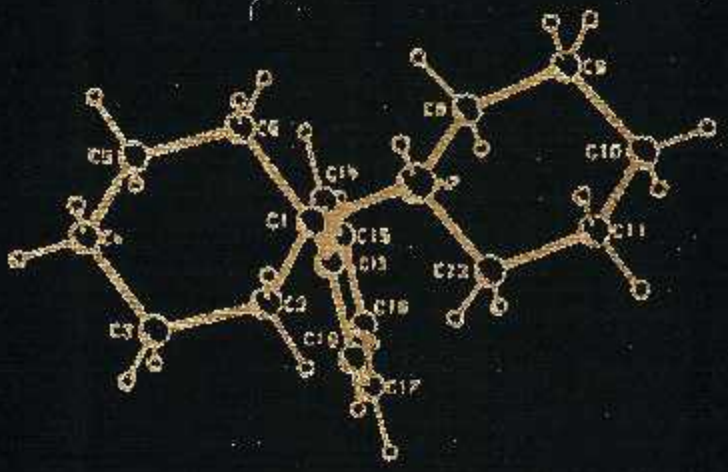
PHENCYCLIDINE AND RELATED ARYLCYCLOHEXYLAMINES



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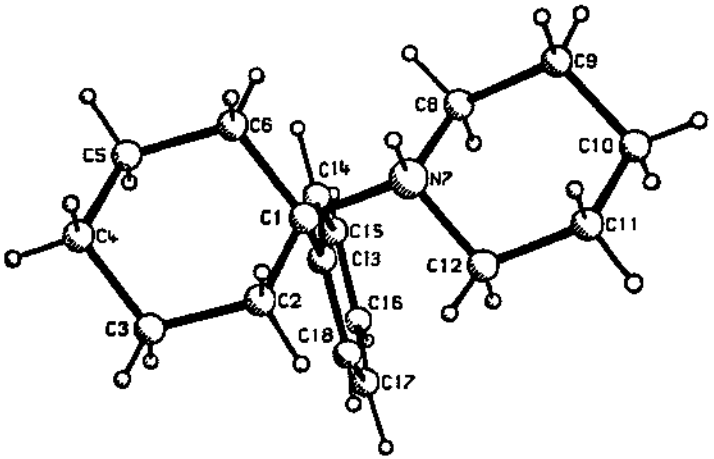
Phencyclidine and Related Arylcyclohexylamines:
Present and Future Applications



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Other Related Books

PCP (Phencyclidine): Historical and Current Perspectives. E.F. Domino, Ed., 1981
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PHENCYCLIDINE AND RELATED ARYLCYCLOHEXYLAMINES: PRESENT AND FUTURE APPLICATIONS

Proceedings of the Joint French-US Seminar on the Chemistry, Pharmacology, Present and Future of the Therapeutic Applications and Drug Abuse Aspects of Arylcyclohexylamines held in La Grande Motte (Montpellier), France, September 20-24, 1982.

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Preface

This book presents the Proceedings of the French-US seminar held in La Grande Motte (France) September 20-24, 1982 under the patronage of the Société Francaise de Chimie Thérapeutique. The seminar was attended by scientists concerned with the chemistry, biochemistry, pharmacology, therapeutic applications and drug abuse aspects of arylcyclohexylamines. Their presentations and subsequent discussions constitute the substance of this book. We thank them for their significant contributions which have advanced our knowledge of this intriguing class of biologically active compounds.

The seminar was sponsored by the Centre National de la Recherche Scientifique (C.N.R.S), the National Science Foundation (N.S.F.), and the Direction de Recherches et Etudes Techniques (D.R.E.T.). In addition, the pharmaceutical companies Beecham/Sobio, Expansia, Merrell Dow, Merck, Sharp and Dohme, Pfizer, Rhône-Poulenc, Sanofi, Sobio and Upjohn contributed to the success of the seminar. Special thanks are due to Burroughs Wellcome, DuPont, Merrell Dow, Pfizer, A.H. Robins, Stuart Pharmaceuticals, and the Upjohn Company for providing additional support for assisting in the editing and publication of this book. The Editors would like to acknowledge Mrs. Ellen Howard for typing the majority of the manuscripts.

