QSPR study on pKₐ values of N-Methoxy-polynitroaniline derivatives

Adrian Beteringhe*

Laboratory of Supramolecular Chemistry and Interphase Processes, Institute “I. G. Murgulescu” of Physical Chemistry of Roumanian Academy, Splaiul Independentei 202, 060021, Bucharest, Roumania

Received 3 January 2005; accepted 24 May 2005

Abstract: A QSPR study is presented for acidities of thirteen N-methoxy-polynitroaniline derivatives. Hammett σ values are known for meta and para substituents, and in the present study values are introduced for ortho-substituents in these N-methoxy-polynitroaniline derivatives. Hammett σ values for ortho-substituents in these N-methoxy-polynitroaniline derivatives were obtained by multiplying para values with 0.65.

Keywords: N-methoxy-polynitroanilines, acidity, QSPR, Hammett σ constants

1 Introduction

Polynitroanilines and their derivatives have been intensely studied because they provide information about conjugation in aromatic systems [1], hydrogen bonding [2] or association by charge transfer [2]. In recent years, we reported the synthesis and properties of N-methoxy-polynitroanilines 1 with various substituents [3-14]. These compounds are acidic, and their pKₐ values have been reported [7,12-14]. Chromogenic properties are important characteristics of such N-methoxy-polynitroaniline derivatives, suggesting applications in analytical chemistry and preparative chemistry.

Other interesting properties of compounds 1 are: (i) oxidation affording persistent free radicals (N-aryl-N-alkoxyaminyls), which are probable intermediates in the disproportionation (self-nitration) of N-methoxy-dinitroaniline derivatives affording picryl derivatives [3-8,10]; (ii) enhancement of their acid-basic properties in the presence of crown ethers [11,15,16]; (iii) their reaction with the stable free radical 2,2-diphenyl-1-picrylhidrazyl

* E-mail: chemworks2003@yahoo.com
leading to new, intensely coloured, betaionic compounds, which present reversible chromogenic and redox properties \[11,17\].

In the present QSPR study we present a rationalization of the influence of substituents on pK\(_a\) values for thirteen N-methoxy-polynitroanilines using Hammett \(\sigma\) constants and propose analogous constants for ortho-substituents.

![Structure of N-methoxy-polynitroaniline derivatives.](image)

Fig. 1 Structure of N-methoxy-polynitroaniline derivatives.

2 Experimental methods

The pK\(_a\) values for compounds 1 were determined electrochemically in a mixed solvent, MeOH:H\(_2\)O (1:1 v/v) by titration with potassium hydroxide (also in MeOH:H\(_2\)O) using a correction of 0.46 pH units due to the mixed solvent \[12,13\].

\[
pK_a = pH - \log \left( \frac{[AH]}{[A^-]} \right)
\]

2.1 Computational method

The overall value of substituent constants was calculated additively using a known strategy \[18, 19\]. Electronic effects of ortho-substituents were calculated using a model developed in this paper (see below). In order to study the electronic effects of substituents on the acidity (pK\(_a\) values) of N-methoxy-polynitroaniline derivatives correlation analysis was used. Cross-validation was made using the “leave-one-out” method.

2.2 Electronic parameters of Hammett type

Hammett was first to quantize electronic effects in aromatic systems \[20\]. He explained the pK\(_a\) values of substituted benzoic acids based on inductive and resonance contributions of substituents. A measure of electronic effects can be obtained by the difference between the pK\(_a\) values for substituted and unsubstituted benzoic acids:

\[
\log K_X - \log K_0 = -(pK_a)_X + (pK_a)_0 = \sigma_X \rho
\]
The above Hammett equation describes the effect of meta and para substituents on the acidity of substituted benzoic acids, and can be extended for rationalizing the effect of substituents on the reactivity and spectral properties of many benzene derivatives [21, 22]. In equation 2, $K_X$ is the equilibrium constant for a substituted benzoic acid, $K_0$ is the equilibrium constant for unsubstituted benzoic acid ($X_0 = H$), $\sigma_X$ is a substituent constant, and $\rho$ is a “reaction constant” which depends on the nature and conditions of the reaction.

