

Substituent effects in 1-nitro-4-substituted bicyclo[2.2.2]octane derivatives: inductive or field effects?

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Abstract Interactions between the NO₂ group and 13 different substituents (BF₂, BH₂, CF₃, CH₃, CHO, CN, F, NH₂, NMe₂, NO₂, NO, OH, OMe) were investigated computationally for bicyclo[2.2.2]octane (BCO) and benzene substituted at 1,4 and 1,3 positions in the ring. Three methods were employed to estimate the character and strength of the substituent effect: substituent effect stabilization energy (SESE), sigma/pi electron donor acceptor index (sEDA/pEDA) and substituent active region (cSAR) parameter. For the first time the sEDA/pEDA parameters were calculated not for the ring but for the NO₂ group. All calculations were performed at the B3LYP/6-31G(d,p) level of theory. For 1,4 derivatives, a direct comparison of slopes of linear regressions between BCO and benzene reveals a much better transmission of the substituent effect in the latter. The ratio of slopes (benzene over BCO) is always larger than 4. It follows that the resonance effects, which are absent in the BCO, dominate in this case. For 1,3 derivatives, because of much lower correlation coefficients, estimated standard deviations (ESD) were used to calculate the ratio instead of the slopes. For these systems the ratio is much closer to the unity, which indicates that only the sigma/through space effects are present and they are of similar magnitude in benzene and BCO. It follows from natural population analysis (NPA) charges that the substituent

effect in the studied systems is due mainly to through-space interactions.

Keywords Substituent effect · SESE · HOMA · pEDA

Introduction

The concept of the substituent effect is one of the most often used in organic chemistry; every day about ten papers appear in which this term is used in the title, abstract or keywords. In a narrower sense, the term is related to changes in chemical, physicochemical or biochemical properties due to the replacement of one chemical group by another. Typically and traditionally, the systems under study, X–R–Y, consist of varying substituents X; the so-called “reaction site” Y, i.e., a fixed group in the series; and the transmitting moiety R. Quantitatively, the substituent effect was defined by Hammett [1–3] by use of the dissociation constants of meta- and para-substituted benzoic acids to define the substituent constants σ (Eq. 1)

$$\sigma_{p(m)} = \log K_{p(m)}(X) - \log K(H) \quad (1)$$

where $K_{p(m)}(X)$ are dissociation constants for para- or meta-substituted (by X) benzoic acids whereas $K(H)$ is for the unsubstituted species. Typical application of the substituent constants was suggested by Hammett himself as linear regressions of logarithms of equilibrium (K) or rate (k) constants plotted against the appropriate sigma constants. Indeed, by 1940, 52 successful applications had appeared [3] of the so-called Hammett equation (Eq. 2),

$$\log K(k)_{p(m)} = \rho \sigma_{p(m)} + \text{const} \quad (2)$$

where ρ , the slope of the linear regression, describes the sensitivity of the reaction to the substituent effect. Many reviews have also been devoted to this subject [4–12].

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Apart from the many successful applications of the Hammett equation, cases where the original Hammett substituent constants have failed have also appeared. In cases when the reaction site Y was strongly electron-donating or -accepting, and for para-substituted reaction series (but not for meta-substituted series) systematic deviations appeared. Therefore, to account for this kind of substituent effect some special substituent constants have to be introduced [13]: for electron-donating reaction sites substituent constants σ_p^- [4, 14] and for electron-accepting reaction sites the substituent constants σ_p^+ [15].

Since that time, there has been a plethora of applications of the Hammett equation (Eq. 2) and some Hammett-like equations [in which other than the original substituent constants (Eq. 1) were used] have been applied successfully not only for benzene derivatives and not only for equilibrium/kinetic properties, but also for many various, mostly pi-electron, systems (aromatic or unsaturated) and for many physicochemical properties including spectroscopy [16], electrochemistry [17] and biochemistry [18].

The original interpretation of the substituent effect by Hammett is as follows: “the substituent produces in general, different changes in electron density on the different carbon atoms of the ring; consequently, its effect differs according to the relative positions of substituents and reactive group” [3]. At the very beginning of study in this field, changes in electron density were interpreted in terms of inductive and resonance effects [3, 19].

