

Effect of Substituents on Some Physical Properties of Para-substituted 2,5-dimethoxyamphetamines

Mohamed M. Abdou*

The effects of substituents on the pK_a 's of a set of 8 psychoactive para-substituted 2,5-dimethoxyamphetamines have been examined using density functional theory (B3LYP/6-31G*) calculations. A variety of quantum chemical parameters were examined as indicators for the variation in the pK_a 's, including the Mulliken, Löwdin and natural population analysis charges (Q_M , Q_L and Q_n) on the amino nitrogen, the energy difference between neutral and protonated molecules (ΔE_{prot}), orbital energies (E_{HOMO} and E_{LUMO}), electronegativity (χ), absolute hardness (η), electrophilicity index (ω) and proton affinity (P.A). Some of these calculated quantities yielded excellent correlation with pK_a .

Introduction

In developing pK_a models it is reasonable to expect that variations in the pK_a should be correlated in some way with the electronic charges at the dissociating atomic position, nitrogen atom in NH_2 and on the acidic hydrogen in NH_3^+ which can serve as good regression parameters⁽¹⁾. Influence of substituents on the physical and chemical properties of compounds has been an important focus of interest in chemistry. The nature and location of substituents affect values of the acid-dissociation constants (pK_a 's)⁽²⁾.

*Associate Professor, Department of Narcotic Research, National Center for Social & Criminological Research. Cairo, Egypt

Because the impact of substituents has implications in many areas of chemistry, it has long been a goal of chemists to understand how these substituents act at a molecular electronic level. The first successful attempt at quantifying these effects came in the form of the Hammett constant (σ)⁽³⁾. In quantitative structure activity and reactivity parlance, the use of Hammett constants is well known⁽⁴⁾. The Hammett equation is given by $\log(k/k_0 = \rho\sigma_p)$ where k and k_a are rate (or equilibrium) constants for the reactions of the substituted and unsubstituted compounds, σ_p is the Hammett constant (substituent constant), and ρ is called the reaction constant. Introduced in the 1930s these constants have enjoyed considerable success in relating changes in a number of physicochemical properties⁽⁵⁾.

Previous efforts⁽⁶⁾ indicate that certain quantum chemical parameters might also serve as useful descriptors for understanding the physical and chemical effects of substituents.

Molecules possessing the 2,5-dimethoxyphenyl-2-aminopropane (2,5-dimethoxy amphetamine) structure unit, which are appended with various substituents at the 4-position (para) of the aromatic nucleus are known to function as psychoactive agents in humans⁽⁷⁾.

The present work examines the applicability of some quantum chemical parameters as descriptors for substituent effects on the pK_a 's of para substituted 2,5-dimethoxy-amphetamines.

Methods

To determine the lowest-energy conformations for each molecule, geometry optimization were performed at the B3LYP/6-31G* with GAMESS-US⁽⁸⁾. Hammett constant were taken from the compilation by Hansch et al.⁽⁹⁾. The values for pK_a 's were calculated by PALLAS software (pK_a module) version 2.0 developed by Compudrug Chemistry Ltd. The SPSS PC (11.5) software package was applied for detail statistical analysis of the models.

Results

Hammett constant

The values for the σ constant employed here, as well as the pK_a , are given in Table I. Hammett σ constants were initially developed to describe the electronic influences of substituents on chemical reactions and equilibria. Accordingly, it is reasonable to expect that they might also provide a reliable measure of the substituents' effects on the pK_a of the amino moiety, and this is indeed the case:

$$pK_a = -1.056 (\pm 0.197) \sigma + 8.94 (\pm 0.06)$$
$$n=8 \quad r=0.982 \quad s=0.072 \quad F=159.807$$

Here n is the number of compounds, r is the correlation coefficient, s is the standard deviation, and F is the Fisher statistic. This is illustrated in Figure 1.

Atomic Charges

Although the atomic charge on an atom in a molecule is not a proper quantum chemical observable, the atomic charge concept has proven to be a valuable tool for the explanation of a variety of chemical phenomena⁽¹⁰⁾.

