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Effect of 4-substitution on psychotomimetic activity of 2,5-dimethoxy amphetamines as studied by means of different substituent parameter scales

Kari Neuvonen,[a,*] Helmi Neuvonen[a] and Ferenc Fülöp[b]

[a]*Department of Chemistry, University of Turku, FIN-20014 Turku, Finland*
[b]*Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary*

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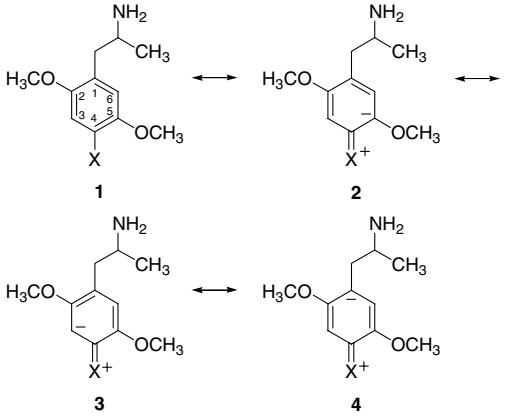
Abstract—Electron-withdrawing substituents at position 4 of 2,5-dimethoxy-substituted amphetamines increase, whereas electron-donating substituents decrease the psychotomimetic activity. The origin of this clearly localized effect is discussed. The uses of modified Hammett substituent scales (σ^- and σ^+), and especially the good σ^+ correlation, strongly suggest that electron-donating substituents decrease the biological activity through a specific effect relating to the extent of the conjugative electron release from the 5-methoxy group to the phenyl ring.

Hallucinogenic phenethylamines are a topic of continuous study. Amphetamines are known to function as agonists at the 5-HT_2 (serotonin-2) receptors. Activation of the 5-HT_{2A} (serotonin-2A) receptors by an agonist ligand has been established as the key pharmacological action of hallucinogenic drugs.[1] 2,5-Dimethoxyphenyl-substituted derivatives form one of the most noteworthy sets of amphetamines (cf. Structure **1**, Scheme 1). Investigations of structure–activity relationships have demonstrated that substituents in the *para* position relative to the aminopropyl side chain exert a marked effect on the hallucinogenic activity.[2–4] The most active compounds identified to date possess an alkyl, alkylthio or halogen group at position 4. The potency increases in the substituent sequence H < OR < SR < R < halogen. When present at position 2, 3 or 5, the same groups tend to result in diminished activities. However, the mechanism(s) by which substitution at position 4 of the aromatic ring affects the biological activity of amphetamines is/are not satisfactorily known. The Hammett substituent constant, σ, is often included in (multiparameter) treatments of biological activities as a descriptor of the electronic effects of the substituents in question. We were interested in establishing whether the use of modified Hammett substituent scales (σ^- and σ^+)[5a] could advance our understanding of the marked variation in psychotomimetic activity of 4-substituted amphetamines.[2–4]



Scheme 1.

When the substitution at one site of a biologically active molecule is varied, the electronic framework undergoes reorganization. This can affect the reactivity, conformation, and solubility of the molecule, the equilibrium between the different potential tautomeric forms, the acid–base properties, the stacking tendency, etc. The better

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* Corresponding author. Tel.: +358 2 3336831; fax: +358 2 3336700; e-mail: kari.neuvonen@utu.fi

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the substituent effects influencing the electronic state of an organic molecule can be understood, the better the effects of substituents on the medicinal properties of a molecule under investigation can be predicted. Systematic analysis of substituent effects on the biological activity of a molecule is a powerful tool with which to study the significance of the changes induced in the electronic state by different substituents.

Although the activity of a molecule is mainly determined by the functional group(s) participating in the ligand–receptor interaction in question, it is also influenced by intramolecular interactions between the functional groups of the molecule. Certain combinations of substituents attached to the molecular framework can enhance or diminish the reactivity, that is, the biological activity. Mechanistic conclusions based on linear free energy relationships have been extremely fruitful in studies of the effects of variations in substitution. In this way, changes in reactivity/activity caused by changes of the substitution in one series of substituted derivatives can be compared with the changes caused in the equilibrium or reactivity/activity in another series by the same changes of substitution. The most typical and the most useful linear free energy relationship is the Hammett equation, which correlates the rates and equilibria of side-chain reactions of *para*- and *meta*-substituted aromatic compounds. In its most conventional form, the Hammett equation is used as shown in Eq. 1, where k is the rate coefficient for a *para*- or *meta*-substituted aromatic derivative, k_0 is that for the unsubstituted compound, σ is the substituent constant for the substituent in question, and ρ is the reaction constant.[6]

$$\frac{\log k}{\log k_0} = \rho\sigma \qquad (1)$$

Usually, the substitution at one site of the molecule is varied and conclusions are drawn on the basis of the magnitude of the reaction constant. A less widely studied aspect is how substitution at other parts of the molecule influences the sensitivity of the reaction in question. Use of the Hammett substituent constants for the prediction of biological activities is a well-established procedure and the σ values reflecting the electron-withdrawing/electron-donating (EW/ED) abilities of substituents have often been included in different (multiparameter) correlations. It was earlier recognized that the correlations obtained with the Hammett substituent constants σ were poor when the substituents in question were able to conjugate effectively with the reaction center. This problem was solved by devising two new sets of σ values.[5a] The σ^- scale is useful for cases in which an EW group interacts with a negative charge. On the other hand, the σ^+ scale can be used when an ED group interacts with a positive charge. On conjugation with the substituent, the positive charge is delocalized. It is somewhat surprising that publications have not appeared in which these related scales were used instead of the Hammett substituent scale in studies of the effects of substituent on the psychotomimetic activities of amphetamines.

