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Abstract Based on a line of evidence (logP, pKa, ^{1}H-, and ^{13}C-NMR, and molecular modeling studies), it appears that cocaine undergoes a hydrophobic collapse which may account for its unprecedented ADME properties, in particular, its exceptional capacity to cross biological membranes. Using molecular simulation techniques, the hypothesis of hydrophobic collapse undergone by the protonated form of cocaine was substantiated using semi-empirical quantum calculations (mainly AM1 and PM3) performed as well as ab initio quantum calculations (6–31 G**). A molecular electrostatic potential map of the internally hydrogen-bonded structure was acquired under AM1 and showed a continuum of high electron density in the central part of the molecule around the methyl ammonium and the two ester moieties. This picture is consistent with the picture of the ammonium being locked between the two C=O and forming a strong "canonical" primary H bond with the methyl ester and a weaker secondary H bond ("non-canonical") with the benzoate ester. Cocaine represents the prototypical example of molecular concision because the pharmacophore and the vector are embedded in the same molecular scaffold.

Keywords Cocaine · Hydrophobic collapse · Stereostructure · Pharmacophore · H bond · Molecular modeling

J. H. Poupaert (✉) · C. N. Kapanda
Medicinal Chemistry, Louvain Drug Research Institute, Université Catholique de Louvain, Avenue E. Mounier 73-40, 1200 Brussels, Belgium
e-mail: jacques.poupaert@uclouvain.be

F. A. Gbaguidi
Laboratoire de Pharmacognosie, Centre Beninois de Recherche Scientifique et Technique, Faculté des Sciences et Techniques, Université d'Abomey-Calavi, 01 PB 06, Porto-Novo, Benin

H. Aichaoui
Equipe de Chimie Pharmaceutique Département de Chimie Faculté des Sciences, Université Badji-Mokhtar, 23000 Annaba, Algeria

C. R. McCurdy
Department of Medicinal Chemistry, School of Pharmacy, The University of Mississippi, University, Oxford, MS 38677, USA

Introduction

A "social molecule" according to the definition given by Testa is a molecular structure capable of "transactions" with its environment (Testa and Bojarski, 2000). In this context, a "transaction" means the cooperative give-and-take transfer of information from one system to another one with mutual adaptation to the common close vicinity. One type of such "transaction" is the effect produced by the solvent on the conformational behavior of the solute. This effect is clearly of paramount importance when rationalizing "transactions" between drugs and biosystems. Polar solvents such as water will tend to favor the more polar conformers, whereas non-polar solvents will shift the conformational equilibrium toward more lipophilic conformers. This phenomenon is known as chameleonic behavior, given that the solute will try to resemble the molecular surrounding in its emergent properties such as polarity, lipophilicity, etc. (Testa and Bojarski, 2000). Indeed, the interplay between a chemical compound and its environment creates a complex system in its own right, as exemplified by solutions. A solute influences the solvent by affecting its organization and some colligative properties, while the solvent often has a marked influence on the solute by constraining its property space and so selecting some of

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its molecular states. Solutions may display emergent properties not existing in the separate components, e.g., chemical reactivity, implying that information has been created upon formation of the complex system (Testa and Kier, 2000).

Such a chameleonic behavior is, in general, the result of a hydrophobic collapse. In other words, the conformers predominating in water hide their hydrophobic side-chains in a hydrophobic core (hydrophobic collapse) and expose their polar groups to the solvent, whereas the more lipophilic conformers mask their polar groups by internal H-bonds and so exposes their hydrophobic side-chains. Molecules undergoing hydrophobic collapse as a result of a transaction are called chameleons (Testa *et al*., 1996). In addition, hydrophobic collapse has been hypothesized as an essential prime event in the folding of globular proteins (Sadgi *et al*., 2003). Biological media are in effect characterized by a high degree of organization. Examples at the macromolecular level include functional proteins (receptors, enzymes, transporters, etc.) or nucleic acids. When a molecule is recognized by such a macromolecule and interacts (binds) productively with it, strongly constraining both of these components in a complex system, the emergent property is the functional response. The chemical is frozen into a single or a very limited number of molecular states (induced fit), whereas the macromolecule is activated by a conformational change (e.g., an allosteric effect). Here again, emergent information appears in the complex (Testa, 1997). Taxol and taxotere are examples of clinically useful drugs that undergo hydrophobic collapse (Vandervelde *et al*., 1993).