Since the early years of studies on substituent effects, there have been many attempts to separate inductive and resonance interactions. The first step was done by using dissociation constants of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids as a direct measure of the inductive effect (defined in this way at that time) [20]. In this reference reaction there were no resonance interactions between the carboxyl group and the substituent, and only the inductive or through-space interactions were possible, named later as field effects (for review see [12]). The new substituent constants were named as inductive with the symbol σ_I .

Later, a new reference reaction, basicity of 4-substituted quinuclidines [21, 22], was suggested as another molecular system where no mesomeric effect is possible. The advantage of the new reference reaction was a greater sensitivity of basicity to substituent effects due to a shorter route of interaction between X and Y. Another way to estimate inductive and resonance contributions was by assuming that substituent constants for meta- and para-positions contain mostly different contributions of the inductive and resonance interactions. Then, by analysis of a properly chosen set of data, the inductive constants σ_I [23] and the resonance constants σ_R were obtained [24]. Controversy between the interpretation of substituent effects as inductive or through-space is not yet decisively resolved [12, 25–32]. It is important to mention that

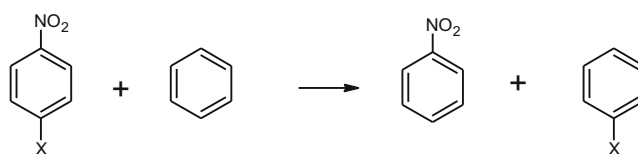
interactions like those in 4-substituted bicyclo[2.2.2]octane-1-carboxylic acid derivatives were named recently as inductive/field interactions.

The aim of this work was to investigate the above problem by using physical models based on quantum chemical calculations. For this purpose, we chose 3- and 4-substituted nitro benzene and 3- and 4-substituted 1-nitro- bicyclo[2.2.2]octane derivatives. The nitro group is a very important substituent for both, given its strong inductive/field effect and high capacity for resonance effects when an electron-donating substituent is located in the para-position [10, 33]. This is clear for para- and meta-substituted benzene, taken here as a reference, for which many important results and interpretations have been presented. The question is how the meta- and para-type substituent interactions in benzene derivatives look out for 1,3 and 1,4-derivatives of 1-nitro-4-substituted bicyclo[2.2.2]octane. The nitro group as a sensor for both resonance and inductive/field interactions formed the subject of our investigations by means of homodesmotic reactions (SESE), by analyses based on natural bond orbital (NBO) methods [34, 35], which allow estimation of changes in sigma and pi electron structures in the nitro group due to substituents from the 3- to 4-positions. For the same purpose, the concept of cSAR (charge of the substituent active region) [36–38], where the total charges of substituents and the fixed group (NO_2) are taken into account, was applied. Finally, analyses of total charges at carbon atoms in rings of nitro-benzene and 1-nitro-bicyclo[2.2.2]octane derivatives were carried out.

Methods

All calculations were performed at the B3LYP/6-31G(d,p) level of theory by employing the Gaussian 03 software package [39]. Geometry optimizations were followed by a frequency check to ensure that the stationary points obtained were true energy minima at the potential energy surface. NBO analysis [34] was performed using the NBO 5.0 program included in Gaussian. A wide range of substituents was applied: BF_2 , BH_2 , CF_3 , CH_3 , CHO , CN , F , NH_2 , NMe_2 , NO_2 , NO , OH , OMe . The substituent effect was investigated by means of three methodologies, as follows:

Substituent effect stabilization energy (SESE) [40, 41] for p-substituted nitrobenzene is defined as the zero-point corrected energy of the homodesmotic reaction (1)



For other structures, similar reactions were employed. A positive sign of the SESE means stabilization of the left side of the equation and thus favorable interaction between the substituent and the nitro group.

