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Hallucinogenic Receptor Models: Interaction of Imidazolium Chloride with Amphetamine Analogs

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SUMMARY

The interactions of several hallucinogenic phenethylamines with the biologically relevant electron acceptor imidazolium chloride have been investigated by monitoring phenethylamine ^{1}H NMR chemical shift changes upon complex formation. Methoxy- and methylenedioxy-substituted phenethylamines interact with imidazolium chloride to form weak charge-transfer complexes that have a relatively narrow range of association constants. The results indicate the formation of a ternary complex in which a chloride ion is hydrogen bonded to a N^+H side chain proton of the drug and a NH imidazolium proton. The imidazolium ring is positioned above a nonsubstituted *ortho*-position of the aromatic ring. Spectral assignment of the two diastereotopic benzylic protons allowed the geometry of the complex to be defined in more detail. Complexation occurs preferentially on that side of the phenethylamine molecule that allows the side chain α-methyl group to face away from the chloride ion and the imidazolium ring. The drug molecule exists in the complex in the preferred *trans* conformation. The biological relevance of this model is discussed.

Early quantitative structure-activity relationship studies of hallucinogenic phenethylamines and tryptamines have shown correlations between high activity and a high energy highest occupied molecular orbital (1-3). More recent theoretical studies by Weinstein *et al.* (4-7) have examined the interaction at the serotonin (5-HT) receptor by modeling the interactions between (a) the protonated amine side chain of the drug and a negative site at the receptor and (b) the aromatic ring of the drug and the 5-HT receptor. The aforementioned computational results have been interpreted as evidence for the formation of a charge-transfer complex by electron donation by the drug molecule to an acceptor component of the receptor active site (1-9). In a recent quantitative structure-activity relationship study of 63 phenalkylamines, however, Clare (10) reported that the activity is better correlated with either the lowest unoccupied π orbital energy or the energy difference between the lowest unoccupied π orbital and the highest occupied π orbital. Although the physical significance of the latter idea is not clear, Clare (10) suggests that the former is consistent with the formation of a charge-transfer complex in which the drug molecule accepts electrons.

In light of these recent computational results, we felt that further experimental investigation was merited. In this study, we have focused our investigation on charge-transfer complexes between several phenethylamines and a model electron acceptor. Hallucinogenic amphetamines have previously been shown to form reversible complexes with the model electron acceptor 1,4-dinitrobenzene, with a modest correlation between complex formation and psychotomimetic activity (11). Although these results have provided experimental evidence for the electron-donating ability of the drugs, there probably exists a large discrepancy between the structural features of this model electron acceptor and those of the acceptor component of the receptor active site. We thus felt that experiments with physiologically more relevant electron acceptor models should provide more realistic models for the hallucinogenic receptor protein. Amino acid residues that can act as potential electron acceptors are the imidazolium ring in histidine, the guanidinium group in arginine, and a protonated terminal α-amino group. Of these, the histidyl imidazolium residue represented the best candidate.

Intra- and intermolecular complexes between imidazolium derivatives and electron-rich indole analogs have been carefully studied by Shinitzky and Katchalski (12). Their findings suggest that the complex formed is of the charge-transfer type, similar to the well known indole-pyridinium complex (13). The electron-accepting imidazolium cation has been used as a model for the 5-HT receptor in several computational studies (4-9). For example, a careful and particularly revealing theoretical study by Weinstein *et al.* (4) examined intermolecular complexes between imidazolium cation and several tryptamines. In that study, Weinstein *et al.* (4) concluded that the binding

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ABBREVIATION: 5-HT, 5-hydroxytryptamine.

forces between the indole and imidazolium moieties are strongly dependent on orientation.