The three single-parameter correlations (1–3 in Table 1) exhibit characteristic differences. A reasonable psychotomimetic activity (A) versus σ correlation clearly proves that electronic effects are of crucial importance in the manifestation of psychotomimetic potency. As the EW character of the 4-substituent increases so does the biological activity ($m_1 > 0$). Both inductive and resonance effects contribute, but the latter predominates as is seen from an inspection of the sensitivities of A to σ_F and σ_R/σ_R^+ (cf. correlations 4 and 5 Table 1, $m_2 > m_1$). Substitution of the σ^- values for the σ scale does not improve the correlation (3 in Table 1). Interestingly, the A versus σ^+ correlation 2 gives an essentially better result than the A versus σ or σ^- correlations. The analogous behavior is seen when comparing correlations 4 and 5. The positive slope of correlation 2 implies that EW substituents at position 4 increase the biological activity. EW substituents are able to stabilize negative charge on the phenyl ring by withdrawing electron density from

Table 1. Calculations on 4-substituted phenyl-2,5-dimethoxy amphetamines with the use of different equations and substituent scales[a]

	Correlation	m_1	m_2	m_3	k	r	n
1	$A = m_1\sigma + k$	240 ± 42			84 ± 8	0.9074	9[b]
2	$A = m_1\sigma^+ + k$	139 ± 10			117 ± 5	0.9822	9
3	$A = m_1\sigma^- + k$	215 ± 43			80 ± 10	0.8825	9
4	$A = m_1\sigma_F + m_2\sigma_R + k$	212 ± 57	279 ± 102		72 ± 24	0.8880	8
5	$A = m_1\sigma_F + m_2\sigma_R^+ + k$	222 ± 27	327 ± 33		91 ± 8	0.9755	9
6	$A = m_1\sigma^+ + m_2\sigma^- + k$	116 ± 17	46 ± 29		111 ± 6	0.9874	9
7	$A = m_1\sigma^+ + m_2E_s + k$	144 ± 15	7 ± 17		126 ± 21	0.9787	8
8	$A = m_1[\sigma + m_2(\sigma^+ - \sigma)] + k$	170 ± 20	0.65 ± 0.16		111 ± 5	0.9884	9
9	$A = m_1\sigma^+ + m_2\log P + k$	137 ± 13	2.4 ± 10		111 ± 26	0.9823	9
10	$A = m_1\sigma^+ + m_3\mathrm{p}K_a + k$	134 ± 10		−38 ± 24	480 ± 230	0.9875	9
11	$A = m_1\sigma^+ + m_2\log P + m_3\mathrm{p}K_a + k$	114 ± 12	19 ± 8	−74 ± 24	772 ± 220	0.9937	9

Biological activities A in mescalin units (MU).

[a] The psychotomimetic activities A expressed in mescaline units (MU) were taken from Ref. 3 originally collected by Shulgin and co-workers. The following substitutions at position 4 (X) were included (substitution, activity, and the designation of the drug in question listed): Br, 150, DOB; Cl, 133, DOC; Et, 75, DOET; I, 133, DOI; Me, 50, DOM; Pr, 80, DOPR; OEt, 9, MEM; OMe, 10, TMA-2; SMe, 40, PARADOT. The substituent parameter values were obtained from Ref. 5a except the E_s values which were obtained from Ref. 5b. Substituent sets used for calculations are based on the availability of the substituent parameters. $\log P$ and $\mathrm{p}K_a$ values are calculated with Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (©1994–2006 ACD/Labs) and were obtained from CAS.

[b] $A = (216 \pm 55)\sigma + (74 \pm 10)$ ($r = 0.7949$), if X = SEt, 50, ALEPH-2 and S-*i*-Pr, 32, ALEPH-4 are included ($n = 11$).

the ring. ED substituents exert an opposite effect. It can be concluded, therefore, that a negative charge experienced from a direction other than from position 4 on the phenyl ring increases the biological activity. The better correlation with σ^+ as compared with σ emphasizes that resonance effects are important in this connection. The conjugative effects of the ED substituents cause the induction of negative charge on the phenyl ring this charge being concentrated in the *ortho* and *para* positions relative to position 4 (Scheme 1). This conjugative effect decreases the activity. In summary, the negative induction caused on the phenyl ring by ED 4-substituents is unfavorable in respect of the biological activity. The efficient inhibition by ED substituents capable of resonance (i.e., σ^+ correlation) suggests that especially the negative induction at position 5 possessing the methoxy substituent (*ortho* to position 4) is unfavorable for psychotomimetic activity (cf. Scheme 1, structure **2**).