Hammett $\sigma_X$ constants for substituents in meta and para positions were taken from literature [18-20, 23-25]. For substituents in ortho positions, where steric effects interfere causing bond angle and torsion angle complications, a “quasi-Hammett” constant was introduced:

$$\sigma_o = 0.65 \cdot \sigma_p$$  

(3)

where $\sigma_p$ is the Hammett constant for the same substituent in para position [18-20,23-25].

For compounds having a carboxy substituent, irrespective of its position, one adds a new term (0.5) representing the supplementary acidity of carboxy group. Both terms (0.65 and 0.50) were obtained by linear regression.

The values of Hammett constants for the substituents in meta and para positions [18-20,23-25], and the values of electronic constants $\sigma_o$ calculated using equation 3 for the substituent in the ortho position of compounds 1 are presented in Table 1.

| Substituent | $\sigma_o$ | $\sigma_m$ | $\sigma_p$ |
|-------------|------------|------------|------------|
| NO$_2$      | 0.51       | 0.78       |            |
| CF$_3$      | 0.35       | 0.54       |            |
| CN          | 0.43       | 0.56       | 0.66       |
| COOCH$_3$   | 0.29       | 0.44       |            |
| COOH        | 0.29       | 0.45       |            |
| CH$_3$      |            |            | -0.17      |

$^a$ The “ortho constants” are derived from the para constants by multiplication with 0.65.

Table 1 Values for Hammett and related substituent constants $^a$.

2.3 QSPR studies

Experimental values for the acidities of thirteen N-methoxy-polynitroanilines [7,11,13,14] and global values ($\Sigma \sigma$) for the Hammett and “quasi-Hammett” substituent constants are presented in Table 2. Data were statistically analysed using a linear regression equation (4), where $A$ is the intercept value and $B$ is the slope value.

$$y = A + B \cdot x$$  

(4)

The value for one ortho-nitro group ($R^2$) is incorporated into the free term $A$ of eq.4.
Table 2 Data for the acidity of 13 compounds 1A – 1M.

|   | R² | R³ | R⁴ | R⁶ | Σσ | pKₐ (obs.) | pKₐ (calc.) | Residual |
|---|----|----|----|----|----|------------|------------|----------|
| A | NO₂ | H  | NO₂ | COOH | 1.57 | 3.65 | 4.25 | 0.60 |
| B | NO₂ | H  | COOH | NO₂ | 1.46 | 4.50 | 4.90 | 0.40 |
| C | NO₂ | H  | NO₂ | NO₂ | 1.29 | 5.00 | 5.85 | 0.85 |
| D | NO₂ | H  | NO₂ | CF₃ | 1.13 | 5.54 | 6.72 | 1.18 |
| E | NO₂ | CN | NO₂ | H  | 1.34 | 6.19 | 5.56 | -0.63 |
| F | NO₂ | H  | NO₂ | CN  | 1.21 | 6.44 | 6.29 | -0.15 |
| G | NO₂ | H  | NO₂ | COOCH₃ | 1.07 | 6.54 | 7.09 | 0.55 |
| H | NO₂ | H  | CN  | NO₂ | 1.17 | 7.54 | 6.52 | -1.02 |
| I | NO₂ | H  | COOCH₃ | NO₂ | 0.95 | 8.60 | 7.75 | -0.85 |
| J | NO₂ | H  | CF₃ | NO₂ | 1.05 | 8.70 | 7.19 | -1.50 |
| K | NO₂ | H  | NO₂ | H  | 0.78 | 9.20 | 8.69 | -0.51 |
| L | NO₂ | H  | H   | NO₂ | 0.51 | 9.99 | 10.2 | 0.22 |
| M | NO₂ | H  | CH₃ | NO₂ | 0.34 | 10.4 | 11.2 | 0.79 |

Fig. 2 Calculated versus observed acidity of thirteen N-methoxy-polynitroanilines 1.