Three separate types of charges have been included in the present study: the Mulliken charges (Q_M)⁽¹¹⁾, Löwdin charges (Q_L)⁽¹²⁾ and the natural charges (Q_n)⁽¹³⁾ derived from natural population analysis (NPA).

To generate charges that correlate with pK_a 's for a series of 8 para-substituted 2,5-dimethoxy-amphetamines, the charges investigated were those for the amino nitrogen $Q(N)$ and the acidic hydrogen $Q(H^+)$ in $Q(NH_3^+)$, and the total charges on the $Q(NH_2)$ and $Q(NH_3^+)$ functional groups. The results of these charge calculations are summarized in Tables II – IV.

Mulliken Charges

The Mulliken charges functioned as excellent pKa regression for the group charges $Q(NH_2)$ ($r = 0.949$) and $Q(NH_3^+)$ ($r = 0.989$). For estimating pK_a 's, Mulliken charges on protonated amino group worked better (Table II and Figure 2).

$$pK_a = - 51.85 (\pm 7.40) Q_M(NH_3^+) + 34.87 (\pm 3.71)$$
$$n=8 \quad r=0.989 \quad s=0.055 \quad F=273.9$$

Löwdin Charges

The Löwdin charges performed well for this series of compounds, they behaved consistently across the two data sets (Figure 3 and Table III). For example $Q_L(NH_3^+)$, $r = 0.814$; $Q_L(NH_2)$, $r = 0.977$. For estimating pK_a 's, Löwdin charges on the amino group $Q_L(NH_2)$ worked better than the corresponding charges on the protonated amino group $Q_L(NH_3^+)$.

The Löwdin charges on the acidic hydrogen $Q_L(H^+)$ and on the amino nitrogen $Q_L(N)$ were especially effective, with $r = 0.983$ and $r = 0.981$ respectively, (Table III and Figure 3). The $Q_L(H^+)$ correlated with pK_a as follows:

$$pK_a = + 86.51 (\pm 15.72) Q_L(H^+) - 19.47 (\pm 5.15)$$
$$n=8 \quad r=0.983 \quad s=0.070 \quad F=169.3$$

Natural charges

The natural charges on the protonated amino group $Q_n(NH_3^+)$ was better at estimating pK_a variation as Mulliken charges (Figure 4 and Table IV). There were also no significant correlation between pK_a and the $Q_n(N)$ ($r = 0.535$), $Q_n(H^+)$ ($r = 0.685$) and $Q_n(NH_2)$ ($r = 0.094$).

$$pK_a = + 73.83 (\pm 17.91) Q_n(NH_3^+) - 36.63 (\pm 11.04)$$
$$n=8 \quad r=0.970 \quad s=0.092 \quad F=95.04$$

Orbital Energies

Koopmans' theorem ⁽¹⁴⁾ assign a physical interpretation to the highest occupied and lowest unoccupied molecular orbital energies (E_{homo} and E_{lumo} , respectively):

$$E_{\text{homo}} \cong -I, \quad E_{\text{lumo}} \cong -A$$

Here, I is the molecular ionization potential and A is the molecular electron affinity. Two related quantities may be defined:

$$\chi = -(E_{\text{homo}} + E_{\text{lumo}})/2$$

$$\eta = +(E_{\text{lumo}} - E_{\text{homo}})/2$$

to the extent that Koopmans' theorem holds, χ is the absolute electronegativity (equivalent to the Mulliken electronegativity) and η is the absolute hardness ⁽¹⁵⁾. It has been shown that η theoretically justifies and allows the quantification of the Hard-Soft-Acid-Base (HSAB) principle ⁽¹⁶⁾. This principle states that hard acids react more readily with hard bases, and soft acids with soft bases. Formal definitions and working equations of hardness and softness are provided in several previous works ⁽¹⁷⁾.

