Progress in Drug Research

Fortschritte der Arzneimittelforschung

Progrès des recherches pharmaceutiques

Editor:
Ernst Jucker

34

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Foreword

Today's drug research is an extremely complex process which, apart from chemistry, pharmacology, toxicology and preclinical trials, includes a variety of sciences such as biotechnology, biochemistry, immunology, physics, biology and even computer sciences. The Table of Contents of the present volume demonstrates this situation and makes it evident that the individual researcher cannot possibly hope to keep abreast of *all* aspects of modern drug research. In this respect, the series of monographs "Progress in Drug Research" provides valuable help and assistance. Those who simply wish to remain informed of the latest trends and developments in drug research can use the 34 volumes so far available as a source of almost encyclopedic character.

Researchers actively engaged in the various scientific fields forming the entity of drug research can benefit from the wealth of knowledge and experience of the respective authors, and they will be assisted in their endeavour to discover new pharmaceutical agents. Moreover, the extensive bibliographies of the individual reviews provide an invaluable overview of the literature most pertinent to today's drug research.

I should like to thank all the authors for their willingness to prepare the reviews and for sharing their insights and experience with the readers. Thanks are also due to Mrs L. Koechlin, H.-P. Thür and A. Gomm of Birkhäuser Publishers for their valuable help in the preparation of this volume.

Basel, March 1990 DR. E. JUCKER

Vorwort

Die Arzneimittelforschung umfasst heute ausser den «klassischen» Bereichen der Chemie, Pharmakologie, Toxikologie und präklinischen Forschung eine Vielzahl anderer Disziplinen, von denen hier nur die Biotechnologie, Biochemie und Biologie sowie die Physik, Immunologie und die Informatik genannt seien. Das Inhaltsverzeichnis des vorliegenden Bandes legt vom kaum mehr überschaubaren Komplex der Arzneimittelforschung Zeugnis ab. So ist es denn auch zu verstehen, dass der einzelne Forscher den Kontakt zum gesamten Komplex nur unter Zuhilfenahme aktueller Übersichtsreferate aufrechterhalten kann. Die Veröffentlichung solcher Übersichtsarbeiten ist das primäre Ziel der «Fortschritte der Arzneimittelforschung». Die Reihe ist somit ein wertvolles Instrument zur Orientierung der Forscher über die grossen Entwicklungen in der Arzneimittelforschung und damit auch zur Aufrechterhaltung des Kontaktes zum Fortschritt auf diesem Gebiet. Dem aktiven Forscher kann die Reihe in seinem eigenen Bereich hingegen noch mehr bieten: Die prägnante Zusammenstellung der neuesten Entwicklungen und Tendenzen sowie die diesen Übersichten zugeordnete – meist sehr umfangreiche – Literatur vermitteln Anregungen und auch Vergleichsmöglichkeiten. So darf hier die Hoffnung ausgesprochen werden, dass die «Fortschritte der Arzneimittelforschung» einen Beitrag zur Entwicklung neuer Medikamente leisten.

Der Herausgeber freut sich, diesen neuen Band dem Leserkreis der «Fortschritte» zu übergeben. Zugleich möchte er auch den Autoren seinen Dank abstatten, die bereit waren, ihre Zeit für die Niederschrift umfangreicher Übersichtsartikel zur Verfügung zu stellen und ihr grosses Wissen mit dem Leser zu teilen.

Dank schulde ich auch dem Birkhäuser Verlag, vor allem Frau L. Koechlin und den Herren H.-P. Thür und A. Gomm. Ohne den grossen Einsatz aller Beteiligten wäre ein Werk wie die «Fortschritte» kaum zu verwirklichen.

Basel, März 1990 Dr. E. Jucker

The use of quantum chemical methods to study molecular mechanisms of drug action

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1 Introduction

Since the end of the sixties quantum chemical calculations have also been applied to the field of drug design, because they can help the medical chemist to answer the persisting question about the relationship between the structure and the biological effect of a pharmaceutical agent.

