuprofen **1**, fenoprofen **2**, benoxaprofen **3**, naproxen **4**, suprofen **5**, ketoprofen **6**, pranoprofen **7**, carprofen **8**, and flurbiprofen **9**. To this series, pirprofen **10**, indoprofen **11** and MK-830 **12** were added (*figures 1* and *2*). This

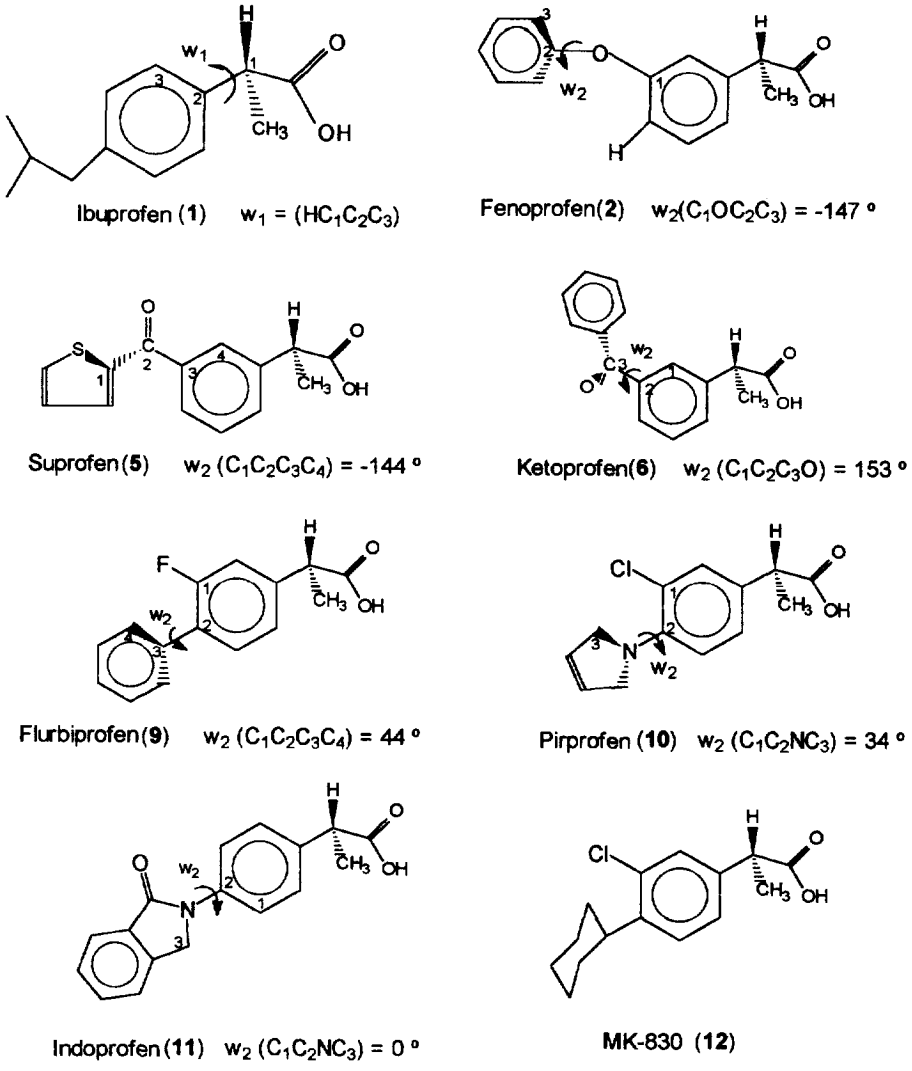

Figure 1. Structure of arylpropionic acids with anti-inflammatory activity.

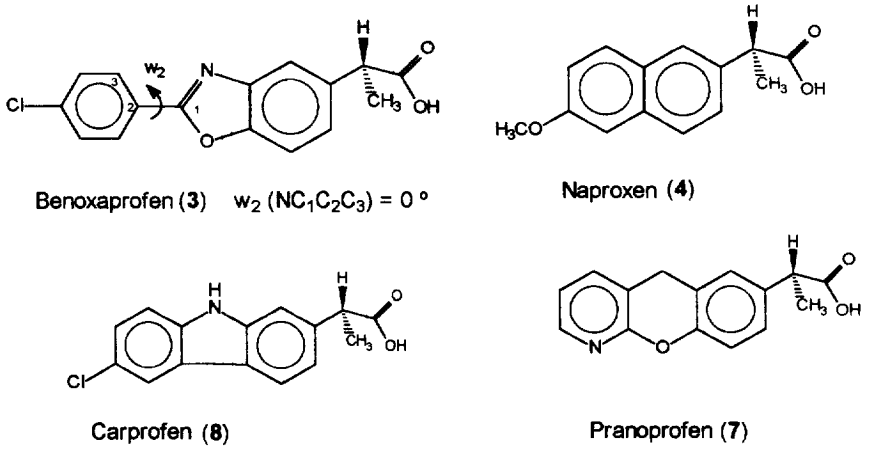

Figure 2. Structure of condensed arylpropionic acids with anti-inflammatory activity.

