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Potential Energy Functions and the Role of the Conformational Entropy of Clonidine-like Imidazolidines in Determining Their Affinity for α-Adrenergic Receptors

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SUMMARY

Energy as a function of the ring interplanar torsional angle was calculated for 12 2-(phenylimino)imidazolidines by the method of perturbation configuration interaction using localized orbitals. The potential energy functions indicate that the molecules may assume any conformation within rather broad limits. The functions were used in calculating the gas phase and solution conformational entropies. The latter were used as the independent variable in regression analysis to derive equations connecting the conformational entropy with pK_i ($pK_i = -\log K_i$) for [^{3}H]clonidine displacement (literature data). As a comparison, correlations between pK_i and several other parameters (modified neglect of diatomic overlap-computed highest occupied and lowest unoccupied molecular orbital energies and dipole moments; pK_a; log P; substituent steric parameters) were sought. Correlation coefficients $C > 0.6$ were obtained with the conformational entropy (−0.77), and the *ortho* steric parameters (−0.71). The correlation with the conformational entropy was not markedly improved by adding other parameters in multiple regression analysis. This result is discussed in terms of the contribution to the ligand-receptor complexation free energy arising from the conformational restriction of the ligands upon binding to the receptor.

INTRODUCTION

In current representations of the interaction of CLI[1] and related drugs with adrenergic receptor(s), it is generally accepted that the phenyl and heterocyclic rings are not co-planar (1–7). The interplanar torsional angle τ (Fig. 1) is assumed to be either near 90° (1–3) or less (4–7). The knowledge of the conformational characteristics of CLI is important for the considerations of topological analogy of CLI with the phenylethylamine-type drugs including the natural adrenergic ligands and, in consequence, of whether both types of drugs interact with the same receptor site or not (8). Moreover, the assumed conformation is important for the calculation of the HOMO and LUMO energies, since the calculated orbital energies strongly depend on τ.

The evidence for the conformation of CLI stems from X-ray structure determinations of crystals, conformational energy calculations, UV photoelectron spectroscopy and NMR work. The structure analysis of crystals indicates only the possible conformation with $\tau = 75°$ and 86° for clonidine [hydrochloride and phosphate, respectively (2, 4)], which is not necessarily the preferred conformation of the free or dissolved molecules. The CNDO/2 calculations (7) for clonidine base yield $\tau = 34°$ with a rather high potential barrier centered at $\tau = 90°$. PCILO calculations for the same molecule yielded a function with slightly asymmetric minima at $\tau = 74°$ and a high barrier between them (5). The calculation by the same method applied to naphazoline (9) results in the conclusion that the most probable conformation is with perpendicular rings, although the conformational situation of the benzylimidazoles is somewhat different. The results of the CNDO-based prediction for the energy level splittings assuming $\tau = 90°$ are in good agreement with those experimentally observed (1). The quality of CNDO/2 results is unreliable in view of the known underestimation of nonbonded repulsions (10), and the PCILO results (5) on clonidine and some related molecules are questionable, too because obviously only a single Kékulé structure has been considered in the orbital localization. The NMR work (3) indicates nonco-planarity, but was not conducted in terms of a more precise conformational analysis. Thus, it appeared useful to reinvestigate theoretically the conformational problem of CLI and related molecules.

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[1] The abbreviations used are: CLI, clonidine-like imidazolidines; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; QSAR, quantitative structure-activity relationship; PCILO, perturbation configuration interaction using localized orbitals; MNDO, modified neglect of diatomic overlap.