Sigma and pi electron donor/acceptor (sEDA/pEDA) indices [35] were calculated for the NO₂ group according to Eqs. (2) and (3).

$$sEDA = \sum_{i=1}^3 \sigma_{X-NO_2}^i - \sum_{i=1}^3 \sigma_{NO_2}^i \quad (4)$$

$$pEDA = \sum_{i=1}^3 \pi_{X-NO_2}^i - \sum_{i=1}^3 \pi_{NO_2}^i \quad (5)$$

where $\sigma_{X-NO_2}^i$ means the sum of occupancies of 2s, 2p_x and 2p_y orbitals and $\pi_{X-NO_2}^i$ means the occupancy of the 2p_z orbital of the *i*-th atom of the NO₂ group for the nitrosubstituted structure. The symbols $\sigma_{NO_2}^i$ and $\pi_{NO_2}^i$ have similar meaning but for structures substituted only by a nitro group. This scheme of calculation allows us to estimate the sigma and pi-electron excess/deficit on the NO₂ group. Calculation of sEDA/pEDA is possible only for planar systems, and the NO₂ group fulfils this requirement.

The charge of substituent active region [36, 37] parameter, named here cSAR¹, was calculated according to Eq. (4) by summing up total natural population analysis (NPA) charges of substituent X and the ipso-carbon atom

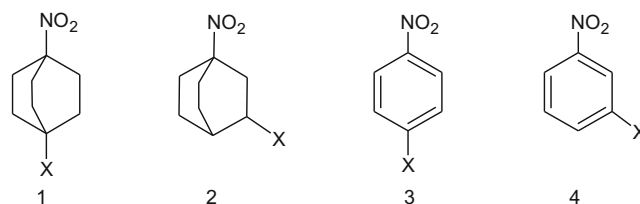
$$cSAR = q(X) + q(C_{ipso}) \quad (6)$$

Two kind of cSAR were employed—calculated for the nitro group and for the variable substituent X.

Results and discussion

For clarity, the obtained results will be discussed in four subsections, dealing with (1) homodesmotic reactions (by means of SESE), (2) NBO theory by means of pEDA/sEDA characteristics then by use of (3) cSAR and, finally, (4) by analysis of total charges at C-atoms in the ring of substituted benzene and bicyclo[2.2.2]octane derivatives. Moreover, since the 1,4-interactions (i.e., between the reaction site—nitro group in this paper—and substituents in position 4), are often the subject of dispute, a more detailed analyses will be carried out mostly on these. Additionally, these interactions are described much more precisely by linear regressions and

¹ Explanation: In our two recent publications the symbol qSAR was used for charge of Substituent Active Region. However, to avoid confusion with QSAR meaning Quantitative Structure Activity Relationships we decided to use the symbol cSAR instead.



Scheme 1 Studied systems: 1 1-nitro-4-di-substituted bicyclo[2.2.2]octane, 2 1-nitro-3-di-substituted bicyclo[2.2.2]octane, 3 p-nitrosubstituted benzene, 4 m-nitrosubstituted benzene

hence may be analyzed with greater reliability. This is not the case for 1,3-interactions, which are discussed separately. Before going into detail, Scheme 1 presents all model molecules taken into consideration in this paper.

All numerical data discussed in this paper are collected in Tables S1–S4 in Supplementary Material.

Application of homodesmotic reactions: SESE vs Hammett substituent constants for 1,4 interactions

Homodesmotic reactions in X-R-Y systems are known as energetic representations of the substituent effect, i.e., the parameter that takes into account all interactions between substituent X, the “reaction site” (in our case the fixed group Y=NO₂) and the transmitting moiety R [41]. For cases where the substituent effect stabilizes the system under study, SESE values are positive. Figures 1 and 2 present the dependency of SESE values on the appropriate substituent constants. Thus, the negative slopes in both figures indicate, as expected, that the increase of electron-attracting power of substituent X leads to a decrease of SESE, i.e. destabilization of both the substituted 1-nitro benzene and 1-nitro-4-substituted bicyclo[2.2.2]octane derivatives. In the latter case, two points—those for CH₃ and H—deviate dramatically, and hence the correlation coefficient for the data was calculated without them.