series of drugs was chosen in order to consider a wide range of molecular structures of aryl-propionic acids with different anti-inflammatory activities in such a way as to obtain more general results that can be extrapolated to other arylpropionic drugs.

The preferred conformations of all these compounds were determined by full optimization of geometry into the AM1 and AMSOL approximations in the gas phase and water solution, respectively. The deprotonation energy values were calculated, and correlated with the anti-inflammatory activities.

The most widely used technique for studying the in vivo activity of these non-steroidal anti-inflammatory agents is the carrageenin-induced paw edema in rats. This technique consists of measuring the ability to inhibit edema produced in the hind paw of the rat by injection of carrageenin, a phlogistic agent [1]. According to this technique, the relative activity with respect to indomethacin, will be taken into account for the study of our series [1, 17].

2. Theoretical methods

The quantum mechanical semi-empirical approach (AM1 Hamiltonian; MOPAC, version 6.1) is a modern version of the MNDO model [18], especially written to reproduce correctly hydrogen bonds [15]. The AM1 approach appears to generate reasonable three-dimensional molecular structures of relatively large organic molecules in the gas phase [20]. Usually, it furnishes better results than the PM3-MNDO when nitrogen atoms are present in the structure [19]. This procedure was used to establish the structures and preferred conformations of the chiral alkyl-carboxy side moiety of the acids and their negative ions. Crystallographic [21–23] and standard coordinates were used as initial geometry of these compounds [24, 25]. The conformations of the alkyl-carboxy moiety were defined by the torsional angle θ_1 (H–C*–C=C(Ar)) corresponding to the hydrogen directly bound to the asymmetric carbon (*figure 1*).

Special attention was paid to the geometry optimization procedure up to reach gradient values lower than 0.01 kcal/mol (standard deviations in energies of 10^{-6} kcal/mol). With this aim, the *precise* and **EF** (eigenvectors following) options of the 6.0 version of the MOPAC package were used [15]. The standard option (D_{max} = 0.05) for geometry increments was used. The charge distributions, dipole moments, ionization potential, electro-affinity, and the HOMO and LUMO frontier orbital energies of the optimized structures were obtained in the same calculations.

In addition, the nature of the extrema reached was analyzed by means of the *force* option in order to verify whether these extrema were actual minima or transition states. In the same calculations the zero point vibration energies are obtained.

The formation energies of the two species, protonated and deprotonated, were determined with full optimization of the geometries, and the zero point vibration energies added. The energy difference between the two species will furnish the deprotonation energy, taking into account that the proton formation energy a from neutral hydrogen molecule possesses a value of 315.017 kcal/mol in the gas phase, i.e. calculated using the AM1 Hamiltonian of the MOPAC package.

From the AM1 geometry obtained in the gas phase, the structure in water solution was determined by using the AMSOL-SM2 program [16] (AMPAC package; version 5.0). The AMSOL program essentially uses the AM1 Hamiltonian operator, but considering the molecule docked into a cavity embedded in a water continuum. The options *precise* and **EF** were also used, the standard geometry increment was decreased five times, but only gradient values lower than 1.0 kcal/mol could be obtained. Even then, some molecules presented convergence difficulties in the SCF or geometry optimization procedures. In particular, no reasonable results were obtained for pranoprofen. The deprotonation energy was calculated in the same way, taking into account that the proton formation energy takes a value of 61.994 kcal/mol in solution in the AM1 scheme with the AMSOL approach.

The physico-chemical molecular descriptors used for the QSAR studies, such as dipole moments, HOMO and LUMO energies, and atomic net charges were obtained in the same quantum mechanical calculations. On the other hand, the log*P*, Π and σ empirical parameters for the different substituents of the aryl ring, which support the propionic moiety, were taken from the literature [26, 27]. Taking into account that the aryl-propionic moiety is common in all the members of the series, the relative σ parameter values were evaluated by addition of the σ_m and σ_p contributions of the substituents in *meta* and *para* position with respect to the propionic group [28]. The Π parameter values were calculated in the same way by addition of the Π contributions of the substituents.