Since one ortho-nitro group (R²) is always present, it was not taken into consideration in equation (5) because its contribution was incorporated into the free term (13.0).

\[
pK_a = -5.59(\pm 0.71) \Sigma \sigma + 13.09(\pm 0.79)
\]  

\[
N = 13 \quad R = -0.92 \quad SD = 0.87 \quad F = 62
\]

\[
R^2 = 0.85 \quad \text{cross-validated } R^2 = 0.80
\]
where $N$ is the number of data points, $R$ and $R^2$ denote correlation coefficients, $\text{SD}$ is the standard deviation of the fit, and $F$ is the Fisher test.

3 Results and discussion

In Table 2 we presented experimentally observed $pK_a$ values (in increasing order) for the acidities (in decreasing order) of 13 substituted N-methoxy-polynitroanilines; also displayed are the differences (residuals) between these two values, and the global values of Hammett-type constants for substituents. Figure 2 shows a linear dependence between calculated and experimental values for the thirteen studied N-methoxy-polynitroanilines.

Among all compounds included in Table 2, only N-methoxy-2,4-dinitroaniline (1K) has an approximately planar molecule; steric hindrance causes torsional nonplanarity [26-29] for all other compounds. Therefore no comparison may be made between the isomeric N-methoxy-2,4-dinitroanilines because one of them is planar (1K) and the other is nonplanar (1L). However, one can compare pairwise compounds differing by permuting a couple of substituents in 2 / 4 positions. In all cases, interchanging 2-NO$_2$ / 4-X with 2-X / 4-NO$_2$ substituents causes an increase (D) of $pK_a$ values (i.e. a lowering of acidity): for 1C, $X = \text{NO}_2$, $D = 0$; for 1F, 1H, $X = \text{CN}$, $D = 0.2$; for 1A, 1B, $X = \text{COOH}$, $D = 0.8$; and for 1G, 1I, $X = \text{COOCH}_3$, $D = 2.1$. These four substituents $X$ appear in the above sequence ordered according to decreasing $\sigma_p$ values. Assuming similar torsion angles for all 2,6-disubstituted compounds, this means that the effect of an electron-attracting substituent is highest in para-position. Since nitro groups have the strongest electron-attracting effect from all substituents involved in this study, it follows that a 2-X / 4-NO$_2$ situation will result in a higher acidity (lower $pK_a$) than a 2-NO$_2$ / 4-X situation. That is, the lower the electron-accepting ability of $X$, the higher the difference $D$ in the above permutation, in agreement with experiment.

For 1D, 1J, $X = \text{CF}_3$, however, we observe the highest $D$ value in Table 2 ($D = 3.2$) despite the fact that for $X = \text{CF}_3$ the Hammett constant is intermediate between the values for $X = \text{CN}$ and $X = \text{COOH}$ or $X = \text{COOMe}$. One explanation is by assuming that unlike the other substituents $X$ involved in these pairwise permutations (which act both by inductive and resonance effects), CF$_3$ acts only by inductive effects, and that this is the cause of this distinct behavior of CF$_3$ and of the largest residuals in Table 2. Accordingly, one would expect also a large $D$ value for N-methoxy-2-methyl-4,6-dinitroaniline (estimated $pK_a \approx 7.2$), when this compound will become available, in the comparison with 1M.

4 Conclusions

In order to explain the different acidic properties of 13 N-methoxy-polynitroanilines (compounds 1A – 1M), a correlational QSPR study was carried out on the basis of Hammett and “quasi-Hammett” substituent constants. The latter take into account electronic effects of ortho-substituents present in the studied structures.
Acknowledgment

The author thanks Professor Alexandru T. Balaban from the Texas A&M University at Galveston, USA, for the support in the elaboration of this paper.