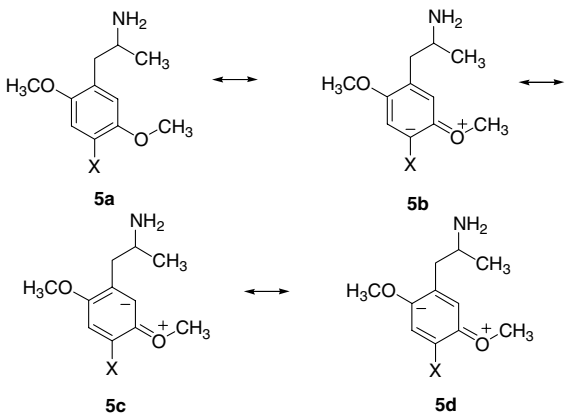
A potential clue to the effect of 4-substitution is the change of the binding of the ligand at the receptor site level. Different theoretical calculations have been performed on amphetamines to elucidate the nature of the different drug–receptor complexes. Using a homology-based model of the 5-HT_{2A} receptor, Chambers and Nichols suggest that the protonated amino group undergoes an ionic interaction with Asp155 in the trans-membrane segment of the seven-helical bundle that comprises the 5-HT_{2A} receptor.[1a] The methoxy substituents at positions 2 and 5 are thought to form hydrogen bonds with Ser159 and Thr160 in trans-membrane segment 3 and with Ser239 in segment 5, respectively. A bulky, hydrophobic ligand is believed to fill a hydrophobic void at the binding site.

Altun et al. investigated the structure–hallucinogenic activity relationships for phenylalkylamines by using the electron-conformational method.[7] Two electronegative atoms attached to the aromatic ring at positions 2 and 5 exist in all strong activity fragments and the disappearance of either of these electronegative groups abolishes or reduces the hallucinogenic activity. Rupp et al. developed a pharmacophoric model for 5-HT reuptake inhibitors.[8] One characteristic of the model is that an electronegative substituent possibly comprising the region of the charge center is located at a distance of 920 pm from the protonated nitrogen atom. Even if these points are important in the receptor binding, as indicated by our results, they do not unambiguously explain the effect of 4-substitution on the experimentally observed psychotomimetic activity. For example, the hydrogen bond acceptor capability of the 2- and/or 5-methoxy groups cannot be assumed to increase in response to EW substitutions at position 4. On the contrary, EW substituents reduce the electron density at the methoxy groups, decreasing the probability of this hydrogen bonding.

It has been proposed that the influence of the substituent at position 4 is based on its orientation relative to the 5-methoxy substituent.[9] On the other hand, the concept of the ED resonance of the methoxy group with the adjacent phenyl ring is well established. This process increases the planarity. Knittel and Makriyannis determined the conformation of the 5-methoxy group as a function of the neighboring substituents (H, Me or OMe).[9a] 5-Methoxy groups with two *ortho* substituents acquire an out-of-plane conformation, whereas those with only one or no *ortho* substituents adopt an in-plane conformation. Only derivatives with in-plane orientations exhibit marked psychotomimetic activities. This orientation is thought to allow easier access of the receptor(s) to this region of the phenyl ring and to the lone pairs of the 5-methoxy group. Our results support this concept. As consequence of the contribution of resonance structures **5b–d** (Scheme 2), the probability of the favorable anti-/planar orientation is increased, resulting in an enhanced biological activity. The contribution of **5b** increases in parallel with the EW power of the substituent at position 4. ED substituents exert opposite effects. Due to the ED conjugation of the substituent at position 4 (Scheme 1, structure **2**), the electron-releasing resonance of the 5-methoxy group is prohibited or at least diminished.

By inductive electron-withdrawal or by resonance EW substituents can stabilize the negative charge at the aryl moiety. Via this mechanism they also increase the psychotomimetic activity. The charge generation represented by resonance structures **5b–d** is in agreement with the results obtained by the CoMFA analysis of a series of 4-substituted amphetamines capable to function as MAO-A inhibitors.[10] A marked positive charge favored area is situated in the vicinity of the 5-methoxy oxygen in the contour plots. On the contrary, there is a negative charge favored area close to the aromatic ring in question.

The influence of steric effects is small (cf. correlations 2 and 7). The significance of log *P* is small, too. According to Eq. 10 (Table 1) the inclusion of the pK_a values slightly improves the σ^+ correlation. The increase of pK_a reflects the increase in the basicity of the NH_2 group, that is, the relative amount of the NH_3^+ form, which is considered to participate in the favorable ionic interaction described above, increases. The negativity of the coefficient m_3 means that decreasing basicity increases the activity. This emphasizes the role of the non-ionic NH_2 form in the receptor binding.



Scheme 2.

In conclusion, when correlating the psychotomimetic activities of substituted amphetamines the σ^+ and/or σ^- scales should be tested in addition to the σ scale. An improved understanding of the mechanism of the effect of 4-substitution was obtained when using the single parameter σ^+ correlation (instead of σ) or a dual-substituent parameter correlation with σ_F and σ_R^+ (instead of σ_F and σ_R).

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