The multiple regression analysis was performed by the backward and forward stepwise method. Statistical significances of the regression equations were tested on the basis of the standard deviations (s), the correlation coefficients (r), the square determination coefficients (R^2) and the Fischer–Snedecor criteria (F). For the individual parameters the Student t-test was used. In order to obtain a better significance criterium of the regression, we have used the square regression coefficients adjusted to the freedom degrees (R_{adj}^2) in some of the regressions, and an additional Durbin–Watson statistical test, and an ANOVA analysis. In all cases, the ANOVA analysis gave a value of p less than 0.05, showing that the relationship between the variables chosen in each case is statistically significant at the 95% confidence level, except for the last regression, where the confidence level was 99%. Besides, the Durbin–Watson statistical test showed that there was no serious autocorrelation in the residuals in all cases.

3. Results and discussion

As expected, two preferred conformations, with respect to the torsional angle θ_1, of similar energy values were encountered for the protonated and deprotonated forms in the gas phase. All the eigenvalues of the Hessian matrices of geometry optimization calculations were found to be positive. This result confirms that two actual minima were reached.

In *table I*, the optimal conformational angles θ_1 and energy values of the protonated (neutral) and deprotonated (ionized) forms of the above-mentioned series of α-arylpropionic acids are given. All structures protonated yielded similar torsional angles θ_1 (nearly 6° or −174°) in which the α-hydrogen atom lies nearly in the aromatic plane. Analogous features occur in the deprotonated compounds which exhibit similar, although larger torsional angles θ_1 (about 14° or −166°), except for fenoprofen. In *table I*, the energy differences between the two species are gathered for each conformation. On the other hand, the central aryl ring and the lipophilic substituents are seen to be generally non-coplanar, except for the compounds **3**, **4**, **7**, **8** and **11** (see the w_2 angle values in *figures 1* and *2*).

Two preferred conformations were also encountered for the protonated and deprotonated forms in water solution. Since the nature of the extrema in water solution could be expected to be the same as in the gas phase this was not verified in a force calculation.

In *table II*, the optimal conformational and energy values of the protonated and deprotonated forms of the same series are given in water solution. These compounds possess similar conformations as in the gas phase. In particular, both forms, protonated and deprotonated, present a torsional angle for the α-hydrogen atom still closer to the aromatic plane, even for fenoprofen. In the same table, the energy differences between the two species are also given.

Since the two conformations possess similar energies, mean arithmetic values for the energies will be considered. Deprotonation energies in the gas phase are then calculated at two different stages. In a first step, as the energy differences between the protonated and deprotonated forms gathered in *table I*, minus the proton energy formation value calculated in the AM1 approach with the MOPAC package. In a second step, the zero point vibration energies found in force calculations were added to the above values. At first sight, negative values for the deprotonation energy were expected in order to be feasible. The positive values found at the two stages of approximation do not seem to be too realistic. But, it is the matter for relative values, that could considerably be lower and even negative in the protein environment, as found in water solution.

The protonation energies in water solution are calculated in the same way by substracting the proton formation energy calculated in the AM1 approach with the AMSOL package. No zero point vibration

Table I. Energy values (in kcal/mol) of the protonated and deprotonated forms of some arylpropionic anti-inflammatory agents in two different conformations of the propionic moiety (torsional angle θ_1 in degrees), calculated by AM1 in the gas phase.