The first publications dealt with the conformative behavior of molecules. In this context, calculations offer a great advantage compared to experimental procedures, because not only the one conformation energetically allowed – e. g. in the crystal – is found, but conformative behavior can be studied throughout the entire conformational space. Therefore it is possible to also recognize such conformations which are energetically less preferred but still allowed. As it is rather unlikely that just the conformation in the crystal or in solution at the receptor will be responsible for triggering the biological effect, computing of conformations is eminently important for drug design. Calculations may provide answers which cannot be obtained using experimental procedures. On the other hand, experimental methods cannot be abandoned, for all computations must be validated by comparision to IR or NMR data. Nowadays conformational computations and geometrical optimizations are increasingly performed using purely empirical force field procedures, which in the meantime have reached a high and reliable standard. Especially large flexible molecules cannot yet be quantum chemically calculated with reasonable effort, even at the time of CRAY supercomputers.

The most important and most widely used molecular property that can be quantum chemically calculated is the electron density distribution or potential field generated round a molecule by the electrons. Here it may never be possible to replace quantum chemical procedures. When two molecules approach each other, whether in a chemical reaction in a test tube or in interaction of a bioactive molecule with the active center of an enzyme or a receptor, always the potential fields of the two molecules guide one another and react with each other. Knowledge of electron distributions therefore is a basic condition for understanding the mechanisms of action of physiological and pharmaceutical substances on the molecular level. For this reason this review covers this aspect in particular.

In order to find out the structure of unknown receptors, one tried to

construct pharmacon-receptor model complexes which were able to functionally explain experimental biological data. In this way ideas about receptor binding sites could be achieved frequently, which in these days, with growing knowledge about the molecular structure of receptors, turn out to have already been very close to reality. Until some years ago it was not possible to adequately describe and evaluate the molecular properties computed. This drastically changed with the appearance of sophisticated computer graphics systems and the corresponding molecular modeling software. These new approaches directly presented a major stimulus for application of quantum chemical methods. For this reason all important molecular modeling software packages also possess interfaces for the most important quantum chemical calculation programs.

1.1 The quantum chemical calculation procedures most commonly used

A synopsis of quantum chemistry shall not be provided here, but just a short description of possible applications of the various procedures, which differ widely with respect to the effort needed for calculating.

Basically, semi-empirical and ab initio methods have to be distinguished. The simplest and also oldest calculating procedure is based on the Hückel Molecular Orbital (HMO) Model, which can describe π electrons only. R. Hoffmann extended the method to σ electrons. The corresponding calculating procedure is called Extended Hückel Theory (EHT). Computations using EHT need little time for calculating, so large molecules can be processed, too. Opposed to this advantage is the disadvantage of poor reliability of the absolute energy contents and geometries. If series of molecules are examined, one can, however, rely on a qualitatively correct prediction of relative stabilities of related systems.

All other semi-empirical procedures are summarized under the specification of Self Consistent Field (SCF) Methods. Using these procedures all one-electron interactions are taken into consideration. This becomes possible by applying the so-called Zero Differential Overlap (ZDO) Approximation. Extension of this approximation to all valence electrons can be realized in different ways. Thus a whole range of SCF procedures exist. The most important of these are the

Complete Neglect of Differential Overlap (CNDO), the Intermediate Neglect of Differential Overlap (INDO), the Modified INDO (MINDO), and the Modified Neglect of Diatomic Overlap (MNDO) procedures. CNDO and MNDO calculations are performed most often. While conformational analyses and geometrical optimizations partly suffer from overestimation of repulsive interactions between atoms, electronic parameters can be described reliably. A strong argument for the reliability of a calculating procedure is the agreement of computed results with experimental data. CNDO and MNDO calculations result in good agreements with e. g. dipole moments and ionization energies. As the semi-empirical SCF procedures are standardized according to experimental data, they can provide rather accurate results within the area of validity of the set of parameters and within a fairly short calculation time.

Using ab initio procedures principally all properties of chemical systems can be computed as accurately as seems feasible, if only one pushes the calculation work to extremes. According to the enormous efforts only very small molecules can be computed by ab initio methods. If slimmed ab initio programs are used, reliability is less than that of semi-empirical procedures. Thus using an ab initio method does not automatically ensure reliability. For this reason such procedures are of significance in drug design for special problems only. Nowadays semi-empirical and ab initio quantum chemical methods are applied more and more to obtain force field parameters for molecular mechanics routines.