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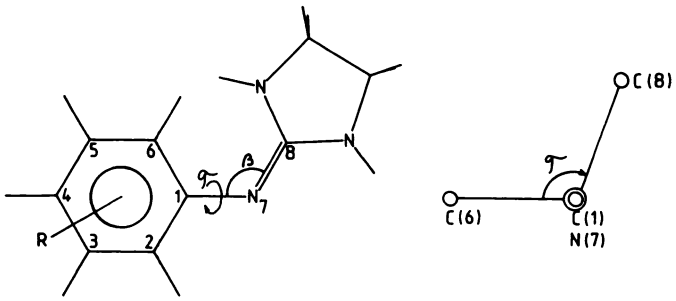

FIG. 1. *Structure of 2-(phenylimino)imidazolidines and the definition of the angles τ and β*

In this paper, we shall deal only with the potential functions of the 2-(phenylimino)imidazolidines which form a structurally homogeneous set, leaving the results concerning some related molecules for discussion in a somewhat different context. The potential energy curves indicate that in the CLI molecules the two rings oscillate rather freely around the $\tau = 90°$ conformation, the individual members of the series differing by the amplitude of the oscillation. The amplitude is mainly determined by the phenyl *ortho* substituents. The role of the size of these substituents in determining the activity was previously demonstrated by QSAR (11), but it was interpreted together with the orbital overlapping as conformation determining as well as involved in the direct fitting of the phenyl ring to the available space at the receptor-binding site (8, 12–14).

The present results have led us to the hypothesis that it is the extent of the conformational space and not any definite conformation that plays the major role in modifying the affinity of the 2-(phenylimino)imidazolidines for the adrenergic receptor(s). In order to test this hypothesis by QSAR, we have to cast it in thermodynamic terms. Using the relationship between the ligand-receptor dissociation constant K_i and the free enthalpy of association $\Delta G = RT \ln K_i$, and expressing ΔG by the component enthalpy and entropy changes, $\Delta G = \Delta H - T\Delta S$, we propose that the loss of the conformational entropy part of ΔS on ligand-receptor binding essentially contributes to the differences in ΔG between various ligands of the series considered.

In order to demonstrate this, we calculated the conformational entropies of 12 2-(phenylimino)imidazolidines from their potential energy functions and used these in the correlation with the experimental pK_i values of De Jong and Soudijn (12). For comparison with other parameters often used in QSAR, we calculated the HOMO and LUMO energies and dipole moments and used this along with available parameters to set up a correlation matrix. The conformational entropy turned out to be the best single parameter in QSAR correlations with pK_i. It has obviously a very limited value for practical QSAR, but the present results demonstrate the importance of conformational entropy for the free energy of the ligand-receptor interaction.

EXPERIMENTAL PROCEDURES

Conformational energy calculations. The PCILO method was used throughout. The average of the conformational energies of all Kékulé structures was taken as the final result (15). The basic input geometry parameters were taken from X-ray structure determinations and supplemented by standard bond lengths and angles (16) if necessary. The energies were calculated at 10° intervals of the torsion angle τ between $\tau = 0°$ and $\tau = 180°$, except for 9 for which the calculation was made for the full torsion (0°–360°). The results were checked by the *ab initio* method with the small STO-3G basis set (17) and with the semiempirical MNDO method (18, 19) for some 2-(phenylimino)imidazolidines.

The conformational energies were calculated for the following molecules: 1) 2-(phenylimino)imidazolidine (calculated also *ab initio* and MNDO); 2) 2-(4-chlorophenylimino)imidazolidine; 3) 2-(3-chlorophenylimino)imidazolidine; 4) 2-(3,5-dichlorophenylimino)imidazolidine; 5) 2-(2,6-difluorophenylimino)imidazolidine; 6) 2-(2,5-dichlorophenylimino)imidazolidine; 7) 2-(2-methylphenylimino)imidazolidine; 8) 2-(2-chlorophenylimino)imidazolidine; 9) 2-((5,6,7,8-tetrahydro-1-naphthyl)amino)-2-imidazoline(tramazoline); 10) 2-(2,6-dichlorophenylimino)imidazolidine (clonidine); 11) 2-(2,6-dimethylphenylimino)-imidazolidine (calculated also with MNDO); and 12) 2-(2,6-diethylphenylimino)imidazolidine.

Orbital energies and dipole moments. These were calculated by the MNDO method in the original parameterization. The dipole moments given in Table 2 conform to the $\tau = 90°$ conformation.