In both cases, the linear regressions of SESE values on σ_p have at least acceptable correlation coefficients at −0.990 and −0.920, respectively. Note that the slopes of linear regression

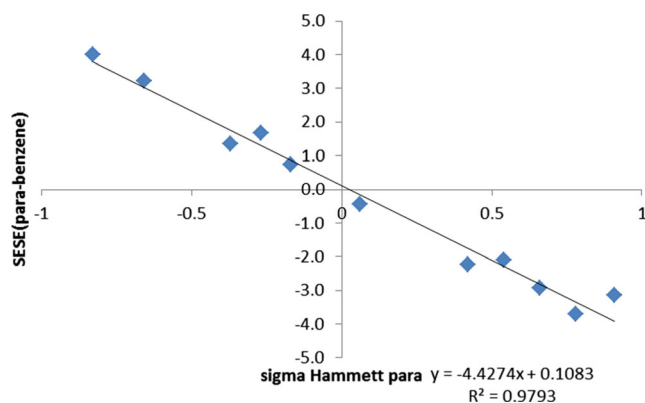


Fig. 1 Correlation between substituent effect stabilization energy (SESE) and Hammett constant σ_p for p-nitrosubstituted benzene derivatives. CC=−0.990

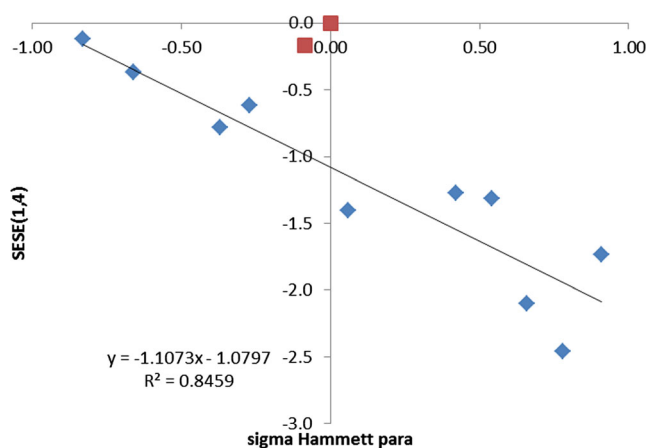


Fig. 2 Correlation between SESE and Hammett constant σ_p for 1,4-disubstituted bicyclo[2.2.2]octane without H and CH_3 . Red squares H and CH_3 . CC=−0.920

in Figs. 1 and 2 are dramatically different: −4.43 and −1.11, respectively. This indicates that the $\text{X}\cdots\text{Y}$ interactions in p-nitrobenzene derivatives are approximately ~4 times stronger than in the bicyclo[2.2.2]octane derivatives. Since the SESE values in para-nitrobenzene derivatives take into account all types of interactions whereas in bicyclo[2.2.2]octane derivatives only the inductive/field effect works, slope ratios of ~4 lead to the conclusion that three-quarters of the interactions in nitrobenzene derivatives are of the resonance type and only one-quarter represent inductive/field effects. Tables S1–S4 in the supplementary material provide all numerical data for SESE and all other characteristics applied in this paper.

Application of sEDA/pEDA characteristics and comparison with SESE

pEDA and sEDA characteristics can be applied only to planar sets of atoms and nitro group fulfils this requirement. Thus, analysis of changes of these parameters for the NO_2 group allows us to describe how the sigma and pi electron structure in the nitro group in 1-nitro-4-substituted benzene and 1-nitro-

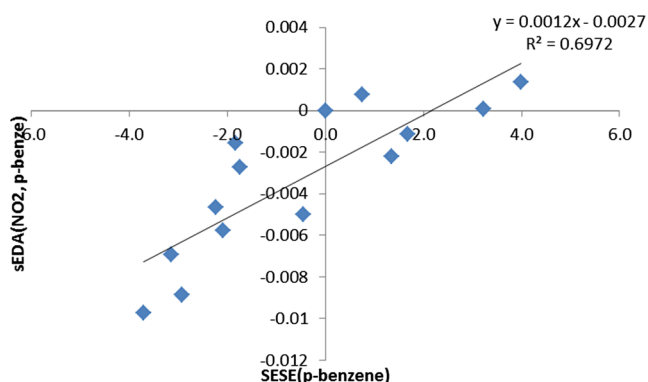


Fig. 3 Correlation between sigma electron donor acceptor index (sEDA)(NO_2) and SESE for p-nitrosubstituted benzene. CC=0.835