Molecule	Protonated form		Deprotonated form		Energy difference
	θ_1	Energy	θ_1	Energy	
Ibuprofen **1**	6.19	−102.6702	14.17	−121.5630	−18.8928
	−174.82	−102.6811	−166.29	−121.6021	−18.9210
Fenoprofen **2**	6.61	−76.1542	−63.89	−97.3517	21.1975
	−172.79	−76.3169	129.00	−98.1700	−21.8531
Benoxaprofen **3**	4.89	−47.9033	13.98	−71.4229	−23.5196
	−175.53	−47.7712	−168.62	−70.2677	−22.4965
Suprofen **5**	5.58	−74.4450	13.69	−96.6815	−22.2366
	−173.84	−74.7577	−165.49	−96.8070	−22.0494
Naproxen **4**	5.51	−97.6890	15.65	−117.9060	−20.2170
	−170.83	−98.3576	−167.04	−118.5032	−20.1456
Carprofen **8**	4.60	−38.9376	12.08	−61.1677	−22.2300
	−174.54	−39.0981	−167.29	−62.3790	−23.2808
Pirprofen **10**	3.62	−43.0618	14.79	−66.0623	−22.9615
	−174.79	−43.1007	−169.26	−65.1286	−22.1117
Ketoprofen **6**	4.70	−79.3888	−0.04	−103.9643	−24.5754
	−172.48	−79.5778	−160.78	−101.4138	−21.8360
Indoprofen **11**	4.10	−60.5943	10.42	−79.2140	−18.6197
	−174.68	−60.6263	−165.02	−80.1690	−19.5428
Pranoprofen **7**	4.99	−66.1608	15.64	−88.9609	−22.8001
	−175.99	−66.1564	−167.29	−88.3577	−22.2013
Flurbiprofen **9**	5.87	−95.1723	13.42	−118.3536	−23.1813
	−174.36	−95.1690	−168.70	−117.7940	−22.6250
MK 830 **12**	5.66	−111.5489	4.90	−133.2856	−21.7367
	−176.13	−111.5444	−168.26	−132.5562	−21.0117

energy was added. Negative realistic values are encountered.

These results are gathered in columns one, two, and three of *table III*, together with the logarithm of the anti-inflammatory activities [30]. The two stages of approximation in the gas phase yield comparable values. In *figure 3*, the protonation energies with the correction for the vibrational zero point are plotted versus the pharmacological activities. In general, the smaller the deprotonation energy, the larger the anti-inflammatory activity. Some compounds, however, such as benoxaprofen **3**, indoprofen **11** and MK-830 **12**, do not fit these results.

In contrast, the deprotonation energies in water solution possess analogous values, except for suprofen **5**, the value of which does not offer too much guarantee because of the convergence difficulties encountered in the geometry optimization calculations. In general, the energy variations for all compounds are too small to be significant and could fall into the calculation error margin. No correlation with the anti-inflammatory activity could be detected.

The poor correlation in the gas phase was not surprising. There are indeed many other factors which affect the biological activity. One of them is the size of the drug. Since prostaglandin cyclo-oxygenase was identified as an important site for the anti-inflammatory aryl acid action, a refined *receptor contour*, which readily accommodates both arachidonic acid (the substrate of cyclo-oxygenase) and various potent anti-inflammatory drugs, was derived from X-ray projection and computer modeling [1, 6]. This hypothetical receptor contour possesses a maximum diameter of about 9 Å. In this study, most molecules of the series have a maximum length in the range of 7–10 Å, which fits quite well with the receptor size. This length, however, has a value of 13 Å for Benoxaprofen **3**. Therefore, the low activity of this drug, with respect to its protonation energy, can be due to a steric problem in the docking into the receptor pocket. Benaxoprofen could be thus considered as an outlier in this correlation.

In the same way, Indoprofen **11** is seen to possess a very large dipole moment and a very low lipophilicity parameter, as will be seen later (see *table IV*). Finally MK-830 **12** has been reported as a very active but toxic drug. Therefore, only qualitative values have been reported in the literature [1, 2]. This high toxicity could affect the actual anti-inflammatory activity, that could be probably lower.

Table II. Energy values (in kcal/mol) of the protonated and deprotonated forms of some arylpropionic anti-inflammatory agents in two different conformations of the propionic moiety (torsional angle θ_1 in degrees), calculated by AM1 in aqueous solution.

Molecule	Protonated form		Deprotonated form		Energy difference
	θ_1	Energy	θ_1	Energy	
Ibuprofen **1**	3.31	−107.7310	6.51	−189.1654	−81.4344
	−176.65	−107.2033	−166.45	−189.1046	−81.9013
Fenoprofen **2**	7.63	−84.1322	−23.92	−166.9209	−82.7887
	−173.70	−84.1406	148.68	−166.5133	−82.3727
Benoxaprofen **3**	4.69	−58.9142	6.63	−141.5559	−82.6417
	−176.66	−58.9913	−173.24	−141.4983	−82.4971
Suprofen **5**	1.77	−108.5232	6.41	−193.7361	−85.2129
	−176.181	−109.5303	–	–	–
Naproxen **4**	4.15	−106.4012	2.86	−188.0105	−81.6093
	−177.97	−106.9821	−172.92	−188.0204	−81.0579
Carprofen **8**	4.90	−50.6852	28.40	−132.0386	−81.3534
	−175.73	−50.6240	−175.98	−132.1230	−81.7146
Pirprofen **10**	2.17	−52.1688	32.30	−133.9166	−81.7478
	−176.88	−52.0697	151.81	−133.9769	−81.9072
Ketoprofen **6**	3.29	−88.9978	2.10	−170.2698	−81.2720
	−172.957	−89.340	−169.78	−171.3313	−81.9913
Indoprofen **11**	1.87	−73.5639	−25.46	−155.6037	−82.0398
	−175.14	−73.5645	−187.43	−155.4703	−81.9058
Flurbiprofen **9**	2.99	−101.7130	32.21	−183.7860	−82.0729
	−174.06	−101.7537	−176.85	−183.8014	−82.0477
MK 830 **12**	5.35	−116.7988	7.45	−198.7031	−81.9043
	−176.12	−116.7998	−173.56	−198.7760	−81.9762