In addition to these quantities, Parr et al ⁽¹⁸⁾ have proposed the electrophilicity power (electrophilicity index, ω) of a molecule in terms of its electronegativity χ and chemical hardness η as

$$\omega = \chi^2 / 2\eta$$

ω describes the electrophilic power of a ligand and also its propensity to soak up electrons. This index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. By definition, it encompasses both the ability of an electrophile to acquire additional electronic charge and the resistance of the system to exchange electronic charge with the environment.

We examined, χ , η , ω , E_{homo} and E_{lumo} as a possible regression descriptors for the pK_a (Table V and Figure 5). Of the five quantities, E_{homo} exhibited the strongest relationship with pK_a .

$$pK_a = +41.91 (\pm 5.50) E_{\text{homo}} + 17.05 (\pm 1.07)$$

$$n=8 \quad r=0.991 \quad s=0.051 \quad F=324.58$$

The other parameters were less effective in describing the pK_a . Omitting the regression equations,

$$\begin{array}{llll} \chi : & n=8 & r=0.959 & s=0.107 & F=68.28 \\ \eta : & n=8 & r=0.909 & s=0.157 & F=28.43 \\ \omega : & n=8 & r=0.932 & s=0.136 & F=39.85 \\ E_{\text{lumo}} : & n=8 & r=0.945 & s=0.123 & F=50.26 \end{array}$$

Relative Proton – Transfer Energy

Protonation energy

Protonation reaction ($A + H^+ \rightarrow AH^+$) is among the most important reactions in chemistry and biology. Protonation / deprotonation is the first step in many fundamental chemical rearrangements and in most enzymatic reactions⁽¹⁹⁾. The protonation energy (ΔE_{prot}) is expressed as:

$$\Delta E_{\text{prot}} = E_{AH^+} - E_A$$

where E_{AH^+} and E_A represent the ground state total energies of protonated and free molecule respectively. The values for ΔE_{prot} correlate well with the pK_a 's (Table VI and Figure 6)

$$pK_a = -0.05550 (\pm 0.01) \Delta E_{\text{prot}} - 4.71486 (\pm 2.73)$$

$$n=8 \quad r=0.979 \quad s=0.077 \quad F=138.91$$

Proton Affinity

Proton affinity (PA), defined as the negative of the molar enthalpy change at 298.15 K, for the reaction $A + H^+ \rightarrow AH^+$ has been calculated according to the expression⁽²⁰⁾.

$$PA = -\Delta E_{elec} - \Delta ZPE + 5/2 RT$$

Where ΔE_{elec} , the change in the electronic energy upon reaction. In our case, it is the difference between ground state energies (electronic + nuclear) taken from quantum calculations with full geometry optimization for the protonated and neutral molecules. The ground state energy of a proton is zero in this formulation. ZPE is the zero point vibrational energy and the constant $5/2 RT$ value corresponds to changes of thermal translational and rotational energies of reactants and products at 298 K and 0 K.

A good correlation was found between PA and the pK_a of the amino group for this set of compounds (Table VII and Figure 7).

$$pK_a = +0.05678 (\pm 0.01) PA - 4.59634 (\pm 2.59)$$

$$n = 8 \quad r = 0.981 \quad s = 0.073 \quad F = 152.25$$

Intercorrelation

Substituents cause changes in the electron density at the dissociating functional group in the studied molecules. Table VIII shows the correlations among atomic charge models for amino nitrogen, acidic hydrogen and the group charges and the other selected parameters. As expected, the parameters that correlated strongly with pK_a also tended to correlate strongly between one another.

Conclusions

This study of parasubstituted 2,5-dimethoxyamphetamine demonstrates that quantum chemical parameters can be used successfully to account for substituent effects. In addition to their ability to quantitatively relate the electronic properties of substituents to their physicochemical effects, an attractive feature of quantum chemical parameters is that they are both flexible and interpretable.