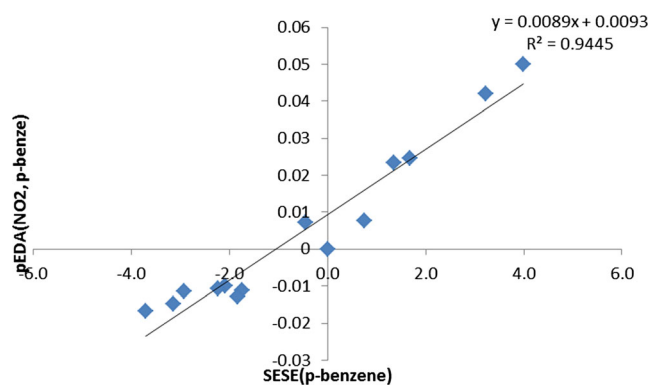


Fig. 4 Correlation between pi electron donor acceptor index (pEDA)(NO_2) and SESE for p-nitrosubstituted benzene. CC=0.972

4-substituted-bicyclo[2.2.2]octane derivatives depends on the substituent effect. Comparing these data then gives us information on changes in the pi and sigma electron structure of the nitro group. Two questions arise: (1) can changes in pEDA and sEDA values (due to the substituent effect) correlated with the SESE now be used as an indicator of the substituent effect? (2) Are these changes similar in these two series?

In the case of p-nitrobenzene derivatives (Fig. 3) the correlation between sEDA on the NO_2 group and SESE is weak (CC=0.835), whereas for pEDA vs SESE (Fig. 4) there is an acceptable correlation, with CC=0.972

Linear regressions in Figs. 5 and 6 show that, for 1-nitro 4-substituted bicyclo[2.2.2]octane derivatives, both the sEDA and pEDA values correlate well with SESE, with CC=0.992 for sEDA and CC=0.940 for pEDA. As expected, the less electron attracting the substituent, the less negative are sEDA and pEDA and hence positive slopes in these regressions are observed.

Comparison of the slopes of sEDA/pEDA data vs SESE for nitrobenzene and nitrobicyclo[2.2.2]octane derivatives leads to a very interesting result. For pEDA, the regression of the slope for para-nitrobenzene derivatives was 0.0089 whereas for nitrobicyclo[2.2.2]octane derivatives it was 0.0012. Thus,

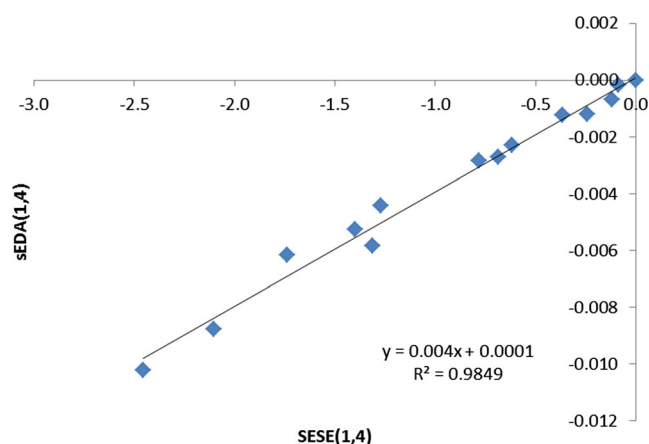


Fig. 5 Correlation between sEDA(NO_2) and SESE for 1,4-disubstituted bicyclo[2.2.2]octane. CC=0.992