Table III. Protonation energy values[a] (in kcal/mol) of some arylpropionic anti-inflammatory agents in the gas phase (without and with correction for zero point vibrational levels) in water solution, and versus the relative anti-inflammatory activity in logarithm.

Molecule	Gas phase		Water solution	Activity[b]
	Without	With		
Ibuprofen **1**	296.110	288.468	−19.674	−0.92
Fenoprofen **2**	293.492	285.941	−20.587	−0.70
Benoxaprofen **3**	292.009	284.292	−20.575	−0.48
Suprofen **5**	292.874	285.196	−23.22[c]	−0.30
Naproxen **4**	294.836	287.132	−19.339	−0.05
Carprofen **8**	292.262	284.663	−19.636	0.08
Pirprofen **10**	292.480	284.701	−19.833	0.15
Ketoprofen **6**	291.811	284.269	−19.638	0.20
Indoprofen **11**	295.936	288.169	−19.979	0.28
Pranoprofen **7**	292.516	284.847	–	0.48
Flurbiprofen **9**	292.114	284.451	−20.066	0.70
MK 830 **12**	293.643	285.931	−19.947	1.00

[a]At AM1 level; [b]logarithm of the relative activity with respect to Indomethacin in vivo activity, carrageenin-edema inhibition assay; [c]only one conformer was retained.

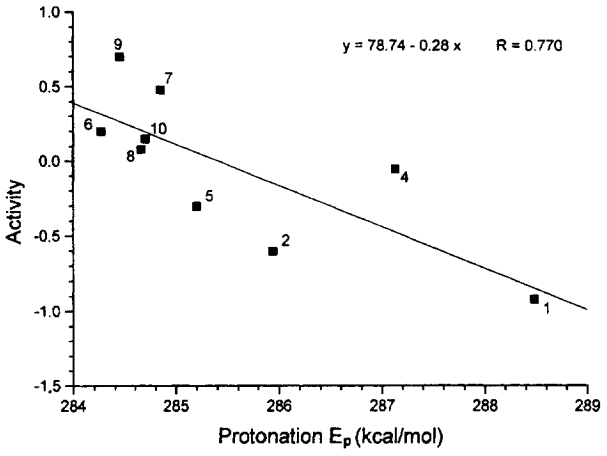

Figure 3. Anti-inflammatory activity versus protonation energy (in kcal/mol).

Taking into account the other nine compounds of this series, a moderate correlation coefficient of 0.770 was obtained. Since it can not be expected that the complex Nonsteroidal Anti-inflammatory Drug (NSAID)–receptor interaction can be described by a single parameter, a high correlation could not be expected [7].

Therefore, other parameters have to be investigated to obtain a more satisfactory regression structure–activity of these compounds. One important physico-chemical property is the lipophilicity which is directly related with the transport of the drug to the biologically active site. There is no experimental standard procedure to determine this property, although the most accepted method is the logarithm of the distribution coefficient of the solubilities in *n*-octanol/water phases. However, within this method many variables can be altered (phase contact time, pH, concentration, phase ratio, etc.) and it is difficult to have a consistent series of experimental data for our series of drugs from the literature [31, 32]. If we estimated that values measured at pH = 7.4 (physiological media) could be valid to represent the environment close to the active site, these experimental values were reported for some members of the series [32,39]. We have correlated them with the activities (*figure 4*). A decrease of the activity with an increase of the lipophilicity was found with a good linear correlation ($A = 0.038 - 0.789 \cdot \log D$, $R = 0.979$). The same tendency was found at pH = 4.5 close to the one in the gastrointestinal environment.