October 1, 1983
Jean-Marc Kamenka
Edward F. Domino
Patrick Geneste
Montpellier and Ann Arbor

Participants and Guests to the French-US Seminar on Arylcyclohexylamines

It was appropriate that the Seminar, whose purpose was present and future application of arylcyclohexylamines, was held in the kindergarten area of VVF Le Ponant "off" season. The American participants were warned of the "spartan" accommodations of VVF, which are designed for families. It turned out that the Local Committee selected a superb setting and arranged a hospitality and cuisine which only the French could achieve. The participants and their guests would like to thank especially Dr. A. Finiels, Mme Michaud, Mr. Parlongue, Mr. Depierre and Mme Follana from the VVF.

Préface

Ce livre présente les travaux exposés au cours d'un séminaire Franco-Americain tenu à la Grande-Motte (Hérault) du 20 au 24 Septembre 1982 sous le patronage de la Société Francaise de Chimie Thérapeutique. Les chercheurs concernés par la chimie, la biochimie, la pharmacologie, les applications thérapeutiques et les usages illicites des arylcyclohexylamines constituaient la majorité des participants. Leurs présentations de travaux et les discussions qui s'en suivirent sont la substance même de ce livre. Nous les remercions de l'importante contribution qu' ils ont apportée a la connaissance d'une série très intriguante de composés biologiquement actifs.

Le séminaire était soutenu par le Centre National de la Recherche Scientique (C.N.R.S.), La National Science Foundation (N.S.F.), et la Direction des Recherches et Etudes Techniques (D.R.E.T.). De plus, les Sociétés Pharmaceutiques Beecham/Sobio, Expansia, Merrell Dow, Merck Sharp and Dohme, Pfizer, Rhône-Poulenc, Sanofi, Sobio et Upjohn ont egalement contribué à sa réussite. Les sociétés Burroughs Wellcome, DuPont, Merrell Dow, Pfizer, A.H. Robins, Stuart Pharmaceuticals et Upjohn doivent être particulièrement remerciées de l'aide supplémentaire apportée pour la préparation et l'édition de ce livre. Les Editeurs voudraient remercier Mme Ellen Howard pour son travail de dactylographie.

October 1, 1983
Jean-Marc Kamenka
Edward F. Domino
Patrick Geneste
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C.N.R.S. N.S.F.

Seminaire Conjoint France - Etats-Unis

CHIMIE, PHARMACOLOGIE, APPLICATIONS THERAPEUTIQUES

presentes et potentielles et problemes poses par l'USAGE

ILLICITE des ARYLCYCLOHEXYLAMINES

Joint France - U.S.A. Seminar

CHEMISTRY, PHARMACOLOGY, present and future of the

THERAPEUTIC APPLICATIONS and DRUG ABUSE ASPECTS

of ARYLCYCLOHEXYLAMINES

20 - 24 Septembre 1982

LA GRANDE MOTTE (Montpellier)

France

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THE BIOLOGICALLY ACTIVE CONFORMATION OF PCP AND ITS CONSEQUENCES: A HYPOTHESIS

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The different possible conformations in equilibrium of the phencyclidine (PCP) molecule in solution (4,6) represent an important physicochemical factor playing a role in both the kinetics of displacement of the molecule and its binding to receptor sites. In aqueous biological medium, however, conformational equilibrium is not the only type of equilibrium to be considered because there is also a protonic equilibrium (Fig. 1).

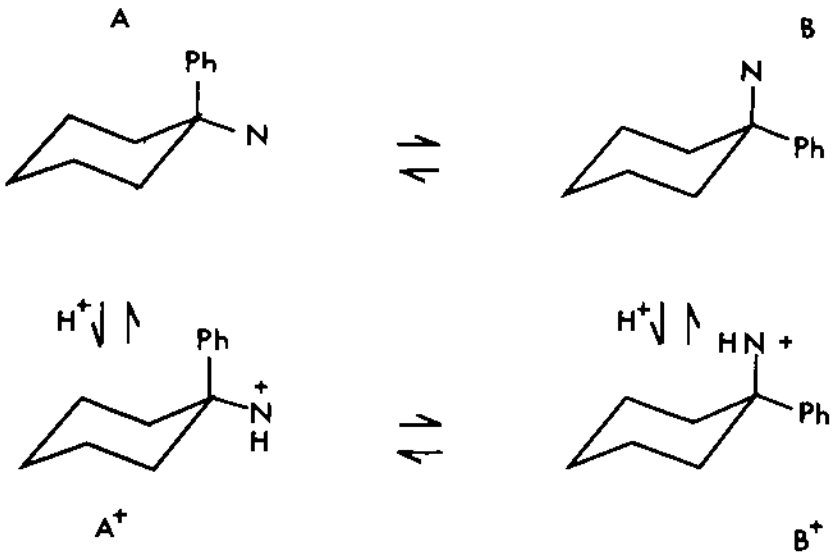


Fig. 1. Conformational and protonic equilibria of the PCP molecule

The positions of the conformational equilibria in the base form and in the protonated form depend on the conformational free energies ΔG° and $\Delta G^{\circ +}$, whereas the protonic equilibria depend on the pH of the medium and the pK of the molecule.