The Löwdin charges were fairly successful in correlating with the calculated pK_a values. It is also clear that, the quantum chemical parameters $Q_M(NH_3^+)$, $Q_n(NH_3^+)$, E_{homo} , ΔE_{prot} , and PA all yield superior regression models for the pK_a . Compared with the descriptors in the studied pK_a models, E_{homo} appears as the most important descriptors which interpreted as measures of molecular reactivity and stability. Compounds that present larger values of E_{homo} are more electron donor, as E_{homo} increases (relative to other molecules); the molecule is less stable and more reactive.

References

- 1- Gross, K. C.; Seybold, P. C.; Peralta-Inga, Z.; Murray, J. S. and Politzer, P. J., Comparison of Quantum Chemical Parameters and Hammett Constants in Correlating pK_a Values of Substituted Anilines, *J. Org. Chem.*, 66, 2001,6919-6925.
- 2- Lowry, T. H. and Richardson, K. S., *Mechanism and Theory in Organic Chemistry*. 3rd ed., New York, Harper Collins, 1987.
- 3- Hammett, L. P., The Effect of Structure Upon the Reactions of Organic Compounds, Benzene Derivatives. *J. Am. Chem. Soc.*, 59,1937, 96-103.
- Hammett, L. P., Linear Free Energy Relationships in rate and Equilibrium Phenomena, *Trans. Faraday Soc.*, 34, 1938, 156-165.
- 4- Hansch, C.; Leo, A. and Taft, R. W., A Survey of Hammett Substituent Constants and Resonance and Field Parameters, *Chem. Rev.*,91, 1991, 165-195.
- March, J., *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*. New York, Wiley & Sons, 1988.

- 5- Jaffé, H. H., A Reexamination of the Hammett Equation, *Chem. Rev.*, 53, 1953, 191-261.
- Shorter, J., *Correlation Analysis in Organic Chemistry: An introduction to linear Free-Energy relationships*. Oxford, Clarendon Press, 1973.
 - Shorter, J., *Correlation Analysis of Organic Reactivity, with Particular Reference to Multiple Regression*. New York, Research Studies Press, 1982.
 - Exner, O., *Correlation Analysis of Chemical Data*. New York, Plenum Press, 1988.
- 6- Gross, K. C.; Seybold, P. G. and Hadad, C. M., Comparison of Different Atomic Charge Schemes for Predicting pK_a Variations in Substituted Anilines and Phenols, *Int. J. Quantum Chem.*, 90, 2002, 445-458.
- Gross, K. C.; Seybold, P. C.; Peralta-Inga, Z.; Murray, J. S. and Politzer, P. J., op.cit., 2001.
- 7- Shulgin, A. T., in *Handbook of Experimental Pharmacology, vol. 55, part 11, Psychotropic Agents*. Hoffmeister, F.; Stille, G., Eds., New York, Springer-Verlag, 1982, pp. 3-29.
- 8- Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Elbert, S. J.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M. and Montgomery, J. A., The General Atomic and Molecular Electronic Structure System, *J. Comput. Chem.*, 14, 1993, 1347- 1363.
- 9- Hansch. C.; Leo, A. and Taft, R. W., op.cit., 1991.
- 10- Lowry, T. H. and Richardson, K. S., op.cit., 1987.
- 11- Mulliken, R. S., Electronic Population Analysis on LCAO-MO Molecular Wave Functions, I, *J. Chem. Phys.*, 23, 1955, 1833-1840.
- Mulliken, R. S., Electronic Population Analysis on LCAO-MO Molecular Wave Functions, II, Overlap Populations, Bond Order and Covalent Bond Energies, *J. Chem. Phys.*, 23, 1955, 1841-1846.
 - Mulliken, R. S., Electronic Population Analysis on LCAO-MO Molecular Wave Functions, III, Effects of Hybridization on Overlap and Gross AO Population, *J. Chem. Phys.*, 23, 1955, 2338-2342.
 - Mulliken, R. S., Electronic Population Analysis on LCAO-MO Molecular Wave Functions, IV, Bonding and Antibonding in LCAO and Valence -Bond Theories, *J. Chem. Phys.*, 23, 1955, 2343-2346.
- 12- Löwdin, P. O., On the Non-Orthogonality problem, *Adv. Quantum Chem.*, 5, 1970, 185-199.