In this review examples of work are chosen with the object of providing a balanced rather than exhaustive view of the field; references are similarly limited, but should provide the reader with entry points to the literature.

2 Conformational analysis

Conformational analysis is an important means to describe the shape of a molecule able to interact with a receptor. Exact knowledge on the energetically possible conformations of a pharmacologically active molecule allows conclusions on the nature of a still hypothetical receptor, and is required to understand the interactions between the pharmacon agent and its receptor. Because of their rotatable bonds most molecules have unlimited possibilities for three-dimensional ar-

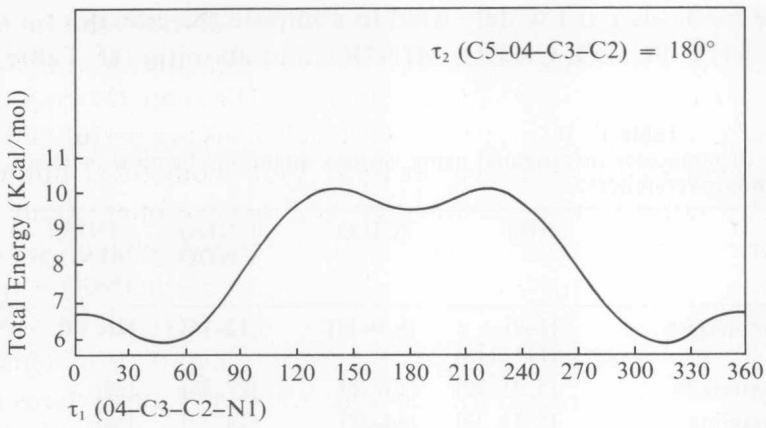
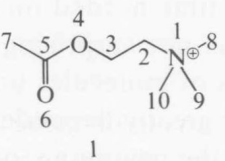


Figure 1
Calculated energy contour for acetylcholine. Angle τ_1 is rotated, angle τ_2 is fixed at 180° [16].

rangements; however, only one out of the many possible conformations is bound to the receptor. The main criterium in picking out the relevant conformations from the many possible orientations is the relative conformational energy. This term provides information on the probability of a given conformation being present at a distinct temperature.

Conformational analysis using Molecular Orbital (MO) methods is performed as follows: After stepwise rotation of the rotatable bonds, the energy of the conformation achieved is calculated. This procedure is repeated until the whole conformational space is covered. Figure 1 shows the result of a conformational analysis of the acetylcholine molecule (**1**). In this example only one bond was rotated in 30°



1

steps. At each step the conformation energy was calculated according to the INDO method. Two or more rotatable bonds may also be examined in this way. Of crucial significance are those conformations which are situated in a local energy minimum. They provide hints on which spatial orientation a molecule mainly occupies.

The methods most widely used to compute the energy of a molecule are EHT, PCILO, CNDO, MINDO, and ab initio (cf. Table 1). They

Table 1
List of molecules investigated using various quantum chemical methods and corresponding references.

	EHT	PCILO	CNDO CNDO/2	MNDO MINDO/3 INDO	ab initio
Cholinergics	[1–8] [111–113]	[6, 9–11]	[12–15]	[16, 17]	[18–20]
Adrenergics	[5, 21, 22]	[23, 26]	[27, 28]	[29]	[30, 31]
Dopamine	[5, 32, 33]	[34–37]	[23, 27]	[38]	
Histamine	[5, 39–46]	[42, 47, 48]			
Serotonin	[5, 49, 50]	[51, 52]			
Neuroleptics	[49]	[54]	[56–59]		
Antidepressants		[53]	[60]		
Psychodysleptics		[55]			
γ-Aminobutyric acid (GABA)	[61]	[62–64]	[65–67]	[68]	
Antibiotics	[69, 70] [115]	[71–80]	[69, 81]		
Antitumor drugs		[82–84, 74] [75, 77–80]	[85]		
Analgetics		[86–94]	[95–97]		
Local anesthetics		[98–101]			
General anesthetics	[102]				
Barbiturates		[103, 144]			
Hormones	[104–106]	[107]			
Vitamins	[108]	[109]		[110]	

differ from each other not only by their accuracy in describing the behavior of real molecules, but also by the time needed for calculating and the memory space used. It is thus not surprising that the choice of computing methods and the sizes of molecules under consideration as well as rotation steps used are greatly dependent on the progress made in computer technology. At the beginning, only small molecules, e. g. the biogenic amines, were evaluated using large rotation steps and the relatively simple EHT method. During the course of time this method was followed by PCILO, CNDO, and MNDO. Nowadays we are able to perform conformational analyses using the ab initio method, assisted by modern vector and parallel computers.