When the molecule interacts with a given receptor, what is the "active" conformation involved in the ligand-receptor complex? Should the interaction be considered one between a protonated form and a basic site, or the contrary? We will present some arguments allowing hypotheses to be made concerning the interactions of derivatives of PCP with the ^{3}H-PCP receptor (8,10,12). The structures of the derivatives studied are shown in Tables 1, 2 and 3.

Influence of conformation on biological activity in vivo and in vitro

A. Rotarod Test

In considering the relative conformational displacements for a pair of stereoisomers, we find in Table 4 that compounds 13-32 and 35-38 illustrate the fact that, practically systematically, the isomer having the greatest percentage of its aromatic group in the axial position (even numbered compounds) gives the best results (i.e., the lowest ED_{50} values). It is remarkable that out of ten pairs of stereoisomers, with very different structures, there is only one real exception: 23 and 24. This leads us to believe that, in spite of the different physicochemical characteristics of the substituents, activity in the rotarod test is associated with a common characteristic, the axial aromatic ring conformation.

B. Binding to the ^{3}H-PCP receptor

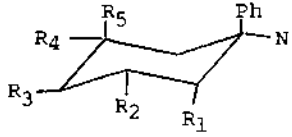
Comparison of the pairs of stereoisomers 13-32 and 35-38 in Table 4 shows the following results. Out of twelve pairs, the compounds with the aromatic ring in the axial position (even numbers) have the best affinity, but four pairs show the opposite result (23-30). It must be emphasized that the four exceptions concern molecules bearing $-OCH_3$ or -OH substituents, and that the same result was found in the in vivo test: 23 and 24.

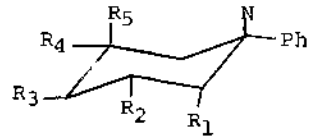
The exceptions observed concern hydrophilic substituents. This leads us to believe that in these cases interactions of the hydrophilic-hydrophobic type are more important than the conformational parameter. This observation does not, however, cast any doubt on the general conclusion drawn from the results of the in vivo and in vitro studies.

Conformational stability in solution and in the solid state

A. Stability in solution

Table 1. Cyclohexyl-substituted molecules in their preferred conformation in the base form (Ph=phenyl, N=piperidine)





No.	No. GK	R_1	R_2	R_3	R_4	R_5	R_1	R_2	R_3	R_4	R_5
1	GK_1	H	H	H	H	H					
13	GK_2						H	H	t-but	H	H
14	GK_3	H	H	t-but	H						
15	GK_4						H	H	CH_3	H	H
16	GK_5	H	H	CH_3	H	H					
17	GK_7						H	CH_3	H	H	H
18	GK_6	H	CH_3	H	H	H					
19	GK_9						CH_3	H	H	H	H
20	GK_8	CH_3	H	H	H	H					
21	GK_{14}						OCH_3	H	H	H	H
22	GK_{15}	OCH_3	H	H	H	H					
23	GK_{41}						H	OCH_3	H	H	H
24	GK_{40}	H	OCH_3	H	H	H					
25	GK_{43}						H	H	OCH_3	H	H
26	GK_{42}	H	H	OCH_3	H	H					
27	GK_{45}						H	H	OH	H	H
28	GK_{44}	H	H	OH	H	H					
29	GK_{47}						H	OH	H	H	H
30	GK_{46}	H	OH	H	H	H					
31	GK_{26}						H	CH_3	H	CH_3	CH_3
32	GK_{25}	H	CH_3	H	CH_3	CH_3					
33	GK_{18}	H	H	di-CH_3	H	H					

Table 2

Phenyl- and piperidine-substituted molecules

No.	No. GK	R_1	R_2	R_3	R_4	R_5
1	GK_1	H	H	H	H	H
2	GK_{20}	H	NO_2	H	H	H
3	GK_{21}	H	H	NO_2	H	H
4	GK_{27}	H	H	OCH_3	H	H
5	GK_{28}	H	OCH_3	H	H	H
6	GK_{29}	OCH_3	H	H	H	H
7	GK_{30}	H	OCH_3	OCH_3	H	H
8	GK_{31}	H	H	H	OH	H
9	GK_{32}	H	H	H	CH_3	H
10	GK_{33}	H	H	H	H	CH_3
11	GK_{35}	H	H	H		
12	GK_{37}	H	OH	H	H	H