Conformational entropies. The gas phase conformational entropies were calculated by the quantum, semiclassical, and classical methods. The reduced angular moments were calculated with equations developed for completely asymmetric molecules (20). The conformational entropies in solution were calculated after Refs. 21–24. With some approximation, the conformational entropy S^t_r is written:

$$S^t_r = -R \sum_i^N p_i \ln p_i \quad (N = 36) \tag{1}$$

where R is the gas constant, N is the number of conformations and

$$p_i = \frac{1}{Q} \exp\left(-\frac{U(\tau) + V(\tau)}{RT}\right)$$

with Q, the partition function:

$$Q = \sum_i^N \exp\left(-\frac{U(\tau) + V(\tau)}{RT}\right)$$

For the intramolecular conformational energy function $U(\tau)$, we used PCILO conformational energies. In the calculation of conformational entropy, the full torsion (360°) was included. The symmetry factor was not included. $V(\tau)$ is the free energy of solvation containing the entropy of solvation. This term was omitted.

Biological data. For the QSAR, the K_i data for [^{3}H]clonidine displacement obtained by De Jong and Soudijn (12) on rat brain suspensions were used.

RESULTS

The potential energy function. The curves obtained by the PCILO method are reproduced in Fig. 2. With identical *ortho* substituents, the curves are symmetrical about $\tau = 90°$ as may be expected from molecular symmetry. The barriers at this conformation are low (≳5 kJ/mol) allowing the molecules to assume at room temperature the perpendicular ring orientation on the average. This is in agreement with the photoelectron spectroscopy results, but both types of results are valid for the molecules *in vacuo*. However, it is not expected that the average conformation would be essentially different in solution. This premise may at least indirectly be corroborated by the results of calculations for the protonated molecules, which demonstrate that the curves are very similar to those of the nonprotonated molecules although the charge distributions are different. This means that

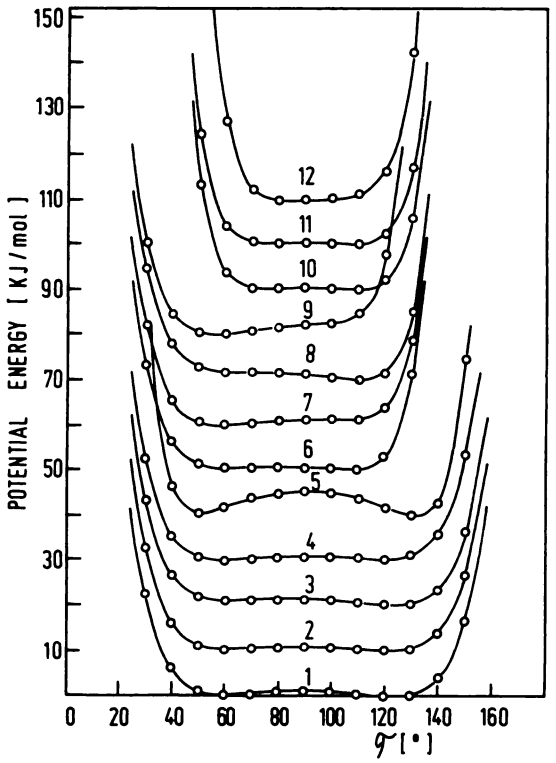

FIG. 2. *PCILO conformational energies of 2-(phenylimino)-imidazolidines*

The ordinate scale refers to compound 1. The minima of the other compounds are shifted upward by 10 kJ/mol for each successive compound. For compound 12, τ_1 (C(3)-C(2)-C(ethyl)-C(ethyl) = 60° and τ_2 (C(5)-C(6)-C(ethyl)-C(ethyl) = 60°. The conformational energies between 180° and 360° are symmetrical with respect to τ = 180°, except for tramazoline, but the differences are very small (~1 kJ/mol). See Experimental Procedures for Compounds 1–12.