Cocaine, the most abused drug worldwide, is a powerful rewarding and addictive substance that activates dopamine (DA) reward pathways by blocking DA transporters (DAT), and thus increasing extracellular DA concentration. Increased DA neurotransmission has been directly linked to euphoria and reward. Moreover, there is compelling evidence in the literature that cocaine also interacts with sigma-1 receptors. Sigma receptors have been well documented as a protein target for cocaine and have been shown to be involved in the toxic and stimulant actions of cocaine. Sigma receptors ($\sigma-1$ and $\sigma-2$) are non-opioid proteins implicated in the pathophysiology of various neurological disorders and cancer. These receptors are involved in the modulation of K^+- and Ca^{2+}-dependent signaling cascades at the endoplasmic reticulum and modulation of neurotransmitter release. Moreover, $\sigma-1$ receptors are emerging targets for the treatment of neuropsychiatric diseases (schizophrenia and depression) as well as cocaine addiction. (Narayanan *et al*., 2011a, b; Fishback *et al*., 2011; Mesangeau *et al*., 2011).

Cocaine hydrochloride as a salt is endowed with exceptional solubility characteristics: while it is expected to be freely soluble in water, more puzzling is the fact that this salt is also readily soluble in a wide variety of organic solvents including ethanol, glycerin, chloroform, etc. Cocaine is also known for its exceptional ADME parameters including its capacity to cross biological membranes (nasal membrane and brain-blood barrier). Many divergent logP values of cocaine have been published (Avdeef, 2003; Bonate *et al*., 1996; Brzezinski *et al*., 1997; Cone *et al*., 2007; Javaid and Davis, 1993; Nakahara *et al*., 1995; Wiczling *et al*., 2006). However, most recent data using more accurate methods tend to indicate a logP value ranging from 2.9 to 3.35. Using the HINT paradigm the ClogP is calculated to be 1.102. The fact that cocaine appears to be experimentally more lipophilic than calculated can be interpreted as the fact that the protonated form of cocaine pendulates between a lipophilic shape in apolar medium and a hydrophilic shape in polar medium. The question thus arises whether this behavior is the result of a hydrophobic collapse. In an effort to shed some light into this problem, we undertook molecular modeling studies and complementarily looked at some clues that can be retrieved in the literature to feed our reflection about this controversial problem.

Results

pKa studies

There is a general consensus to accept a pKa value for cocaine around 8.7 ± 0.1. This value can be considered as normal as it falls within the classical range for tertiary amines. Therefore, most of cocaine present at physiological pH is protonated. However, a small fraction remains unprotonated. This strategical pKa value allows for inversion of the direction of protonation at the N-methyl moiety as depicted in Fig. 1 and giving rise to the diastereoisomeric species **1a** and **1b** in which the bridgehead nitrogen becomes an additional stereogenic center in the protonated form of cocaine (Fig. 1).

Indeed, Tröger's base (Fig. 2) (Tröger, 1887) represents a historical example which was used to demonstrate that not only carbon, but also nitrogen is capable of creating a chiral center. The nitrogen inversion normally leads to the fast equilibrium between the enantiomers, but in Tröger's base this pyramidal inversion is impossible due to high internal conformational strain, and consequently, the nitrogen atoms are chiral centers. The resolution of the enantiomers was first carried out by Prelog and Wieland, 1944. It is noteworthy that racemization of Tröger's base occurs via protonated species, a mechanism similar to that suggested for nitrogen epimerization of cocaine.