In this report, we investigate the interaction of several hallucinogenic amphetamines with imidazolium chloride in solution, by ^{1}H NMR spectroscopy. We report here the association constants for complex formation, which reflect the relative affinity of the drug's aromatic ring for the acceptor molecule. We also provide information about the three-dimensional geometry of the complex formed. Such an approach allows us to assess the directional effects exerted by the aromatic ring and the side chain during complex formation and thereby gain insights into the molecular mechanism of action of these drugs.

Intermolecular complex formation between electron donor and electron acceptor molecules can be conveniently followed by ^{1}H NMR spectroscopy. The interaction between donor and acceptor induces changes in the ^{1}H NMR chemical shifts of both molecules. Generally, the rate of exchange between the free and complexed molecules is fast on the NMR time scale and thus the experimentally measured chemical shift is the weighted average of chemical shifts for the free and complexed states. The concentration dependence of the chemical shift changes for different protons of a given molecule allows the determination of association constants (14–19).

Studies of drug-electron acceptor interactions have been conducted using an excess of the donor compound (11, 14–16). In our study, however, we have chosen the reverse system (18). By adopting this procedure, it is possible to detect changes in chemical shift for several protons within the drug molecule. Differences in magnitude and direction of the chemical shift changes for the individual protons can then provide topological information regarding the orientation of the aromatic ring of the amphetamine with respect to the imidazolium ring. Additionally, the use of very low drug concentrations minimizes self-association of the drug molecules. Self-association, such as that observed for mescaline hydrochloride (20), hampers not only the determination of association constants but also the interpretations concerning the geometrical aspects of the drug-electron acceptor interaction.

The experimental results of this study were analyzed according to a method developed by Dimicoli and Helene (18). The use of this method assumes interaction of a donor molecule with a self-associating acceptor, present in excess, to form a 1:1 reversible complex. Complex association constants (K_c, in M^{-1}) were then calculated using eq. 1

$$\Delta D_{obs}/[A_o] = [-(K_C - K_S)\ DD_{obs}] + [(K_C/(K_C - K_S))\ \Delta D_{AD}] \quad (1)$$

where ΔD_{obs} (in Hz) is the observed change in chemical shift of a given donor proton in the presence of the acceptor molecule (i.e., the weighted average chemical shift of the donor proton for the free and complexed states) relative to the chemical shift of that donor proton in the absence of the acceptor molecule, ΔD_{AD} (in Hz) is the change in chemical shift of the donor proton in the pure complex relative to the chemical shift of that proton in the absence of the acceptor molecule, K_S (in M^{-1}) is the self-association constant of the acceptor molecule, and $[A_o]$ (in M) is the concentration of the acceptor molecule. A plot of $\Delta D_{obs}/[A_o]$ versus ΔD_{obs} gives a straight line with a slope of $(K_s - K_c)$. In order to determine the value of K_s, the ^{1}H NMR chemical shifts of acceptor molecule protons were measured as a function of varying acceptor concentration and the results then were analyzed according to eq. 2 (18, 20),

$$\Delta A_{obs}/[A_o] = 2\ K_s\ \Delta A_2 \quad (2)$$

where $[A_o]$ represents the concentration of acceptor molecules, ΔA_{obs} is the observed chemical shift for a given acceptor proton, and ΔA_2 is the shift for the same proton in a dimer, both measured relative to the extropolated $[A_o] \rightarrow 0$ monomer shift for that proton. A plot of $(\Delta A_{obs}/[A_o])1/2$ versus ΔA_{obs} gives a straight line with a slope and an x-intercept of $-(K_s/2\Delta A_2)$ and $2\Delta A_2$, respectively.