TABLE 1

Comparison of PCILO, ab initio STO-3G, and MNDO relative energies for 2-(phenylimino)imidazolidine and 2-(2,6-dimethylimino)imidazolidine

τ	2-(Phenylimino)-imidazolidine			2-(2,6-Dimethyl-imino)imidazolidine	
	PCILO	*Ab initio* (STO-3G)	MNDO	PCILO	MNDO
degrees		*kJ/mol*		*kJ/mol*	
0	177.2	194.1	271.9		
30	21.7	37.1	42.9	384.7	124.9
50	0.6	1.5	3.4	17.3	16.3
70	0.0	0.0	0.7	0.0	3.4
90	0.3	1.6	0.0	0.3	0.0

the volume effects of the *ortho* substituents are dominant in determining the shape of the potential functions. Hence, there should be no major changes in solution. As a check of the method of computation (PCILO), we also calculated the conformational energies at several τ values by the *ab initio* method for 2-(phenylimino)imidazolidine and both for this and the 2,6-dimethyl analogue by the semiempirical MNDO method. The results are given in Table 1. The PCILO and *ab initio* results are in harmony whereas MNDO obviously overestimated nonbonded interactions. This and the underestimation of resonance effects are known deficiencies of the MNDO method in calculating the potential energy curves of conjugated systems (25).

The central barrier vanishes for both molecules under the MNDO scheme, and it is very low for 2-(phenylimino)imidazolidine under the *ab initio* (STO-3G) basis scheme. The barrier opposing the co-planar arrangement (τ = 0°) of the rings is quite high even for the case of the nonsubstituted phenyl ring, but is lowered by optimizing the β angle (Fig. 1). Thus, for 2-(phenylimino)-imidazolidine, the *ab initio* optimized β value for τ = 0° was 133° (compared with β = 114° at τ = 90°), and the difference between the τ = 0° and τ = 90° energies equals 58.7 kJ/mol. This indicates that the potential functions with optimized β would be wider than those calculated with a fixed value of β. However, such optimization would require excessive computer time for the whole series.

Since it is not certain whether the CLI interact with the receptor in the protonated form or otherwise and in view of the importance of their pK_a for activity *in vivo* demonstrated by QSAR (13), we have calculated the potential energy functions also for some representative protonated CLI. The effect of protonation is very small and consists mainly of slightly modifying the height of the central barrier (~1 kJ/mol) which is due to the removal of the conjugation of the lone electron pair from the bridging nitrogen.

The main results of the conformational energy calculations are that the CLI considered may assume any conformation within the limits of the steeply increasing extremes of the curves and that the individual molecules differ by the allowed conformational space. The conformations observed in the crystals are well within this space.

Conformational entropy. The computed potential energy functions were used for calculations of the entropy of internal rotation S_{ir}. The calculations were done both for the gas phase and solution. We shall consider only the latter, because they are more closely related to the conditions under which the ligand-receptor interaction evolves. The treatment adopted is based on the continuum model of solvation as developed by Scheraga (22) and Hopfinger (23). In this model, the molecules are treated as if they were in the gas phase, subsequently adding the free energy of solvation $V(\tau)$ to the conformational energy function $U(\tau)$. The former also contains the solvation entropy. However, we omitted the $V(\tau)$ term because it may be expected to vary but little between the individual molecules belonging to a structurally similar series. Moreover, the contribution of $V(\tau)$ to the sum $U(\tau) + V(\tau)$ is not substantial because of the steepness of the potential energy function at the extremes. The calculated S^s_{ir} values are given in Table 2.

Quantitative structure-activity relationships. The HOMO and LUMO energies were calculated for the τ = 90° conformation, this being the most probable. The HOMO energies of the orbitals predominantly located at the phenyl ring of the protonated and nonprotonated molecules are listed in Table 2. The LUMO and imidazoline HOMO energies are not listed, because they did not yield significant correlations. Table 2 also contains

TABLE 2

Biological and physicochemical parameters of the 2-(phenylimino)imidazolidines)