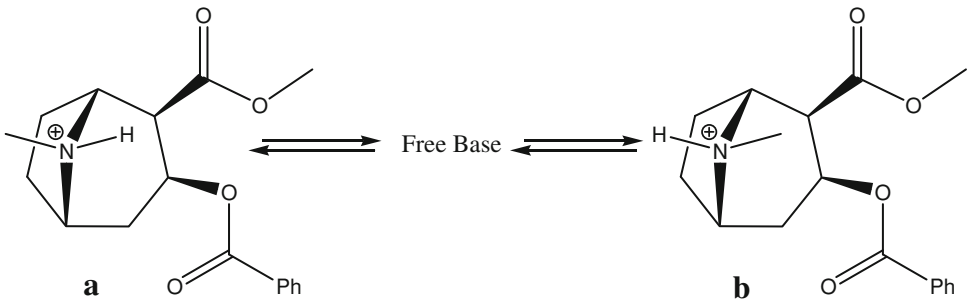

Fig. 1 Protonation of cocaine and stereogenic nitrogen center inversion

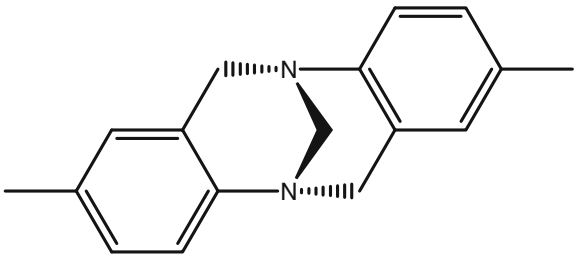

Fig. 2 Structure of Tröger's base

^{1}H- and ^{13}C-NMR

Cocaine hydrochloride is readily soluble in water and a large variety of organic solvents. Cocaine is known also for its exceptional capacity to cross biological membranes (nasal membrane and brain-blood barrier). There is substantial evidence (^{1}H- and ^{13}C-NMR) that cocaine undergoes a dramatic conformational change when passing from water to an organic solvent (CD_2Cl_2) to water. ^{13}C-NMR δ for the methyl ester C=O shifts from 175.71 ppm (D_2O) down to 170.08 ppm (CD_2Cl_2), while the benzoate C=O shifts from 169.11 ppm (D_2O) down to 165.89 ppm (CD_2Cl_2) (Glaser *et al*., 1988).

Interestingly enough, both carbonyl moieties are affected, the methyl ester ($\Delta\delta$ 5.63 ppm) more significantly than the benzoate ($\Delta\delta$ 3.22 ppm). The latter value appears "regular" or as expected ($\Delta\delta$ 3.90 ppm) for methyl acetate (Gottlieb *et al*., 1997).

A similar picture emerges when looking at the methylammonium N–CH_3 signal. The impact of this eventful conformational change is even more dramatic ($\delta\Delta$7.42 ppm) (Avodovich and Neville, 1983; Baker and Borne, 1978; Carroll *et al*., 1982).

Molecular modeling

Using molecular simulation techniques, we have tried to substantiate the hypothesis of hydrophobic collapse undergone by the protonated form of cocaine using molecular dynamics and semi-empirical quantum calculation (mainly AM1, also PM3) performed on the species **1a** and **1b** and ab initio quantum calculation (6–31G***) performed on the model compound **2** in which for simplifying cocaine's structure and consequently speeding up calculation the phenyl group of the benzoyl side-chain was substituted by hydrogen.

Equilibration between **1a** and **1b** (Fig. 1) is expected to take place via the free base species with pyramidal inversion of the nitrogen. The energy difference ($\Delta\Delta$Hf) between **1a** and **1b** was found to be 7.9 kcal/mol (AM1) and 6.7 kcal/mol (PM3) always in favor of **1a**. A rather similar figure ($\Delta\Delta$Hf = 7.2 kcal/mol) was found using ab initio quantum (6–31 G***) along with PM2 energy correlation). Species **1a** forming an internal hydrogen bond between the methylammonium and the methyl ester is thus favored in vacuo and has also been found in the solid state (Wood *et al*., 2008) as well as in solution in CD_2Cl_2 (Glaser *et al*., 1988). On the other hand, structure **1b** is expected to be the predominant species in water as the acidic hydrogen bond donor N^+–H can be more readily solvated by water. Using the OPLS force-field (molecular mechanics), we found out that when inserted in a water box, **1b** indeed interacts with the solvent by forming extensive H bonds more readily than **1a**. A molecular electrostatic potential (ESP) map of the internally hydrogen-bonded **1a** structure was acquired under AM1 and showed a continuum of high electron density in the central part of the molecule around the methyl ammonium and the two ester moieties. This picture is consistent with the picture of the ammonium being locked between the two C=O and forming a strong primary H bond (termed "canonical" by Thomas A) with the methyl ester and a weaker secondary H bond ("non-canonical") with the benzoate ester (Thomas *et al*., 2001; Vargas *et al*., 2000). This view is consistent with the high $\Delta\Delta$Hf value observed above.