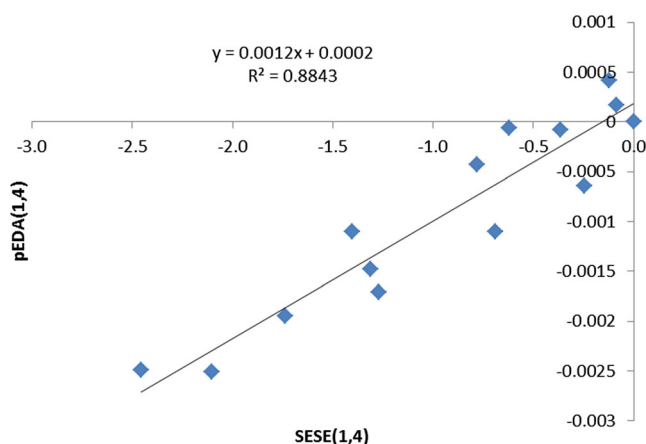


Fig. 6 Correlation between pEDA(NO₂) and SESE for 1,4-di-substituted [2,2,2] bicyclo[2.2.2]octane. CC=0.940

the substituent effect acting on the pi-electron structure in the nitro group is 7.42 times stronger for benzene derivatives than that observed in bicyclo[2.2.2]octane derivatives. The opposite situation takes place for regressions of sEDA vs SESE: the ratio of slopes is 0.3 indicating a stronger substituent effect (expressed by sEDA) in the bicyclo[2.2.2]octane derivatives. However, any deeper analysis here is precluded since the correlation coefficient for sEDA vs SESE regression is too low to draw any reliable conclusions.

Analysis of cSAR on the nitrogroup in 4-substituted nitrobenzene and bicyclo[2.2.2]octane 1,4-derivatives

cSAR(Y)-values are quantitative measures of the electron state of the group Y attached to a given position of the system in study. This state depends on the moiety R to which group Y is attached. Thus, if the moiety R has a variable ability to interact with Y, e.g., by means of varying substituent X in a fixed position, then cSAR(Y) will be a measure of substituent effect of X to group Y. To test this let us look at the regressions of cSAR(NO₂) plotted against SESE. We did this for both systems of interest, i.e., 4-substituted nitrobenzene and

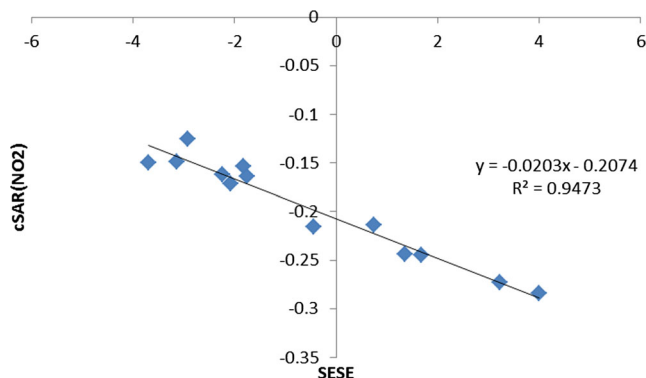


Fig. 7 Dependence of charge of the substituent active region (cSAR)(NO₂) on SESE for para-nitrosubstituted benzene derivatives. CC=−0.973

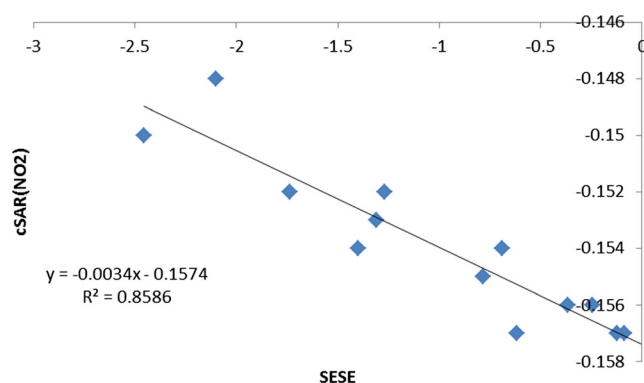


Fig. 8 Dependence of cSAR(NO₂) on SESE for 1,4-di-substituted bicyclo[2.2.2]octane derivatives. CC=−0.927

bicyclo[2.2.2]octane derivatives, present the results in Figs. 7 and 8.