Because of a lack of experimental data for all compounds studied the physico-chemical parameter Π, which is related to the lipophilicity of the whole molecule, was considered. Taking into account that all

Table IV. Main physico-chemical features of some arylpropionic anti-inflammatory agents obtained in the AM1 approach: protonation energy, E_p (in kcal/mol), dipole moments in Debyes, Π and σ parameters, and charge on the asymmetric carbon atom in the protonated and unprotonated form, $q(C^*)$ as well as relative activities (in logaritmic values) with respect to Indometacine.

Molecule	Activity	E_p	μ	Π	σ	$q(C^*)^a$	$q(C^*)^b$
Ibuprofen **1**	–0.92	288.47	2.15	2.04	–0.12	–0.050	–0.164
Fenoprofen **2**	–0.70	285.94	2.27	2.08	0.25	–0.052	–0.168
Benoxaprofen **3**	–0.48	284.29	2.39	1.93	0.05	–0.050	–0.167
Suprofen **5**	–0.30	285.2	3.27	1.31	0.34	–0.051	–0.162
Naproxen **4**	–0.05	287.13	2.50	1.30	–0.03	–0.052	–0.167
Carprofen **8**	0.08	284.66	2.66	1.17	0.13	–0.053	–0.170
Pirprofen **10**	0.15	284.70	2.67	1.03	–0.35	–0.043	–0.167
Ketoprofen **6**	0.20	284.27	2.70	1.05	0.34	–0.050	–0.164
Indoprofen **11**	0.28	288.17	5.14	0.60	–0.19	–0.044	–0.162
Pranoprofen **7**	0.48	284.85	3.64	0.37	–0.11	–0.048	–0.164
Flurbiprofen **9**	0.70	284.45	2.52	2.10	0.33	–0.053	–0.171
MK 830 **12**	1.00	285.93	2.49	3.22	0.22	–0.051	–0.166

[a]Protonated form; [b]unprotonated form.

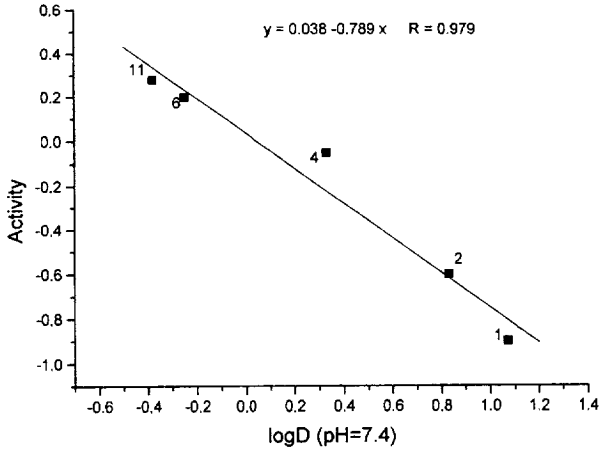

Figure 4. Effect of the lipophilicity on the anti-inflammatory activity.

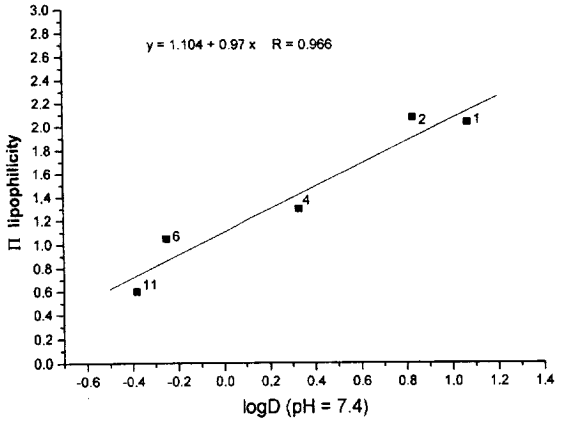

Figure 5. Correlation between the experimental values of lipophilicity and the parameter Π.

the members of the series possess an arylpropionic moiety, only the substituents were considered to determine the parameter Π [26] (*table IV*). These Π values were first checked by comparison with the experimental data of log*D* at pH = 7.4. A good correlation was obtained with a slope close to 1 (*figure 5*), which confirms that these theoretical parameters may be used as a lipophilicity parameter.

In *figure 6*, the in vivo anti-inflammatory activity was also correlated with the parameter Π. It is found that the higher the lipophilicity, the lower the activity. Flurbiprofen **9** and MK-830 **12** do not fit this correlation. As mentioned before, the qualitative character of the MK-830 activity could justify one to consider this drug as an outlier. On the other hand, other factors, such as the protonation energy, could have a much higher significance in the activity of Flurbiprofen. For the other members in this series, a linear correlation with a satisfactory coefficient was obtained (R = 0.953). This correlation is consistent with the experimental results.