Discussion

Stereostructure—Activity Relationship. Importance of Ammonium N–H Direction

In the case of opioid compounds, there is a consensus nowadays to accept that a specific spatial orientation of the N–H linkage can have a deep impact of the interaction

ligand–receptor. In particular, in the case of rigid opioid ligands, there is strong evidence that a specific spatial orientation of the nitrogen feature in respect of the rest of the molecule, and notably the aromatic group, is important for a productive interaction of the ligand with the receptor.

This feature was already recognized by (Belleau and Morgan, 1974) who drew attention to this aspect when he discovered that racemorphan analog **3** was devoid of analgesic agonist or antagonist activity, while compound **4** retained analgesic activity. (Belleau *et al*., 1974) attributed the inactivity of **3** to the inappropriate nitrogen lone-pair orientation or alternatively to incorrect ammonium–hydrogen bond orientation as shown in the Fig. 3.

To our pleasure, we were pleased to note that NMR and molecular modeling provide the same picture and substantiate the prevalence of **1a** in the biological medium. ^{1}H and ^{13}C NMR slow exchange spectra of atropine sulfate/mesylate, homatropine hydrobromide, and benztropine mesylate solutions concur in showing that at equilibrium the equatorial:axial N–CH_3 diastereomeric mixt. was ~7:1 (D_2O) and 18:1 (CD_2Cl_2). A similar preponderance of equatorial N–CH_3 diastereoisomer was observed for cocaine salts in both solvents (only equatorial isomer noted in D_2O ^{13}C NMR spectrum, ~18:1 equatorial:axial ratio found in CD_2Cl_2) (Pedersoli *et al*., 2008).

According to (Testa 2000), mathematical approach allows one to derive the optimum value of log P for transport to a given location within the time frame of a biological assay. Evidence for an optimum lipophilicity for CNS drugs was already found in 1968 by Hansh who was then able to assert that for drugs to gain rapid access to the CNS, they should preferably have a logP value typically in the vicinity of 2.0. Subsequently, further investigations in different classes of CNS agents led to the "Principle of Minimum Hydrophobicity in Drug Design". The ideal drug candidate to successfully reach clinical studies should have been designed with the idea of keeping lipophilicity as low as possible, provided this can be done without loss of affinity to the target receptor. The requirement of minimal lipophilicity derives from the dilemma that a drug must be capable of delivering a dense message toward the biological target—i.e., the drug should be able to convey rich transactions (in other words, information-rich pharmacophore)—while still being able to transport itself to the relevant biosystem. The "Principle of Minimum Hydrophobicity" goes far beyond the nowadays illustrious Rule of 5—as formulated by Lipinski—or the subsequently Weber's rule, which are more latitudinarian in terms of hydrophobicity (Lipinski *et al*., 2001; Weber, 1996).