- 13- Reed, A. E.; Weinstock, R. B. and Weinhold, F. A., Natural Population Analysis, *J. Chem. Phys.*, 83, 1985, 735-746.
- 14- Koopmans, T. A., Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den Einzelnen Elektronen eines Atoms, *Physica*, 1, 1933, 104-113.
- 15- Parr, R. G. and Pearson, R. G., Absolute Hardness : Companion Parameter to Absolute Electronegativity, *J. Am. Chem. Soc.*, 105, 1983, 7512-7516.
- Pearson, R. G., Absolute Electronegativity and Hardness : Applications to Organic Chemistry, *J. Org. Chem.*, 54, 1989, 1423-1430.
- 16- Parr, R. G. and Pearson, R. G., op.cit., 1983.
- 17- Geerlings, P.; De Proft, F. and Langenaeker, W., Conceptual Density Function Theory, *Chem. Rev.*, 103, 2003, 1793-1874.
- De Proft, F. and Geerlings, P., Conceptual and Computational DFT in the Study of Aromaticity, *Chem. Rev.*, 101, 2001, 1451-1464.
- 18- Parr, R. G.; Szentpaly, L. V. and Liu, S., Electrophilicity index, *J. Am. Chem. Soc.*, 121, 1999, 1922-1924.
- 19- Stewart, R., *The Proton: Appellation to Organic Chemistry*. New York, Academic Press, 1985.
- Carol, F. A., *Perspectives on Structure and Mechanism in Organic Chemistry*, New York, Brooks-Cole, , 1998.
- 20- McQuarrie, D. A., *Statistical Mechanics*, New York, Harper & Row, 1976.

Table I. Hammett σ constants and pK_a values for substituted 2,5-dimethoxyamphetamines

Substituent	σ	pK_a
H	0	9.08
p-methyl	-0.17	9.08
p-nitro	0.78	8.13
p-thiomethyl	0	8.9
p-ethyl	-0.15	9.1
p-butyl	-0.16	9.08
p-propyl	-0.13	9.11
p-chloro	0.23	8.62

Figure 1. Correlation between Hammett constants and pK_a

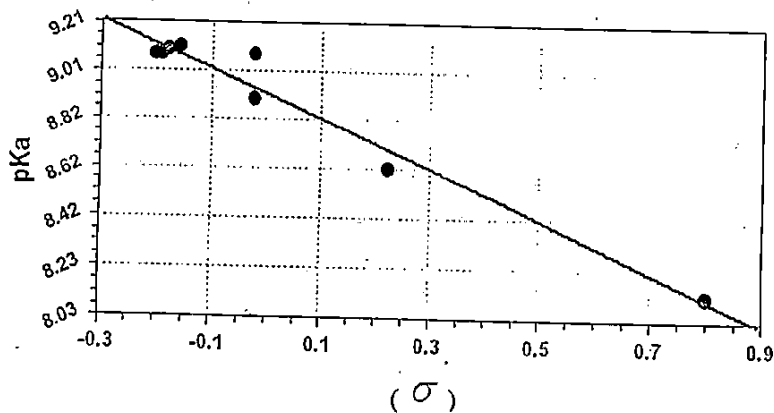


Table II. Calculated Mulliken charges for substituted 2,5-dimethoxyamphetamines

Substituent	$Q_M(N)$	$Q_M(H^+)$	$Q_M(NH_2)$	$Q_M(NH_3^+)$
H	-0.7168	0.7374	-0.1306	0.4989
p-methyl	-0.7172	0.4139	-0.1320	0.4970
p-nitro	-0.7161	0.4171	-0.1230	0.5149
p-thiomethyl	-0.7170	0.4152	-0.1289	0.4996
p-ethyl	-0.7168	0.4139	-0.1314	0.4972
p-butyl	-0.7342	0.4369	-0.1338	0.4969
p-propyl	-0.7327	0.4373	-0.1331	0.4964
p-chloro	-0.7166	0.4149	-0.1279	0.5075
r	0.399	0.409	0.949	0.989