Experimental Procedures

Materials. Imidazolium chloride was prepared by the addition of imidazole (Sigma Chemical Co., St. Louis, MO) to an ethereal hydrochloric acid solution. The resulting precipitate was filtered and then recrystallized in isopropanol. Imidazolium and drug nitrate salts were prepared by the addition of equivalent amounts of dilute nitric acid to the free bases of each compound. After evaporation of solvent, the resulting nitrate salts were purified by recrystallization in isopropanol. Amphetamine hydrochloride (**11**) was purchased from Sigma. The hydrochlorides of 2,3,4-trimethoxyamphetamine (**1**), 3,4,5-trimethoxyamphetamine (**6**), and 2,3-methylenedioxy-4-methoxyamphetamine (**8**) were provided by Dr. A. T. Shulgin (University of California, San Francisco). The compounds 2,3,4-, 2,4,5-, and 3,4,5-trimethoxytoluene (**12–14**) were obtained from Dr. D. E. Nichols of Purdue University. The remaining drugs were obtained from the Drug Supply Program of the National Institute on Drug Abuse (Bethesda, MD).

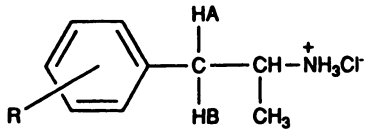
^{1}H NMR spectra. The high resolution ^{1}H NMR spectra were recorded with a Bruker WH-270 NMR spectrometer equipped with an Aspect 2000 computer and operating at a frequency of 270.13 MHz. The NMR samples were prepared in deuterated methanol (Aldrich Chemical Company, Milwaukee, WI) as 0.01 M solutions of drug hydrochloride or nitrate salt with various concentrations (0.0–0.8 M) of the imidazolium chloride or imidazolium nitrate salts. The chemical shifts are reported in Hz and were measured relative to the internal standard tetramethysilane. All spectra were recorded at a constant 298°K.

Results and Discussion

Addition of imidazolium chloride to the methoxyamphetamine hydrochlorides **1–10** resulted in a concentration-dependent shift to higher frequency for all drug proton NMR resonances (Table 1). These results are shown graphically in Fig. 1 for proton H_6 of 2-methoxy-4,5-methylenedioxyamphetamine (**10**). As Fig. 1 shows, increasing concentrations of imidazolium chloride induce a downfield shift for H_6, with a maximal change in chemical shift of 15.2 Hz at a 0.8 M concentration of acceptor. Table 1 lists selected chemical shift changes and association constants for all the phenethylamines. The chemical shift changes reported are for those protons that experience the most pronounced change in chemical shift. The changes in chemical shift for the individual protons of each drug molecule are given as a percentage of the value for that proton with respect to the maximal change in chemical shift for each compound. For example, in the case of 2,3,4-trimethoxyamphetamine (**1**) the maximal change in chemical shift is 26.1 Hz for proton H_A, whereas the chemical shift changes of H_5, H_6, and H_B are 25%, 66%, and 51% of that value, respectively. Also listed in Table 1 are the association constants of complex formation, K_c[13]. In order to calculate K_c, a value of K_s of 0.2 M^{-1} was used in eq. 1.

TABLE 1

Association constants (K_c) for complex formation and chemical shift changes of phenethylamine protons as a percentage of the maximal value observed



	R	K_c	Maximal shift	Change							
				Aromatic ring					Side chain		
				H_2	H_3	H_4	H_5	H_6	H_A	H_B	CH_3
		M^{-1}	Hz	% of maximum							
1	2,3,4-Trimethoxy	1.6	26.1				25	66	100	51	38
2	2,4,5-Trimethoxy	2.0	24.1		18			100	85	58	38
3	2,5-Dimethoxy-4-bromo	1.9	29.8		3			100	74	56	34
4	2,5-Dimethoxy-4-methyl	1.9	23.9		8			100	92	62	43
5	4-Methoxy	1.7	36.1	39	5		5	39	100	30	27
6	3,4,5-Trimethoxy	1.7	37.6	63				63	100	31	25
7	3,5-Dimethoxy-4-ethoxy	1.8	37.9	62				62	100	32	23
8	4-Methoxy-2,3-methylenedioxy	1.9	22.8				13	66	100	45	40
9	3-Methoxy-4,5-methylenedioxy	1.7	38.7	68				33	100	30	27
10	2-Methoxy-4,5-methylenedioxy	1.9	20.2		5			75	100	58	47
11	None (amphetamine)	0.6	18.8	15	15	15	15	15	100	77	30