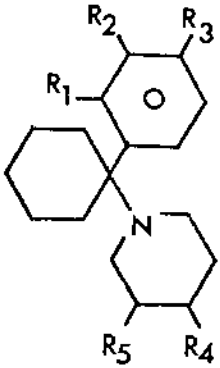
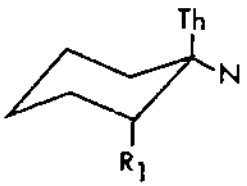
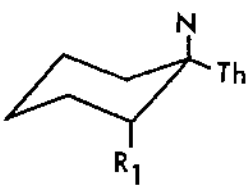


Table 3

2-Thienyl derivatives in their preferred conformation in the base form (Th=thienyl, N=piperidine)





No.	No. GK	R_1	R_1
34	GK_0	H	
35	GK_{12}		CH_3
36	GK_{11}	CH_3	
37	GK_{16}		OCH_3
38	GK_{17}	OCH_3	

Table 4

Physical and biological parameters of the molecules studied

No.	pK	Δ	ED_{50} (mg/kg, s.c.)	K_d (μM) (^{3}H-PCP)
1	8.29	1.03	4	0.25
2	7.18	1.33	110	11.5
3	7.25	1.37	>150	25
4	8.45	0.80	20	1.2
5	8.09	0.90	4.8	0.09
6	8.67	0.74	26	0.5
7	8.59	0.49	115	9.5
8	7.98	-	42	2.2
9	8.22	0.88	20	0.4
10	8.16	1.01	7.14	0.16
11	7.56	-	2.1	0.08
12	7.42	-	2.2	0.03
13	5.84	4.06	150	100
14	8.14	0	150	30
15	7.68	2.22	>150	0.5
16	8.30	0.55	5.5	0.13
17	7.03	3.54	>150	0.6
18	8.29	0.75	22	0.6
19	6.50	3.46	125	1.6
20	7.75	1.64	7.4	0.12
21	7.50	2.41	150	5
22	8.72	0.62	20	0.83
23	6.80	2.65	10	1.1
24	7.91	1.06	39	3
25	8.01	0.66	112	4.2
26	8.01	0.46	49	4
27	8.24	1.16	-	8.3
28	8.23	0.47	-	17
29	7.02	0.63	-	0.89
30	8.03	-	49.9	2.2
31	5.80	3.74	>150	16
32	8.24	0.21	94	6.3
33	8.27	0.66	93	5
34	7.81	1.61	2.3	0.026
35	6.59	3.63	>150	1
36	7.31	2.47	3.5	0.04
37	7.37	3.15	24	10
38	8.36	1.09	3.6	0.4

Studies described previously (4,6) showed that the preferred conformation of PCP in solution is the conformation with the phenyl group axial, in the base form (ΔG^{o+}= -1.1 kcal/mol) and particularly in the protonated form (ΔG^{o+}= -4.4 kcal/mol). In the latter case, we can consider the system conformationally homogeneous. For the thiophenyl analog of PCP, 34, the effects are similar, although less intense (ΔG^{o+}=-0.6 kcal/mol, ΔG^{o+}=-3.3 kcal/mol). It follows that in solution the protonated form is highly stabilized with an axial aromatic ring.

B. Stability in the solid state

The study of the X-ray diagrams of PCP hydrochloride crystals indicates that the molecule also takes on a conformation with the phenyl group in the axial position. The error in the interpretation of Argos et al. (1) has been corrected, because we have verified that their experimental results agree perfectly with ours (2,3).

Discussion and working hypothesis

In solution as well as in the solid state, the thermodynamic stability point of protonated PCP is the same conformation. We can reasonably imagine that in the PCP receptor complex, an environment intermediate between order in the solid and disorder in solution, the protonated form having the aromatic ring in the axial position is the most stable. In other words, the complex formed most easily because, it corresponds to a conformational energy minimum, and is stabilized by protonation, is the one where PCP is protonated with its phenyl group in an axial position. From the biochemical studies (8) showing the presence of acid functions in the receptor site, on the one hand, and given the in vivo and in vitro results above, on the other hand, we arrive at the following working hypothesis: the base form with the axial phenyl group is recognized by the ^{3}H-PCP receptor, where it is protonated and stabilized in its lowest energy conformation. This hypothesis leads to at least two consequences:

1. In the affinity studies, the total concentration of PCP or its derivatives is not the important factor, but rather the concentration of the base form present at the pH of the medium.