Figure 2. Correlation between pKa and the charge on protonated amino group

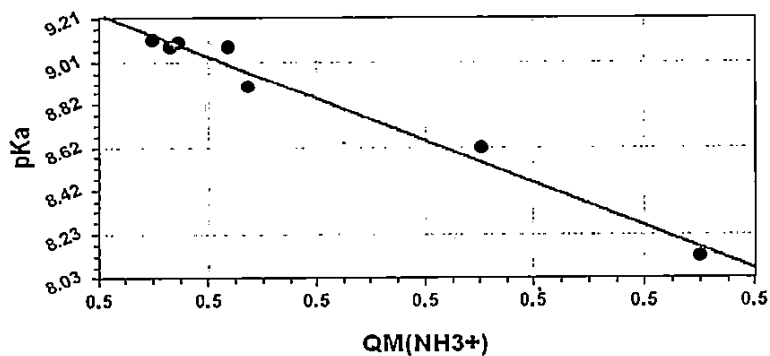


Table III. Calculated Löwdin charges for substituted 2,5-dimethoxyamphetamines

Substituent	$Q_L(N)$	$Q_L(H^+)$	$Q_L(NH_2)$	$Q_L(NH_3^+)$
H	-0.5619	0.3298	-0.0552	0.6234
p-methyl	-0.5632	0.3290	-0.0561	0.6218
p-nitro	-0.5501	0.3191	-0.0495	0.6432
p-thiomethyl	-0.5598	0.3288	-0.0541	0.6235
p-ethyl	-0.5610	0.3290	-0.0560	0.6221
p-butyl	-0.5628	0.3308	-0.0566	0.6225
p-propyl	-0.5641	0.3305	-0.0554	0.6018
p-chloro	-0.5562	0.3247	-0.0531	0.6355
r	0.981	0.983	0.977	0.814

Figure 3. Correlation between pKa and the Löwdin charges on the acidic hydrogen

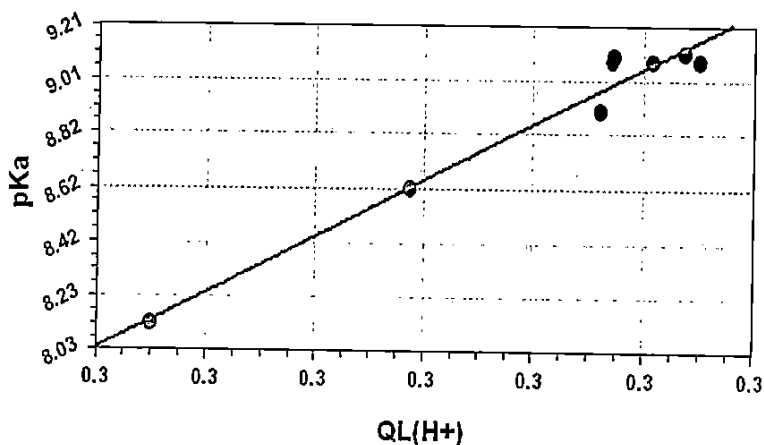


Table IV. Calculated natural charges for substituted 2,5-dimethoxyamphetamines

Substituent	$Q_n(N)$	$Q_n(H^+)$	$Q_n(NH_2)$	$Q_n(NH_3^+)$
H	-0.9253	0.4921	-0.1813	0.6192
p-methyl	-0.9252	0.4732	-0.1819	0.6188
p-nitro	-0.9267	0.4643	-0.1784	0.6078
p-thiomethyl	-0.9258	0.4726	-0.1808	0.6176
p-ethyl	-0.9252	0.4733	-0.1819	0.6186
p-butyl	-0.9202	0.4932	-0.1729	0.6197
p-propyl	-0.9201	0.4932	-0.1726	0.6197
p-chloro	-0.9260	0.4633	-0.1804	0.6107
r	0.535	0.685	0.094	0.970