References

[1] G.W. Wheland: *Resonance in Organic Chemistry*, Wiley, New York, 1955.
[2] I.D. Rae: “A proton magnetic resonance study of molecular overcrowding in N-alkyl-o-nitroanilines”, *Austral. J. Chem.*, Vol. 18, (1965), pp. 1807–1810.
[3] E. Kolehmainen, K. Laihia, G. Stanciuc and A.T. Balaban: “Strong para-substituent effects on rotational barriers in N-alkoxy-4-R-2,6-dinitrobenzenamines. Dynamic 1H-NMR study”, *Rev. Roum. Chim.*, Vol. 44, (1999), pp. 475–478.
[4] G. Stanciuc, M.T. Caproiu, A. Caragheorgheopol, H. Caldararu, A.T. Balaban and R.I. Walter: “Factors affecting stability and equilibria of free radicals. XII. N-Alkoxypicrylamines and ESR spectra of the corresponding capto-dative persistent aminyls”, *J. Magn. Reson.*, Vol. 75, (1987), pp. 63–72.
[5] G. Stanciuc, M.T. Caproiu, A. Caragheorgheopol, H. Caldararu, T. Constantinescu and A.T. Balaban: “Factors affecting stability and equilibria of free radicals. XVI. Preparation and EPR spectra of capto-dative N-alkoxy-dinitrophenyl-aminyls”, *Rev. Roum. Chim.*, Vol. 34, (1989), pp. 1895–1905.
[6] G. Stanciuc, M.T. Caproiu, A. Caragheorgheopol, H. Caldararu, T. Constantinescu and A.T. Balaban: “Factors affecting stability and equilibria of free radicals. XV. EPR evidence of formation of N-alkoxypicramides on oxidation of N-alkoxy-dinitroanilines. Electronic structure of aminyl radicals”, *Z. Naturforsch.*, Vol. 44b, (1989), pp. 1459–1463.
[7] N. Zarna, G. Stanciuc, T. Constantinescu, F. Chiraleu, H. Caldararu, A. Caragheorgheopol, M.T. Caproiu, M. Ionescu and A.T. Balaban: “Electronic structure and acido-basic properties of some N-alkoxy-polyanilines”, *Roum. Chem. Quart. Rev.*, Vol. 2, (1994), pp. 67–81.
[8] T.J. Sumi, G. Stanciuc, S. Kasa and H. Joela: “Hyperfine coupling of N-alkoxy-N-polynitrophenylaminyl radicals determined by ENDOR and TRIPLE resonance spectroscopy”, *Magn. Reson. Chem.*, Vol. 33, (1995), pp. 511–517.
[9] N. Zarna, T. Constantinescu, G. Stanciuc, A. Caragheorgheopol, H. Caldararu, A.T. Balaban, K. Laihia and E. Kolehmainen: “Hydrophobic supramolecular complexes of various cations with 18-crown-6 as the ligand and N-methoxy-picramide as the anion pair in a water/methylene chloride two-phase system: complexes with isn’t in document -amino acids, their characteristics and conditions for formation”, *Supramolecular Science*, Vol. 2, (1995), pp. 37–40.
[10] G. Stanciuc, N. Zarna, N. Spataru, T. Constantinescu, A. Caragheorgheopol, H. Caldararu and A.T. Balaban: “Factors affecting stability and equilibria of free radicals. Part XXII. Bond dissociation energy of N-alkoxy-polynitroanilines”, *Rev. Roum. Chim.*, Vol. 41, (1996), pp. 755–761.
[11] I.C. Covaci, T. Constantinescu, M.T. Caproiu, C. Draghici, P. Ionita, C. Luca, G. Stanciuc, M. Maganu and A.T. Balaban: “3,5-Dinitro-4-methoxyaminobenzoic acid and its derivatives”, *Rev. Roum. Chim.*, Vol. 44, (1999), pp. 333–340.
[12] D.O. Popescu, P. Ionita, N. Zarna, I. Covaci, A. Stoica, A. Zarna, D. Nourușcu, F. Spafișiu, M.T. Caproiu, C. Luca, F. Badea, T. Constantinescu and A.T. Balaban: “Hydrazyl and aminyl analogs, liquid membranes and stationary phases for gas chromatography”, *Roum. Chem. Quart. Rev.*, Vol. 6, (1998), pp. 271–282.