2. There must be a relationship between the conformational displacements of the compounds with an axial phenyl group and the affinity for the receptor.

To a certain extent, it is possible to verify the hypothesis by studying its consequences.

Relationship between the affinity for the receptor site and the rotarod test

If our hypothesis is correct, the linear relationship which appears to exist between the ED_{50} values (rotarod test) and the K_d (11) values takes on a much greater importance if the concentrations of the base form are taken into account instead of those of the hydrochloride salts. Using the pK values (4) of the analogs of PCP, measured in MCS and extrapolated to water, we can express the ED_{50} values in moles of base per kg and the K_d values in moles of base per liter. Fig. 2 shows that a linear relationship with a good statistical significance is obtained

$$\log ED_{50} = 0.68\ (\pm\ 0.04)\ \log K_d - 0.92\ (\pm\ 0.31)$$
$$n=28 \qquad s=0.239 \qquad r=0.959 \qquad F=295$$

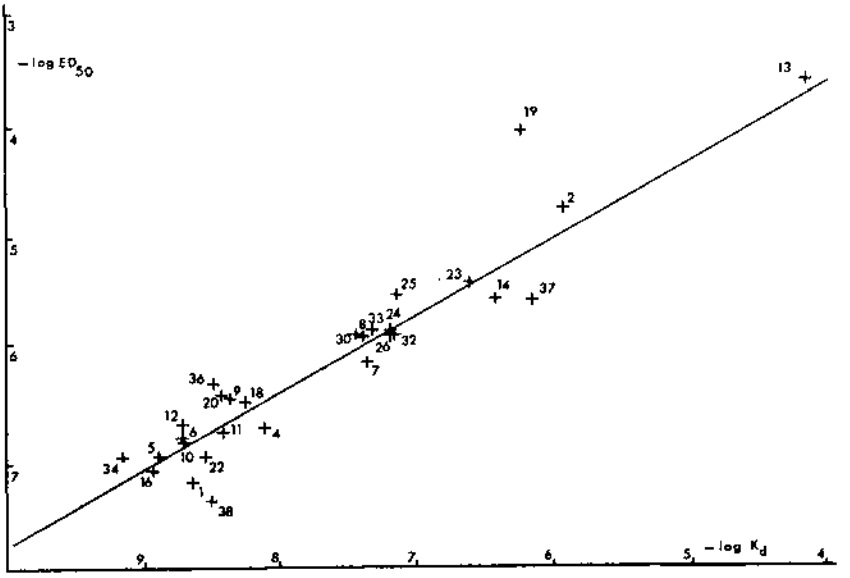


Fig. 2. Relationship between ED_{50} (rotarod test) and K_d (PCP receptor). Both parameters are expressed in terms of the base concentration with respect to the pK and pH values (7.4 *in vivo*, 7.7 *in vitro*).

The fact that 28 out of 29 molecules tested fit the correlation (19 does not) seems to validate our hypothesis and to establish the fact that interaction with the ^{3}H-PCP receptor has a direct consequence on the rotarod test.

After correction for ionization, the rank order of efficacy at the receptor site is: 34 > 16 > 5 > 6 > 12 > 10 > PCP, the least effective being: 13 > 2 > 37 > 14 > 23 > 25.

Possible relationship between conformation and affinity for the ^{3}H-PCP receptor site

To investigate the possible relationship between conformation and affinity, it is necessary to have a parameter which expresses the conformational displacement in one direction or another. In fact, it would be desirable to use ΔG°, but determination of this parameter for a large number of diversely substituted compounds poses many problems, especially the need to prepare the conformationally homogeneous reference compounds, having the same substitutions as each of the molecules studied.

Consequently, we preferred to use the parameter $\Delta = \log P - \log P_A$, where P is the partition coefficient (octanol-water), and P_A is the calculated partition coefficient of the molecule in the A conformation (5) (Fig. 1). The smaller the value of Δ, the closer the molecule is to the conformation supposed to be active. The reference molecules 14 and 13 have Δ values of 0 and ≈4 (5,6), respectively.

Plotting log K_d (expressed in terms of the concentration of the base) as a function of Δ, we see that a general relationship does not exist for the entire series, but we can generate parabolic curves from the reference compounds which group all of the derivatives (Fig. 3). This is not unexpected:

1. Given the fact that Δ is an expression of lipophilicity, one would expect to find parabolic relationships, which are typical of quantitative structure-activity relationship studies (7).