Figure 4. Correlation between pKa and the natural charged oh the protonated amino group

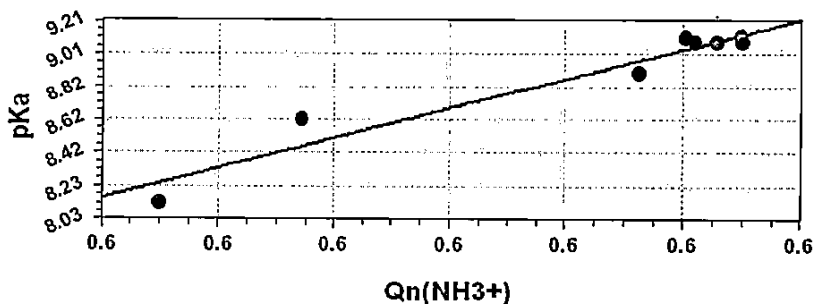


Table V. Calculated electronegativity (χ), hardness (η), electrophilicity (ω), HOMO energy (E_{homo}) and LUMO energy (E_{lumo}) for substituted 2,5-dimethoxyamphetamines

Substituent	χ	η	ω	E_{homo}	E_{lumo}
H	0.0949	0.0971	0.0463	-0.1910	0.0022
p-methyl	0.0910	0.0975	0.0426	-0.1885	0.0065
p-nitro	0.1456	0.0720	0.1472	-0.2130	-0.0736
p-thiomethyl	0.1018	0.0919	0.0578	-0.1950	-0.0102
p-ethyl	0.0922	0.0974	0.0436	-0.1891	0.0047
p-butyl	0.0924	0.0981	0.0435	-0.1906	0.0057
p-propyl	0.0960	0.0964	0.0478	-0.1913	0.0004
p-chloro	0.1045	0.0956	0.0571	-0.2001	-0.0089
r	0.959	0.909	0.932	0.991	0.945

Figure 5. Correlation between pKa and the HOMO energy

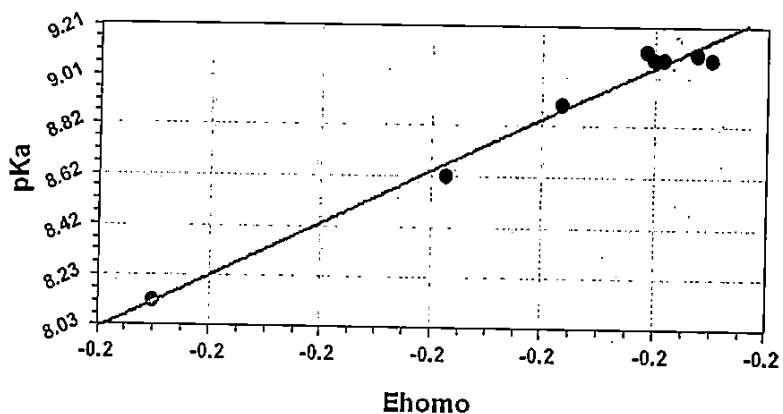


Table VI. Calculated ZPE, total energy (E), protonation energy ΔE_{prot} for substituted 2,5-dimethoxyamphetamines

Substituent	ZPE (Kcal/mol)	Total energy (Kcal/mol)	ΔE_{prot} (Kcal/mol)
H	168.9633	-634.5797	-247.6109
p-methyl	186.4162	-673.8982	-248.8366
p-nitro	170.4577	-839.0739	-233.1431
p-thiomethyl	187.2915	-1072.0799	-244.4750
p-ethyl	205.3488	-713.2114	-248.8054
p-butyl	240.2406	-791.8345	-250.4105
p-propyl	222.3222	-752.5224	-248.9507
p-chloro	163.0191	-1094.1732	-238.4256
r			0.979