At this point both factors, the protonation energy E_p and the lipophilicity Π, have to be considered together in order to correlate them with the activity. A moderate correlation was found for all the molecules of the series, obtaining the following equation:

$$A = 40.75\ (\pm 23.30) - 0.14\ (\pm 0.08) \cdot E_p - 1.83\ (\pm 0.59) \cdot \Pi + 0.54\ (\pm 0.16) \cdot \Pi^2$$

with $r = 0.782$, $s = 0.402$, $F = 4.20$, $n = 12$.

The value of the Π coefficient, however, appears to be too high and reveals that something more than hydrophobic effects should be involved [28]. Therefore, other theoretical molecular descriptors were also taken into account. The frontier HOMO and LUMO orbital energies can also play an important role in charge transfer interactions with the hydrophobic binding site at the receptor. The energy of these orbitals for the protonated and unprotonated forms as well as the differences, i.e. the hardnesses, have also been included in *tables IV* and *V*. Taking these physicochemical parameters into account, different multivariable regression studies were carried out. Only the

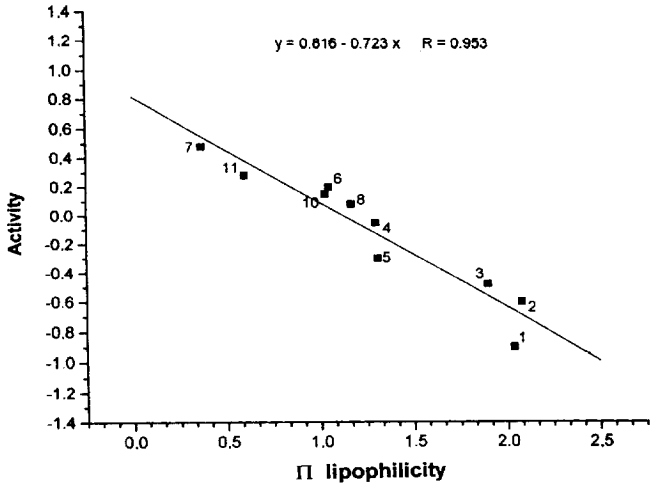

Figure 6. Relationship between the anti-inflammatory activity and the parameter Π.

Table V. Frontier orbital energies (E_{HOMO} and E_{LUMO}), hardnesses of some arylpropionic anti-inflammatory agents (in ev.) obtained in the AM1 approach.

Molecule	E^a_{HOMO}	E^a_{LUMO}	Hardness[a]	E^b_{HOMO}	E^b_{LUMO}	Hardness[b]
Ibuprofen **1**	–9.42	0.17	9.59	–4.37	3.60	7.97
Fenoprofen **2**	–9.06	–0.01	9.05	–4.65	3.07	7.72
Benoxaprofen **3**	–9.13	–1.03	8.10	–4.67	1.14	5.81
Suprofen **5**	–9.55	–0.75	8.80	–4.56	1.48	6.03
Naproxen **4**	–8.67	–0.42	8.25	–4.52	2.40	6.91
Carprofen **8**	–8.63	–0.54	8.09	–4.63	2.08	6.71
Pirprofen **10**	–8.49	0.06	8.55	–4.57	2.96	7.54
Ketoprofen **6**	–9.17	–0.50	8.67	–4.57	2.96	7.54
Indoprofen **11**	–8.73	–0.58	8.15	–4.45	1.37	5.82
Pranoprofen **7**	–8.99	–0.30	8.68	–4.59	2.05	6.64
Flurbiprofen **9**	–9.13	–0.46	8.67	–4.62	2.24	6.86
MK 830 **12**	–9.49	–0.07	9.42	–4.54	3.25	7.79

[a]Corresponding to the protonated form; [b]corresponding to the deprotonated form.

HOMO energies for the protonated form, E^a_{HOMO}, furnish a slight improvement, but the coefficient of Π appears to be too high as well. Taking into account the dipole moment μ and the HOMO energy for the deprotonated form, E^b_{HOMO}, as additional factors, the following correlation was obtained for all the molecules of the series:

$$A = 158.87\ (\pm 57.79) - 0.46\ (\pm 0.15) \cdot E_p + 0.20\ (\pm 0.06) \cdot \Pi^2 + 0.51\ (\pm 0.17) \cdot \mu + 0.90\ (\pm 0.43) \cdot E^a_{HOMO} + 4.94\ (\pm 2.75) \cdot E^b_{HOMO}$$

with $r = 0.863$, $s = 0.377$, $F = 3.5$, $n = 12$. An improvement of the regression was obtained, but too many parameters were included to be useful. The inclusion of other parameters related to the frontier orbitals, such as the LUMO energies and hardnesses, yielded worse correlations. Nevertheless, the atomic net charge of the asymmetric carbon in the protonated and deprotonated forms slightly improved the correlation, but not enough to justify the introduction of these variables in the regression study. A similar effect was observed with the inclusion of the electric dipole moment μ and the electronic factor σ.