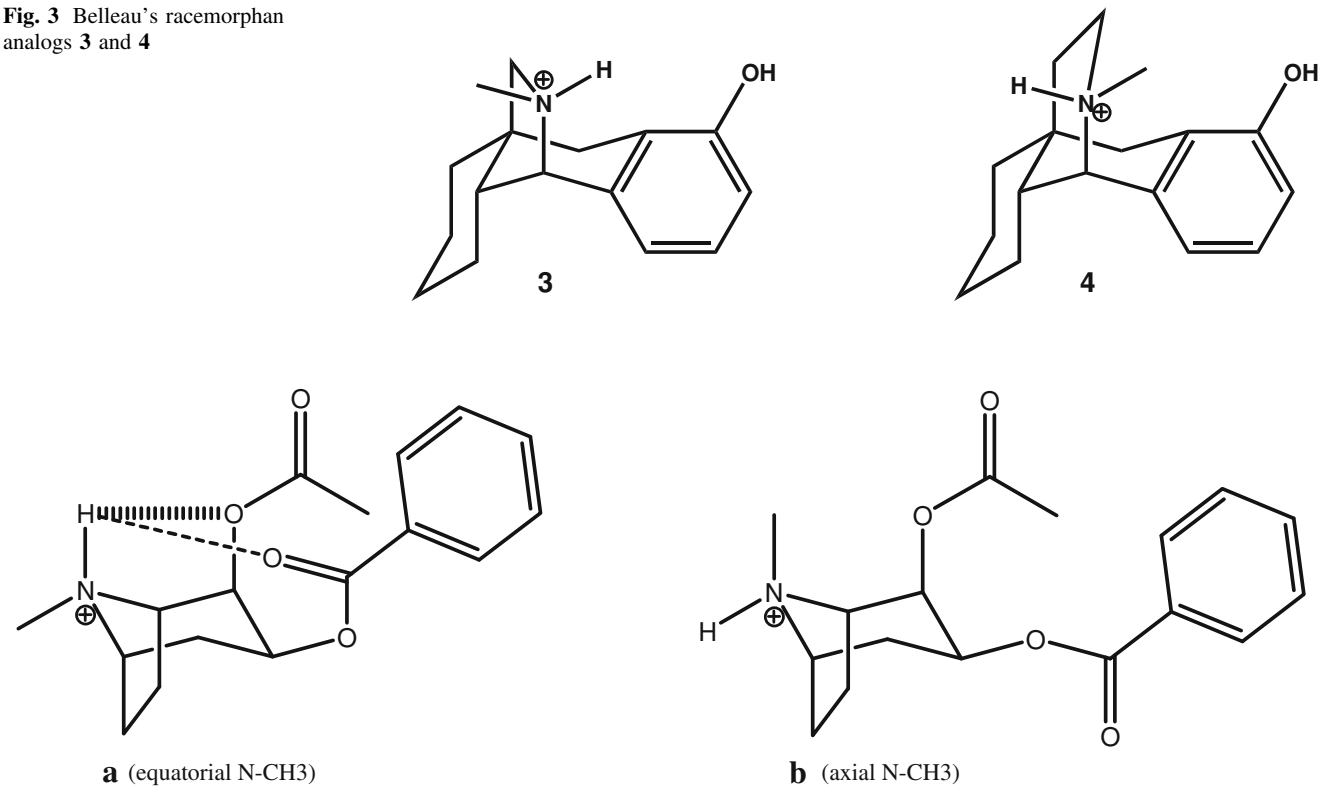

Fig. 3 Belleau's racemorphan analogs **3** and **4**

Fig. 4 Representations of **1a** and **1b**. The internally hydrogen-bonded compact nitrogen configuration **1a** (*right*) shows two types of hydrogen bonds (ıııııı classical hydrogen bond is termed canonical by Thomas A; - - - - - - non-classical or secondary hydrogen bond). The conformationally-extended nitrogen configuration **1b** (*left*) is more pharmacologically relevant

Cocaine can be regarded as a "Janus" molecule. In the Roman mythology, Janus is the god of beginnings and transitions; he is usually represented as a two-faced god since he looks both to the future and the past. In analogy, we propose that the internally hydrogen-bonded configuration **1a** is important for transport as a consequence of hydrophobic collapse, while configuration **1b** is more pharmacologically relevant because the N–H bond is looking outward allowing clastic (Belleau and Morgan, 1974; Belleau *et al*., 1974) binding to take place with a hydrogen bond accepting moiety present in the receptor or enzyme proteins. Since, for cocaine, the pharmacophore (responsible for the pharmacological effect(s)) and the vector (group of atoms responsible for the ADME properties) moieties are embedded in the same molecular scaffold, we can speak of "molecular concision." Indeed, to become druggable, any pharmacomolecule must be able to accomplish two tasks: the first one is to reach the critical biophase where the target is located; and the second one is to be recognized by the biological target. These two events are critical to produce macroscopic therapeutic effects. By "clastic," we intend the property of a molecular system made of separate entities that fuse to form a new-born functional self-contained organization. This definition is a re-formulation of the concept defined by (Kolb 1987, 1984) Fig. 4.

Conclusion

Conclusively, based on a line of experimental evidence (logP, pKa, ^{1}H-, and ^{13}C-NMR, molecular modeling studies), it appears that cocaine undergoes a hydrophobic collapse which may account for its unprecedented ADME properties, in particular, its exceptional capacity to cross biological membranes (nasal membrane and brain-blood barrier). Cocaine represents the prototypical example of a drug molecule with high degree of druggability owing to low molecular weight (303.4 da), low lipophilicity ($\log D = 1.0$), and low heteroatom content ($n = 5$) along with high chemical information. Cocaine is the perfect achievement of molecular concision because pharmacophore and vector are intimately embedded in the same molecular scaffold. As a social drug, cocaine is not far from the ideal drug as formulated by Prof. Bernard Testa.

§ This paper is dedicated to Prof. Philip S. Portoghese of the University of Minnesota for his multiple accomplishments and spirit in medicinal chemistry.

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