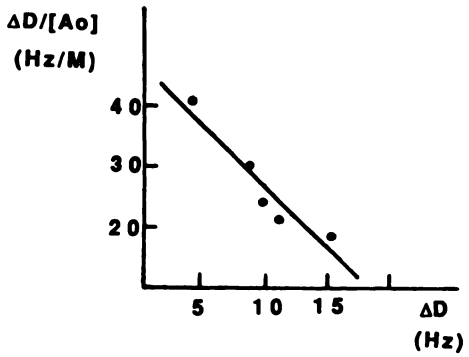


Fig. 1. Graphical representation of complex formation between 2-methoxy-4,5-methylene-dioxyamphetamine (**10**) and imidazolium chloride, plotted as the change in chemical shift for drug proton H_6 (Hz)/concentration of imidazolium chloride (M) versus the change in chemical shift (Hz) for H_6. The NMR samples were prepared in CD_3OD as a 0.01 M solution of drug or a 0.1 M solution of drug with 0.1 M, 0.3 M, 0.4 M, 0.5 M, or 0.8 M imidazolium chloride.

This value is an upper limit determined as described above using eq. 2. The low K_c value is a reflection of the relatively low affinity of imidazolium chloride for self-association in methanol.

As shown by the data, the individual protons of a given drug molecule are each affected differently by the presence of the electron acceptor molecule. A generally observed trend for all the methoxy- or methylenedioxyphenethylamine analogs is that the protons with the most pronounced changes in chemical shift are the *ortho* aromatic protons (H_2 and H_6) and the side chain protons (H_A, H_B, and CH_3). Of these, the two benzylic side chain protons, H_A and H_B, are diastereotopic. Their respective chemical shifts have been assigned unambiguously by comparison with the ^1H NMR spectra of stereospecifically ^2H-labeled analogs (21). The chemical shift changes of H_A are of much greater magnitude than those of H_B for all drug molecules studied. For the unsubstituted amphetamine hydrochloride (**11**), there are no significant chemical shift changes for the aromatic protons. Large changes in chemical shift are, however, observed for the side chain protons.

The chemical shift data of Table 1 indicate that methoxyamphetamines **1–10** interact with imidazolium chloride to form complexes that involve both the electron-rich aromatic ring and the phenethylamine side chain. Interaction between imidazolium chloride and the side chain of the drug molecule presumably occurs at the protonated amino group. In the case of amphetamine, **11**, the chemical shift data suggest that, because the aromatic ring of the drug is not activated by the presence of electron-donating groups, the interaction between the drug and imidazolium chloride occurs predominantly at the ammonium head.

The calculated association constants for the methoxy- and methylenedioxyamphetamines fell within a very narrow range (K_c = 1.6–2.0 M^{-1}). These values indicate relatively weak complex formation.

Role of the chloride ion. The chloride ion is capable of ion pair formation in nonaqueous solvent. In order to probe its possible role in complex formation, we performed parallel complexation experiments using the nitrate salts of imidazole and a representative methoxyamphetamine (**9**). Nitrate has a much curtailed ability to form ion pairs, compared with the chloride anion. The results of this parallel study are represented graphically in Fig. 2 and the chemical shift changes are listed in Table 2. The data show that complex formation between amphetamine and imidazolium nitrate induces much smaller changes in the chemical shifts of the individual drug protons. The association constant for complex formation is less than half the value for complexes involving the chloride ion, indicating much weaker complex formation. These results suggest that the ability to form ion pairs is an important aspect of an interaction between an acceptor molecule and hallucinogenic amphetamines.