No.	pK_i[a]	log P[b]	pK_a[b]	μ	S_{ir}[a]	E_s^{2+6}[c]	HOMO neutral	HOMO protonated
				D	*J/mol·K*		*eV*	*eV*
1	6.900	−1.92	10.05	4.882	30.649	0.00	−8.689	−13.159
2	7.495	−1.24	9.78	6.173	30.611	0.00	−8.907	−13.246
3	7.310	−0.98[d]	9.56[d]	5.731	30.536	0.00	−8.973	−13.122
4	6.979	0.15[d]	8.98[d]	6.186	30.448	0.00	−9.239	−13.303
5	7.721	0.16[d]	8.18[d]	4.725	29.248	−1.50	−9.107	−13.354
6	8.031	0.65	8.50	5.325	28.875	−1.06	−9.162	−13.279
7	7.959	−1.82	10.23	4.879	28.825	−1.24	−8.671	−13.025
8	7.886	−0.67	9.15	5.018	28.729	−1.06	−8.918	−13.208
9	8.319	−0.77	10.56	4.224	27.189	−1.24	−8.655	−12.643
10	8.569	0.62	8.05	4.829	27.097	−2.12	−9.150	−13.398
11	8.252	−1.54	10.53	4.884	27.014	−2.48	−8.656	−12.911
12	7.620	−0.88	10.61	5.455	26.369	−2.62	−8.660	−12.856
C[e]		0.283	−0.096	−0.576	−0.772	−0.714	0.090	0.223

[a] From Ref. 12.
[b] From Ref. 13.
[c] Substituent steric parameters from Ref. 11.
[d] Calculated using regression equations in Ref. 13.
[e] Correlation coefficients with pK_i.

the other parameters used in QSAR. Since not all pK_a and log P values were available in the literature, the missing ones were calculated from the well known correlations (13). The regression analysis was made using the pK_i values as the dependent variable. Affinity data from only one source (12) were used to avoid discrepancies between data from different laboratories. The highest correlation coefficient is scored by S^s_{ir}. The linear regression yields Eq. 2:

$$pK_i = -1.068(\pm 0.27)S^s_{ir} + 15.108 \qquad (2)$$

where $n = 12$, $r = 0.772$, $s = 0.347$, $F = 14.75$, and $p = 0.003$. Compound 12 is considerably off the straight line. By removing this from the regression, Eq. 3 is obtained.

$$pK_i = -1.471(\pm 0.19)S^s_{ir} + 17.966 \qquad (3)$$

where $n = 11$, $r = 0.931$, $s = 0.209$, $F = 58.98$, and $p < 0.001$.

The corresponding graphic representation is given in Fig. 3. The deviation of 2-(2,6-diethylphenylimino)-imidazolidine is caused either by the too large size of the *ortho* substituents or by the extra entropy of the ethyl groups.

Eqs. 2 and 3 cannot be improved significantly by introducing additional parameters such as the dipole moment and the HOMO energies. The latter parameters appeared promising in view of the rather high correlation coefficient in previous QSAR (13). The *ortho* substituent volume parameters as independent variable were quite successful:

$$pK_i = -0.384(\pm 0.12)E_s^{2+6} + 7.326 \qquad (4)$$

where $n = 12$, $r = 0.714$, $s = 0.382$, $F = 10.427$, and $p = 0.009$. S^s_{ir} values correlate with E_s^{2+6}. The correlation coefficient is 0.93.

DISCUSSION

Most of the previous work on QSAR of imidazolidines and related compounds refers to biological data obtained from *in vivo* or isolated organ experiments. Among the most successful parameters were those related to transport properties (13) and to the *ortho* substituent size E_s^{2+6} (11). In contrast to the QSAR based on ED values, the pK_a and partition coefficients do not correlate with pK_i. HOMO energies and some other electronic parameters appeared to improve significantly the correlations with ED (11, 13). In the set under examination, the phenyl HOMO energies, particularly those of the non-protonated molecules, have a low correlation coefficient. The dipole moment has a relatively high coefficient, but none of these parameters markedly improved the correlation with the conformational entropy.

