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Short communication

On the interactions of catecholamines with *N*-methylnicotinamide cation: a UV spectral study

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Summary — The associations between catecholamines and an appropriate aromatic π-electron acceptor (*N*-methylnicotinamide cation) have been studied as models allowing, through stacking interactions, understanding of the contribution of the catechol moieties to the drug affinity to receptor sites.

Apparent association constants and enthalpies of various complexes have been determined by UV absorption spectroscopy. The experimental results suggest that catechol rings significantly and specifically contribute to the receptor affinity of catecholamines.

Résumé — Sur les interactions des catécholamines avec le cation *N*-méthylnicotinamide : une étude par UV. *On a étudié les associations des catécholamines avec un accepteur aromatique d'électrons π (cation de N-méthylnicotinamide) comme modèles moléculaires permettant de mieux comprendre la contribution du noyau du catéchol à l'affinité pour les récepteurs. On a aussi déterminé par UV les constantes et les enthalpies apparentes d'association de quelques complexes. Les résultats expérimentaux suggèrent que le noyau du catéchol contribue de façon significative et spécifique à l'affinité des catécholamines pour les récepteurs.*

charge–transfer interactions / stacking / apparent association constants / thermodynamic parameters / catechol

Introduction

It is well known that the pharmacological activity of a drug, and consequently the interaction at the molecular level between a drug and a receptor, is a result of several contributions each involving different portions of the interacting structures. Correlations between structural features of a given set of molecules and binding forces or interactions with the receptor are possible [1]. Catecholamines are believed to interact with adrenergic receptors at 3 binding sites involving the following molecular portions of the drugs: the ammonium cation, the catechol moiety and the eventual β-hydroxy group [2]. The function of the catechol aromatic nucleus is 2-fold: a) to determine the type of drug activity [3, 4] (if in a given molecule the aromatic ring is *p*- and *m*-OH substituted, agonist character will most likely prevail); b) to contribute to the drug affinity for the receptor in addition to the primary contribution of the cationic side chain.

Several investigations of complex formation in aqueous solution between catecholamines and adenine nucleotides, particularly ATP [5], have provided insights into the role of the different molecular portions of the whole interacting systems. The following types of interactions are known to contribute to the association: a) stacking between the catechol and the purine rings; b) hydrogen bonding between catechol hydroxyls and purine nitrogens; c) electrostatic attraction between the protonated ammonium cation and the negative phosphate group.

For a better understanding of the specific contribution of the aromatic moiety to the affinity for the receptor site (*i.e.*, to better analyse the contribution of a single type of interaction to the whole binding process) we have studied a series of π-complexes between some catecholamines and a model compound simulating only the flat portion of the receptor site where π-π interactions are effective. In particular we present here quantitative characterization of stacking between some catecholamines (Table I) and an appropriate aromatic π-electron acceptor. The *N*-methylnicotinamide cation, C, has been chosen since a new absorption band, assigned to an intermolecular charge–transfer transition, is present in the electronic absorption spectra of each system considered; this allows the spectrophotometric determination of apparent association con-

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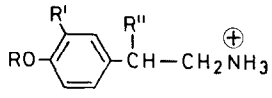
stants and related thermodynamic parameters. In addition, C does not self-associate and its structure is pH independ-ent.

Table I. Compounds studied in the present work[a].



Compound	Abbreviation	R	R'	R''
Tyramine	T	H	H	H
Octopamine	O	H	H	OH
Dopamine	D	H	OH	H
Norepinephrine	N	H	OH	OH
4-Methoxyphenylethylamine	MeT	CH_3	H	H
3,4-Dimethoxyphenylethylamine	MeD	CH_3	CH_3O	H

[a]Phenethylamine, a compound without ring substituents, is not included in the present study since it is a weaker π-electron donor in comparison with the studied catecholamines (see its value of the gas-phase ionization potential [7]). Consistently, the electronic absorption spectra of a system containing phenethylamine and the *N*-methylnicotamide cation do not show π-π charge–transfer bands and no thermodynamic parameters are obtainable through UV spectra.

Results and Discussion

Apparent equilibrium constants, K^{AD}, and association enthalpies, ΔH^o, have been obtained spectrophotometrically (see Experimental protocoles) assuming a 1:1 molecular association [6] and are reported in Table II.

Their values at pH 1 show that the affinities to the receptor site model of the aromatic rings of the examined catecholamines are of the same order of magnitude. An effect of the number of OH groups present in the catechol moieties and a significant contribution of the β-OH substitution of the lateral chain are, however, evident. This is a consequence of the known influence of the OH groups on the π-electon donor character of the aromatic ring [7].

Differences in the behaviour of various conformers are not to be expected since the near equivalence in electronic terms of the catechol ring of dopamine conformers has been proposed [8].

Association constants at physiological pH (when the ammonium group is still cationized [9]) would be more appropriate, but their determination is hindered in some cases (D and N) by oxidation processes involving the phenolic groups. These experimental difficulties are avoided by using stable *O*-methylated derivatives but with the reservation that the corresponding absolute K^{AD} values might be different from those of non-methylated compounds. As shown by the numerical values presented in Table II, methoxyl groups in the aromatic ring have some influence on its "affinity to the receptor site" [4].

Data obtained at pH 7 (see Table II) indicate that K^{AD} values appreciably increase at neutral pH.

ΔH^o values have been obtained through van't Hoff plots for apparent association constants. Their sign is equal to

Table II. Apparent equilibrium constants (K^{AD} M^{-1}), association enthalpies (ΔH^o kcal mol^{-1}) for 1:1 catecholamines (see Table I) and *N*-methylnicotinamide cation (C) association at 28°C.

Complex	pH=1		pH=7	
	K^{AD}	ΔH^o	K^{AD}	ΔH^o
T-C	0.22	−2.4	1.1	−2.5
O-C	0.57	−2.6	0.84	−2.3
D-C	0.68	−3.2	–	–
N-C	0.77	−3.8	–	–
MeT-C	0.17	−2.7	0.26	−2.0
MeD-C	0.62	−3.2	1.35	−3.2

that found for association of purines, *etc.* [5]. The trend observed in the thermodynamic parameters upon substitution of hydroxyl group in the molecules interacting with C is analogous, particularly at pH 1, to that obtained for catecholamine–ATP complexes which are stabilized by the previously mentioned 3 types of interactions.

The above results suggest that the aromatic rings significantly and specifically contribute to the receptor affinity of catecholamines.

Experimental protocols

Material

All the compounds used in this work were hydrochlorides (reagent grade commercial products) or salts prepared from the free bases as described previously [6].

UV measurements

The absorption spectra were obtained with a Varian 2200 spectrophotometer at controlled temperatures (±0.1°C). Procedures and spectral analysis were as in the previous paper [6].

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