Role of the side chain. The chemical shifts of the side chain protons are greatly affected by interaction with the acceptor, and the side chain is assumed to have very significant

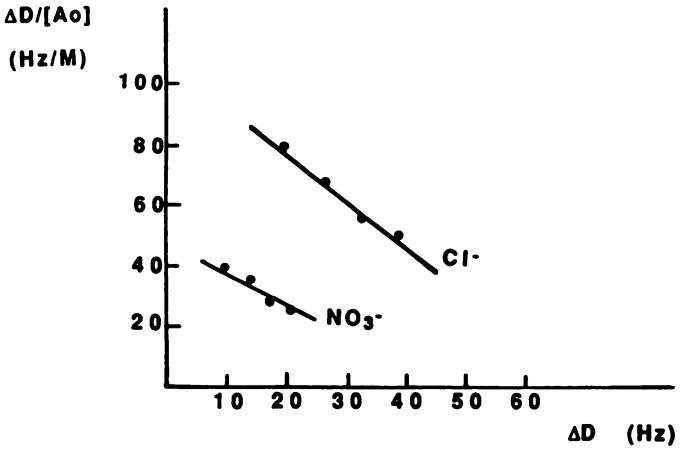
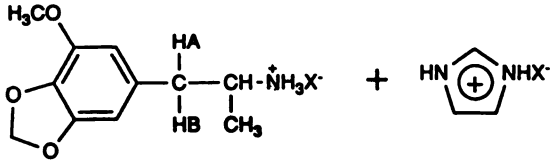


Fig. 2. Graphical representation of complex formation between 3-methoxy-4,5-methylenedioxyamphetamine (**9**) and imidazolium chloride or imidazolium nitrate, plotted as the chemical shift change for drug proton H_6 (Hz)/concentration of the acceptor (M) versus the chemical shift change for H6 (Hz). The NMR samples were prepared in CD_3OD as a 0.01 M solution of drug with 0.2 M, 0.3 M, 0.6 M, or 0.8 M imidazolium chloride or nitrate.

TABLE 2

Maximal change in chemical shift for protons of 3-methoxy-4,5-methylenedioxyamphetamine (9) (0.01 M in CD_3OD) upon interaction with imidazolium chloride (0.8 M) or imidazolium nitrate (0.8 M)



X	Maximal shift					K_c
	H_2	H_6	H_A	H_B	CH_3	
			Hz			M^{-1}
Cl^-	26.4	12.9	38.7	11.7	10.6	1.7
NO_3^-	6.6	1.5	8.4	5.1	2.2	0.8

participation in complex formation. Thus, the question of its possible involvement in orienting the imidazolium acceptor on the surface of the drug aromatic ring must be addressed. In order to obtain information on this aspect of complex formation, we carried out parallel experiments substituting the methoxyamphetamines (**1**, **3**, and **6**) with the corresponding methoxy toluenes (**12–14**). The results of these complexation experiments are summarized in Table 3. For the methoxyamphetamines, interaction of imidazolium chloride with the aromatic ring of the drug occurs predominantly at the *ortho* position. For the methoxytoluenes ($K_c^{13} = 0.7\ M^{-1}$), the interaction is no longer restricted to the *ortho* positions. In the case of unsymmetrically substituted **13** and **14**, for example, two types of complexes apparently form, each centered at each of the unsubstituted ring positions. Compound **15**, because of its symmetry, provides opportunity for only one type of interaction. The aforementioned results suggest that the phenethylamine side chain exerts a strong orienting influence during the complexation of the imidazolium and phenethylamine rings.

Preferred side chain conformation. The measurement of ^1H-^1H vicinal coupling constants (^3J) remains an important and direct method used in the conformational analysis of small

TABLE 3

Drug aromatic ring interaction: maximal chemical shift changes for several methoxyamphetamines and their corresponding methoxytoluenes

NMR samples were prepared in CD_3OD as 0.01 M methoxyamphetamine or methoxytoluene with 0.1 M, 0.3 M, 0.4 M, 0.5 M, or 0.8 M imidazolium chloride. The maximal chemical shift changes were measured at an acceptor concentration of 0.8 M.