2. The fact that the conformational modifications are a result of the changes in the substituents leads to steric, hydrophobic and other interactions which are all different. Fig. 3 shows that, according to the type of interaction created by replacing the t-butyl group of 13 or 14 by other groups in different positions of the molecule, the role of conformation is more or less important with respect to af-

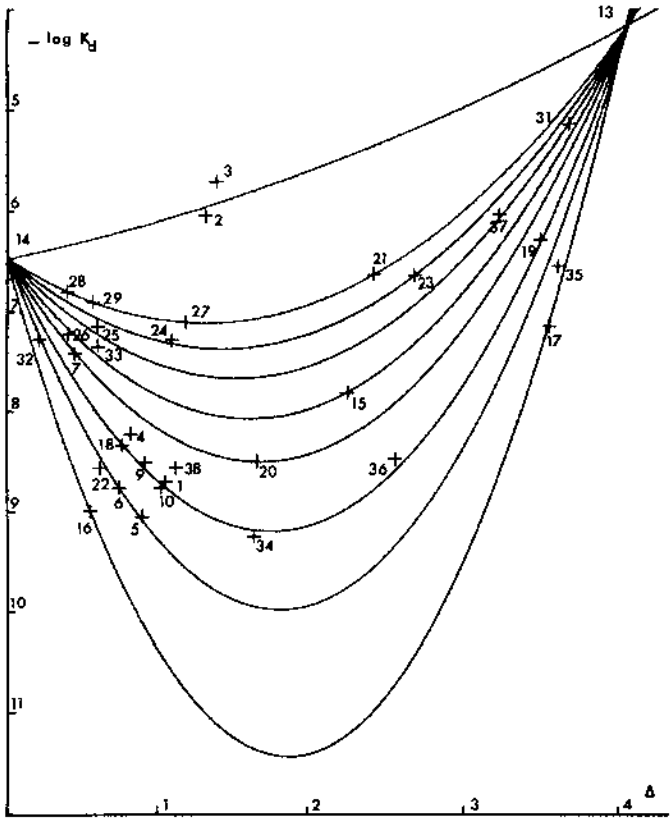


Fig. 3. Relationship between the K_d (PCP receptor) expressed in terms of the base concentration with respect to pK, pH and conformation (Δ parameter, see text)

finity. It also seems possible, by correctly quantifying the parameters expressing the different interactions at the receptor site, to find a quantitative structure-activity relationship for the series.

It should be noted that if the most axial position of the aromatic ring corresponds to the best affinity for a given pair of stereoisomers, Fig. 3 indicates that in general the best affinities are obtained (minima of the curves) for mobile systems in which conformation A is in majority but not exclusive. For example, 1 (PCP) and 34 (thienyl PCP) are sit-

uated on the same curve, but 34 has a better affinity that 1, with a conformation that is less displaced towards the axial aromatic ring conformer (-0.6 kcal/mol as compared to -1.1 kcal/mol).

Conclusion

The results show the role played by the concentration of the base form, and that of the conformation of the molecules in the expression of the biological activity of PCP and its derivatives.

It is interesting to note that mathematically there is a relationship between the rotarod test and the affinity for the ^{3}H-PCP receptor site. This relationship seems indeed to be specific, since attempts to show a relationship between the rotarod test and affinity for the opiate μ and cerebral muscarinic receptors (9) were negative.

There are coherent factors which lead us to believe that at the receptor site the derivatives of PCP take on a conformation in which the aromatic ring in the axial position is stabilized by ionic bonds with acid residues. To conceive new molecules, we are confronted with the following imperatives:

1. At the site of activity there must be as high a concentration of the base form as possible, therefore, molecules with the lowest pK values.

2. The molecules must be mobile, with their conformational equilibria at a minima in the curves in Fig. 3.

Such molecules can only be obtained by chemical modifications, which themselves have an effect on the interaction at the level of the receptor, because of the inherent physicochemical characteristics of the substituents introduced. Only a very precise study of the changes in affinity constants caused by substituents at different locations on the PCP ring can lead to a logical formulation of molecules with strong affinity and probably high specificity. One important factor must also be taken into consideration: the chirality factor for molecules having an asymmetric carbon atom. Indeed, the studies described herein were carried out on racemic mixtures, whereas the receptor most certainly has an asymmetric structure.

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SUBJECT INDEX