Figure 6. Correlation between Pka and energies of protonation

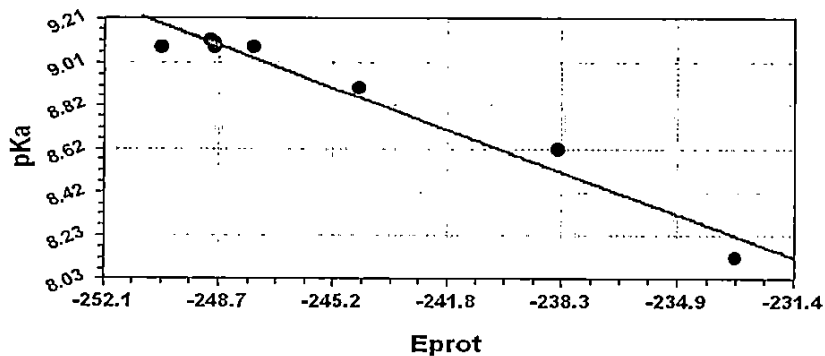


Table VII. Calculated Proton Affinity (PA) for substituted 2,5-dimethoxyamphetamines

Substituent	PA (Kcal/mol)
H	239.7374
p-methyl	214.1237
p-nitro	225.6819
p-thiomethyl	237.1618
p-ethyl	241.7054
p-butyl	242.3543
p-propyl	240.9349
p-chloro	230.9389
r	0.981

Figure 7. Correlation between pKa and the proton affinity

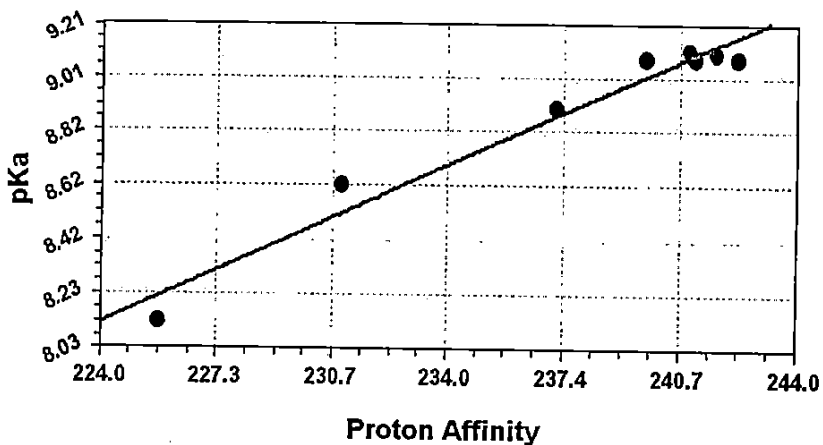


Table VIII. Correlations among selected parameters

	σ	$Q_M(NH_3^+)$	$Q_L(H^+)$	$Q_n(NH_3^+)$	$E_{hom o}$	ΔE_{prot}	PA
σ	1	0.963	0.936	0.875	0.974	0.921	0.92
$Q_M(NH_3^+)$		1	0.962	0.968	0.954	0.971	0.97
$Q_L(H^+)$			1	0.945	0.918	0.932	0.92
$Q_n(NH_3^+)$				1	0.889	0.965	0.96
$E_{hom o}$					1	0.934	0.94
ΔE_{prot}						1	0.99
PA							1

تأثير المشتقات على بعض الخواص الفيزيائية
لمركب ٢، ٥ داي ميثيل امفيتامين

محمد عبده

تم دراسة تأثير ثمانى مشتقات لمركب ٢، ٥ ثنائى ميثوكسى امفيتامين على ثابت التفكك باستخدام نظرية كثافة المجموعة . العديد من عوامل كيمياء الكم تم دراستها كمؤشر للتغيير فى ثابت التفكك ، وشملت الشحنات ميليكمان ولودن والطبيعية على ذرة النيتروجين ، بالإضافة إلى فرق الطاقة بين المركب المتأين والطبيعى وطاقة المدارات . وأوضحت الدراسة وجود علاقات جيدة بين هذه العوامل وثابت التفكك .