Compound	Maximal shift							K_c
	H_2	H_3	H_4	H_5	H_6	OCH_3	CH_3	
					Hz			M^{-1}
2,3,4-Trimethoxy-toluene				3.0	6.3	2.9		0.0 0.7
amphetamine				6.6	17.3	2.6, 3.7, 2.3		1.6
2,4,5-Trimethoxy-toluene		7.3			5.9	5.9, 5.9, 4.4	1.5	0.7
amphetamine		4.4			24.1	4.8, 6.2, 5.8		2.0
3,4,5-Trimethoxy-toluene	5.9				5.9	5.9 (m), 3.7 (m)	3.7	0.7
amphetamine	23.5				23.5	6.2 (m), 2.6 (m)		1.7

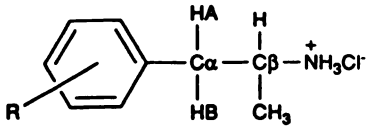
molecules. This method is based on the Karplus equation, which relates ^3J values to the corresponding dihedral angles (22–24). By using this approach, conformational changes in the phenethylamine side chain can be followed by observing changes in the vicinal coupling constants between the β-benzylic protons and the α-methine proton. The two β-benzylic protons of the phenethylamines constitute the AB portion of an ABC spin system. Initial estimates of the spectral parameters were obtained by standard methods (23), assuming that the corresponding spectra were approximately ABX. The parameters were then refined by spectral simulation and iteration using the Nicolet ITRCAL program. The coupling constants thus obtained were considered to be average values arising from a mixture of possible staggered rotamers. The relative population of each rotamer was then extracted by simple analogies, which include J_g and J_t terms for the coupling constants of perfectly staggered *gauche* and *trans* vicinal protons (24).

With amphetamine salts in solution, the two principal staggered conformers are ones in which the ammonium group is antiperiplanar with the phenyl ring (*trans*) and one in which the ammonium group is synclinical with the phenyl ring while the methyl group is antiperiplanar (*gauche*) (25). Listed in Table 4 are representative examples describing the changes in amphetamine conformer ratio upon addition of imidazolium chloride. The data show that there is an increased preference for the *trans* conformer in the presence of imidazolium chloride, which suggests that this conformer is also involved in the formation of the most stable complex.

Ternary complex. The results described above provide evidence that electron-rich phenethylamines in methanol form ternary complexes with the imidazolium cation and the chloride anion. In this complex, the chloride ion is hydrogen bonded to a N^+H phenethylamine proton and a NH imidazolium proton. Simultaneous chloride hydrogen bonding with two or three protons is frequently encountered in the crystal structure of amine hydrochlorides (26). The imidazolium ring is positioned on the unsubstituted *ortho* position of the aromatic ring while the phenethylamine side chain maintains a *trans* orientation. The observed differences in chemical shift changes between the two diastereotopic benzylic protons provide us with more detailed information on the geometry of the complex, because the magnitude of the chemical shift change is an indication of the

TABLE 4

Influence of complex formation with imidazolium chloride on the $^3J_{AX}$ and $^3J_{BX}$ coupling constants and rotamer distribution (P) about the Cα-Cβ bond



Compound	$[A_0]^a$	$^3J_{AX}$	$^3J_{BX}$	P(trans)	P(gauche)
	M	Hz	Hz		
1	0.0	7.7	6.4	0.56	0.39
	0.8	8.1	5.9	0.61	0.32
2	0	6.9	7.1	0.45	0.48
	0.8	7.0	6.2	0.47	0.36
7	0.0	7.3	6.8	0.51	0.44
	0.8	7.9	6.4	0.59	0.39
8	0.0	7.7	6.6	0.56	0.41
	0.8	8.1	6.2	0.61	0.36
9	0.0	7.7	7.0	0.56	0.47
	0.8	8.1	6.2	0.61	0.41
10	0.0	6.9	6.7	0.45	0.43
	0.8	7.3	6.4	0.51	0.39

[a] As defined in eq. 1.