[13] I.C. Covaci, T. Constantinescu, M.T. Caproiu, F. Dumitrascu, C. Luca and A.T. Balaban: “New N-methoxy-dinitro-aniline derivatives: Synthesis, structure and pKa values”, *Rev. Roum. Chim.*, Vol. 44, (1999), pp. 531–537.

[14] I.C. Covaci, T. Constantinescu, M.T. Caproiu, C. Luca and A.T. Balaban: “Solid supramolecular complexes of potassium salts of N-methoxydinitroaniline derivatives and Methoxyamino-3,5-dinitropyridine with 18-crown-6 ether”, *Eur. J. Org. Chem.*, (2000), pp. 3569–3573.

[15] N. Zarna, G. Stanciuc, T. Constantinescu, A.T. Balaban, K. Laihla and E. Kolehmainen: “Hydrophobic supramolecular complexes of alkali cations with 18-crown-6 as ligand and N-methoxy-2,4,6-trinitroaniline as pair anion in a two-phase system”, *Rev. Roum. Chim.*, Vol. 41, (1996), pp. 875–881.

[16] A.T. Balaban, N. Frangopol, N. Negoița, P.T. Frangopol and M. Paraschiv: “Factors affecting stability and equilibria of free radicals. V. Synthesis and spectra of polynitrophenyl-alkoxy-amines”, *Rev. Roum. Chim.*, Vol. 14, (1969), pp. 941–945.

[17] T. Constantinescu, M.T. Caproiu, N. Zarna, H. Caldararu, G. Stanciuc, M. Radu, V. Badescu and A.T. Balaban: “Reaction of 2,2-diphenyl-1-picrylhydrazyl (DPPH) with N-alkoxy di- and trinitroanilines”, *New J. Chem.*, Vol. 41, (1997), pp. 575–579.

[18] H.H. Jaffé: “A reexamination of the Hammett equation”, *Chem. Rev.*, Vol. 53, (1953), pp. 191–261.

[19] P.R. Wells: “Linear free energy relationships”, *Chem. Rev.*, Vol. 62, (1962), pp. 171–219.

[20] L.P. Hammett: “The effect of structure on the reaction of organic compounds. Benzene derivatives”, *J. Am. Chem. Soc.*, Vol. 59, (1937), pp. 96–103.

[21] K.B. Wiberg: “Substituent Effects on the Acidity of Weak Acids. 2. Calculated Gas-Phase Acidities of Substituted Benzoic Acids”, *J. Org. Chem.*, Vol. 67, (2002), pp. 4787–4794.

[22] K.B. Wiberg: “Substituent Effects on the Acidity of Weak Acids. 1. Bicyclo(2.2.2)octane-1-carboxylic Acids and Bicyclo(1.1.1)pentane-1-carboxylic Acids”, *J. Org. Chem.*, Vol. 67, (2002), pp. 1613–1617.

[23] C. Hansch and A. Leo: *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley-Interscience, New York, 1979.

[24] C. Hansch, A. Leo and R.W. Taft: “A Survey of Hammett Substituent Constants and Resonance and Field Parameters”, *Chem. Rev.*, Vol. 91, (1991) pp. 165–195.

[25] A. Pross, L. Radom and R.W. Taft: “Theoretical approach to substituent effects. phenols and phenoxide ions”, *J. Org. Chem.*, Vol. 45, (1980), pp. 818–826.

[26] R.D. Topson: “Discussion of theory and experiment”, *Prog. Phys. Org. Chem.*, Vol. 16, (1987), pp. 85–124.

[27] M. Charton: “The application of the Hammett equation to ortho-substituted benzene reaction series”, *Can. J. Chem.*, Vol. 38, (1960), pp. 2493–2499.

[28] V. Balish and M. Uma: “Steric enhancement of resonance”, *Tetrahedron Lett.*, Vol. 25, (1960), pp. 21–25.

[29] M.J. Kamlet: “Spectral effects of hydrogen-bonding in substituted anilines”, *Israel J. Chem.*, Vol. 1, (1963), pp. 428–429.