Finally, considering only the three physico-chemical parameters: E_p, Π and E^a_{HOMO} for all the members of the series, except Flurbiprofen **9** and MK-830 **12**, a good regression was obtained with a high correlation coefficient and a low standard error:

$$A = 17.99\ (\pm 4.93) - 0.05\ (\pm 0.01) \cdot E_p - 0.64\ (\pm 0.05) \cdot \Pi + 0.26\ (\pm 0.08) \cdot E^a_{HOMO}$$

with $r = 0.989$, $R_{adj}^2 = 0.966$, $s = 0.081$, $F = 86.9$, $n = 10$. The activity predicted by this regression equation fits quite well with the experimental activity values (*figure 7*). The coefficient of Π is lower than 1, which is consistent with an actual hydrophobic effect [28]. The addition of the electronic factor σ only slightly improves the correlation ($r = 0.994$). On the contrary, the exclusion of the parameter E^a_{HOMO} in this regression yielded a lower correlation ($r = 0.971$, $R_{adj}^2 = 0.926$).

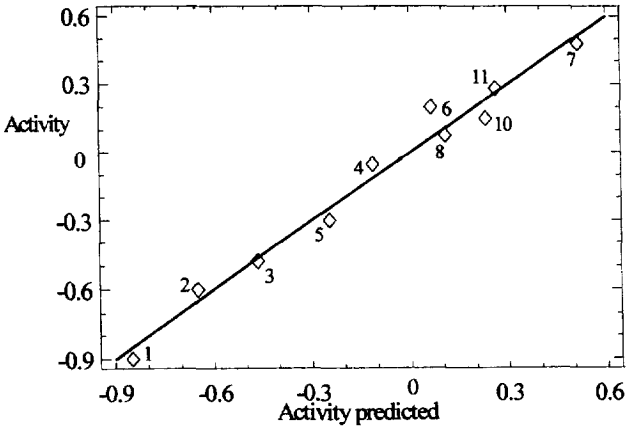

Figure 7. Experimental anti-inflammatory activity versus activity predicted by means of the QSAR study.

This result shows that at least two processes should be considered to understand the activity of these drugs: the transport mechanism to the receptor and the drug–receptor interaction. For the first process, the lipophilicity parameter presumably plays an important role. In the second process, we need to consider at least two steps, the kinetics of which would depend on the drug–receptor association kinetic constant (k_1) and the dissociation constant (k_2) of the carboxylic acid moiety. The first step seems to be controlled by the HOMO orbital energy where the drug could act as a charge donor to the hydrophobic pocket of the receptor. In the second step, the deprotonation energy of the carboxylic moiety could take place to promote the interaction with the polar site of the receptor. This multistep mechanism model has been accepted in the interaction of other ionizable drugs with the receptor [26].

4. Conclusions

Our theoretical calculations and QSAR studies on a series of arylpropionic acids with anti-inflammatory activity have yielded a satisfactory relationship between the deprotonation energy in the gas phase and the anti-inflammatory activity. The smaller the deprotonation energy in the gas phase, the larger the anti-inflammatory activity. This relationship, however, was not found with the deprotonation energy calculated in aqueous phase. The anti-inflammatory phenomenon in a living cell is obviously a very complex process in which some additional factors need to be considered.

A satisfactory negative relationship between the lipophilicities and the activities was also found. Moreover, the energies of the HOMO frontier orbitals have a significant effect on biological activities, showing a donor charge transfer interaction between the hydrophobic part of the drug and the receptor. Therefore, a relatively good correlation between the anti-inflammatory activities and the deprotonation energies, HOMO energies, and lipophilicity parameters is found for the series after discarding Flurbiprofen and MK-830. The lipophilicity effects could be related to the transport mechanism of the drug. The deprotonation energy could be related to the interaction with the receptor at the polar active site, and the HOMO energies with the interactions between the drug with the hydrophobic pocket of the receptor.

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