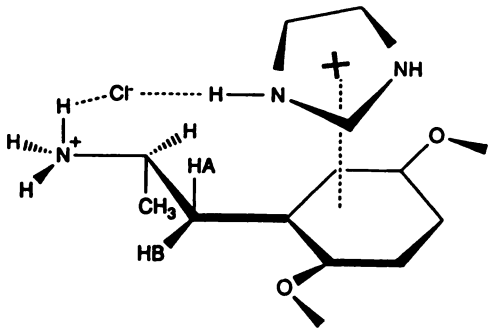


Fig. 3. Complex formation between phenethylamine and imidazolium chloride. Complexation occurs preferentially on that side of the phenethylamine molecule that allows the side chain α-methyl group to face away from the chloride ion and the imidazolium ring.

proximity of the proton in question to the complexing imidazolium chloride (14, 15). The data indicate that complexation occurs preferentially on that side of the phenethylamine molecule that allows the side chain α-methyl group to face away from the chloride ion and the imidazolium ring (Fig. 3).

Conclusion

A likely sequence of events leading to the formation of the ternary complex involves initial complex formation between the phenethylamine ammonium head and the imidazolium cation through the intermediacy of the chloride anion. The imidazolium ring is then oriented on the electron-rich aromatic ring of the drug. The preference for the unsubstituted *ortho* position as the site of interaction is dictated (a) by the geometric constraints of hydrogen bond size and angle and (b) by a preference for alignment of its positively charged nitrogen atoms along the vector running between the high electron density 2,5-methoxy substituents. This last concept has been elaborated upon by Weinstein *et al.* (4–7) with tryptamine analogs.

It is tempting to speculate that a sequence of events similar to that described for the hallucinogenic receptor model is occurring at the serotonergic receptor active site. Initial interaction presumably occurs between the phenethylamine ammonium head and an anionic site at the 5-HT receptor (e.g., aspartate residue). In the model a N^+H proton is hydrogen bonded to the chloride ion. The next step involves charge-transfer complex formation between the electron-rich phenyl ring of the drug and a corresponding electron-deficient site of the receptor active site. This corresponds to the interaction between the drug and the imidazolium cation in the model. The geometry of alignment of the aromatic ring on the active site is to a large extent dictated by the initial electrostatic interaction. A favorable, or productive, alignment of the phenyl ring on the active site will depend on the nature and pattern of ring substituents. These will determine the electron density pattern of the aromatic ring and its steric features, which are a function of the conformational properties of the substituents.

The results for the pharmacologically inactive 2,3,4-trimethoxyamphetamine (**1**) are interesting. The 2,3-methoxy groups are in an out-of-plane conformation, which is presumably responsible for the lack of activity (27). It has been suggested previously that the receptor involved in the action of hallucinogenic amphetamines may include a relatively planar region that could interact with the aromatic portion of the drug, whereas some other portion of the receptor may fold over the drug molecule (28, 29). The steric bulk associated with an out-of-plane orientation may influence the ability of the drug aromatic ring to closely approach an electron acceptor at the receptor active site. Thus, it may be argued that the relatively small surface of the imidazolium ring is incapable of reflecting the steric demand of the active site and hence is unable to mimic the negative steric interactions operating between **1** and the hallucinogenic active site.

We are continuing our studies of hallucinogenic receptor models in order to better understand interactions between hallucinogenic methoxyamphetamines and the 5-HT receptor. Still under investigation are the roles of solvent and of the aromatic substitution pattern of the drug in the formation of a charge-transfer complex between the phenethylamines and the imidazolium cation. Also of interest is the impact of steric modifications of the imidazolium cation on the formation of a charge-transfer complex.

Acknowledgments

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