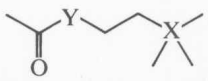
2.1 Cholinergics

Kier [1,2] examined acetylcholine (**1**), nicotine (**3**), muscarine (**2**), and

2,3 see figure 3

muscarone using EHT. By comparing the distances between functionally important residues, he proposed a muscarinic and a nicotinic receptor model. This model was based on the fact that for acetylcholine his computations revealed two energetically equally favorable conformations. Kier postulated that one conformation affects the muscarinic receptor, whereas the other binds to the nicotinic receptor (cf. Fig. 2).

This model correlates the biological activity of acetylcholine to its conformational flexibility. Chidichimo demonstrated that the flexibility decreases if the oxygen atom is replaced by an atom with a greater van der Waals radius [13]. The lower effectiveness of acetyl selenocholine (**4**) could be explained very well by Kier's model. Ri-



1; 4; 5; 6

1:	Acetylcholine	X = N	Y = O
4:	Acetylselenocholine	X = N	Y = Se
5:	Phosphonium acetylcholine	X = P	Y = O
6:	Arsenium acetylcholine	X = As	Y = O

chards found great structural flexibility for acetylcholine and other biogenic amines [5]. He assumes that in all biogenic amines first the protonated nitrogen atom is recognized by the receptor and bound to

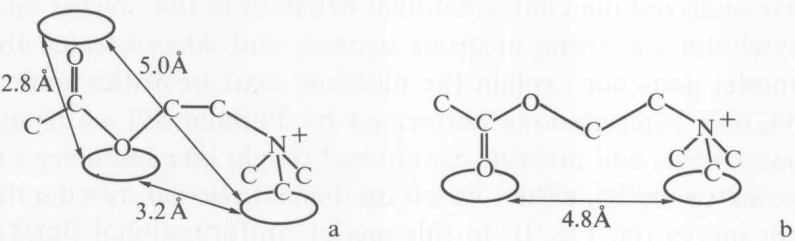


Figure 2
The cholinergic receptor models of Kier showing the interacion of the preferred conformers of acetylcholine with (a) the muscarinic and (b) the nicotinic receptor [6].

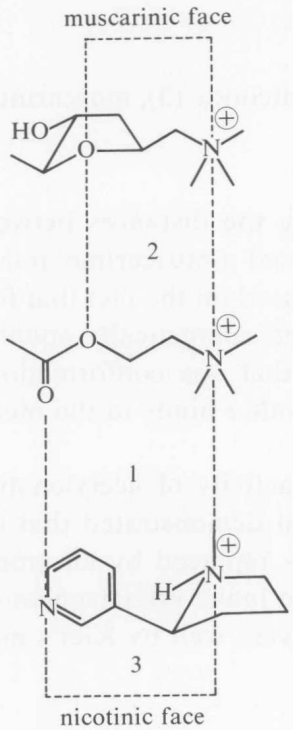


Figure 3
Muscarinic and nicotinic pharmacophore of acetylcholine according to Pullman [9].

negatively charged receptor regions. Because of the structural flexibility the ligand subsequently may adapt itself optimally to varying receptor conditions. In this context Richards does not mention the usual "lock and key" receptor model, but the "hand and glove" receptor model, whereby the hand and the glove represent the receptor and the flexible ligand, respectively.

Kier's receptor model is contradicted by results obtained by Reed [6]. He analyzed the conformational behavior of the reverse ester of acetylcholine, a strong nicotinic agonist, and demonstrated that Kier's model does not explain the nicotinic activity of this molecule. The PCILO computations performed by Pullman [9] on acetylcholine, muscarine, and nicotine cannot be brought into harmony with Kier's receptor model, either. Based on this data he described a new receptor model (cf. Fig. 3). In this model conformational flexibility does not play a role any longer; for the same acetylcholine conformation binds to both the muscarinic and the nicotinic receptor.