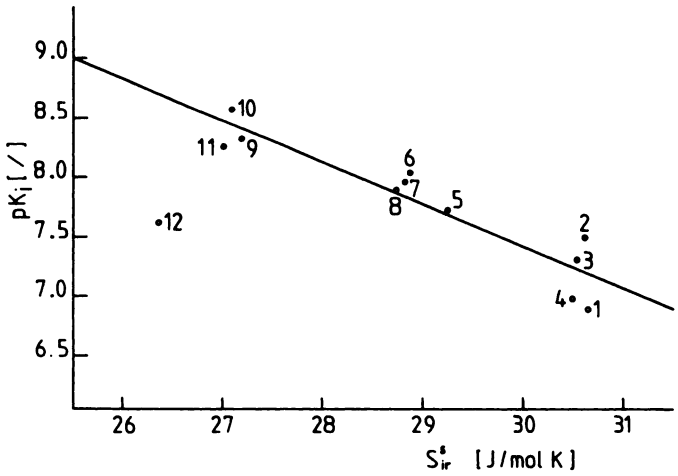

FIG. 3. *Correlation of pK_i with the conformational entropy S^s_{ir} (Eq. 3)*

The significant correlation of pK_i with the *ortho* substituent size (Eq. 4) fits well the demonstrated role of the conformational entropy (Eqs. 2 and 3) in determining the relative affinities for the receptor. In the present context, the role of the substituent size lies not in determining the fit of the ligands to some receptor cavities in a possibly appropriate conformation, but in limiting the conformational space: the stiffer ligands have the higher affinity.

There are two possible interpretations of this finding. One corresponds to the "induced fit" hypothesis (26). The more rigid ligands will be more efficient in eliciting the conformational change in the receptor characteristic of agonist activity. In the other interpretation, we have to consider the entropy changes on ligand-receptor binding. Besides the entropy change due to the loss of the translational and rotational degrees of freedom, the conformational entropy of the free ligand is changed to the much smaller vibrational entropy of the bound ligand. No large difference is expected in the change of the first two kinds of entropy between the ligands of very similar structure and the main differences between various ligands will be due to variations in the reduction of conformational entropy. Obviously these differences must be large enough relative to the variations in the enthalpy part of ΔG of binding in order to be perceived.

Hence, it is useful to make at least a rough estimate of the magnitude of this contribution to ΔG. For this, the absolute entropy in solution would be needed, but our calculated S°_{ir} values are, in fact, only relatively meaningful due to the simplification adopted. However, following the arguments advanced by Jencks (26) in the treatment of the essentially similar process of enzyme-substrate binding and of intramolecular cyclizations, we may assume that the conformational entropy in solution does not essentially differ from that of the molecules in the gas phase. With this assumption and with the conformational entropy of 2-(phenylimino)imidazolidine *in vacuo* (42 J/mol·*K*) calculated by the classical method, the contribution $T\Delta S$ to ΔG of binding of the 2-(phenylimino)imidazolidines would amount to ~13 kJ/mol, which is comparable to the enthalpy contribution. Clearly, the conformational entropy differences alone will correlate with the affinities only if the structural differences influencing the enthalpic contribution to ΔG are small or running parallel to the entropic.

The relation between the conformation of the thyroid hormones and analogues and their affinity for the nuclear receptor presents a situation similar to CLI. Andrea *et al.* (27) have used the free energy ΔG_{lock} required to lock the ligands into the mutually perpendicular conformation of the two phenyl rings in quantitatively expressing this relation. Although ΔG_{lock} and S°_{ir} are formally different quantities, they are related by having the same physical origin, i.e., the restriction of internal motility. Also connected with the present problem is the question whether the role of the *ortho* substituents lies mainly in influencing this motility or in supplying additional interactions with the receptor. The latter possibility has been shown (27) to be less likely by considering the hydrophobicity of the substituents.

The results of examining the conformational energy functions of both the CLI and the thyroid hormone analogue series demonstrate the importance of internal motility in QSAR. The calculation of the corresponding thermodynamic quantities is rather demanding and hardly possible in practical applications of QSAR. However, these results suggest caution in seeking QSAR with molecules for which significant differences in conformational freedom may exist.

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