In both cases, the correlation coefficients are acceptable and the difference in values of slopes is of interest. The ratio of the slopes for nitrobenzene and bicyclo[2.2.2]octane derivatives is 5.97, i.e., the nitro group in the bicyclo[2.2.2]octane derivatives is 5.97 times less sensitive to the substituent effect than in benzene. This means that the purely sigma-skeleton of bicyclo[2.2.2]octane systems is a worse transmitter of the substituent effect by a factor of 5.97.

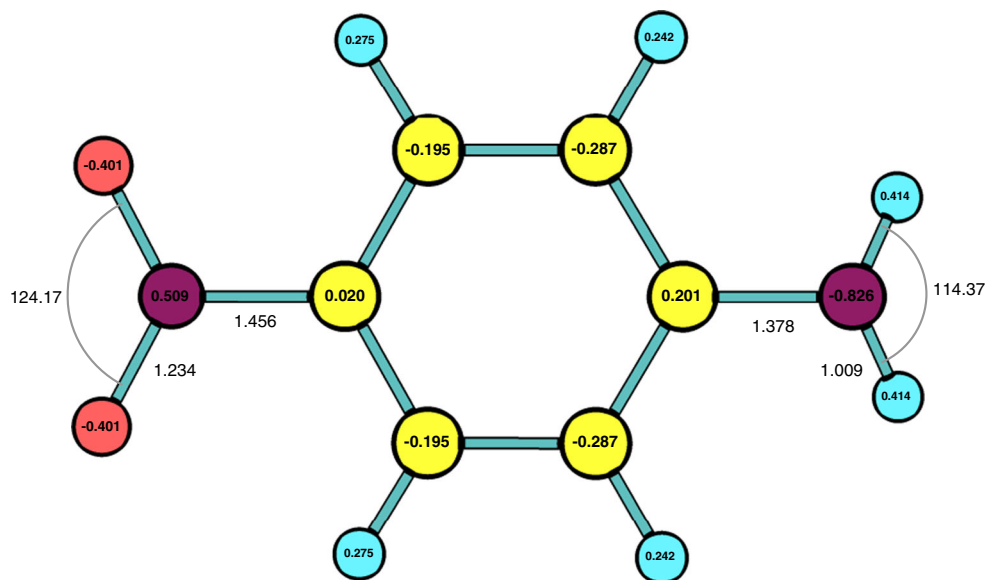
Analyses of data for both series: 1,4 and 1,3 interacting systems by use of estimated standard deviations (ESD)

In all cases of 1,4 interactions, the linear regressions had acceptable correlation coefficients. Direct comparison by a ratio of data for benzene over those for bicyclo[2.2.2]octane derivatives indicates significantly better communication between substituents and the nitro group in benzene derivatives. Up to now, the data for 3-substituted nitro-derivatives of benzene and bicyclo[2.2.2]octane have not been discussed. In this situation, a simple way of describing how much stronger the interactions estimated for a given reaction series are

Table 1 Estimated standard deviation (ESD) values for substituent effect stabilization energy (SESE), and sigma/pi electron donor acceptor index (sEDA/pEDA) substituted in 3 and 4 positions for benzene and bicyclo[2.2.2]octane derivatives. For complete data, see [Supplementary material](#)

P	Benzene	Bicyclo[2.2.2]octane	Ratio
SESE 1,4	2.42	0.782	3.08
SESE 1,3	1.61	1.76	0.908
pEDA(NO ₂)1,4	0.0221	0.00099	22.3
sEDA(NO ₂)1,4	0.0036	0.0032	1.12
pEDA(NO ₂)1,3	0.0057	0.00106	5.37
sEDA(NO ₂)1,3	0.0053	0.00352	1.51
cSAR(NO ₂) 1,4	0.0525	0.00284	18.5
cSAR(NO ₂) 1,3	0.0102	0.00431	2.36

Fig. 9 Scheme of 1-nitro-4-amino-benzene with total charges at atoms, and showing some geometry parameters



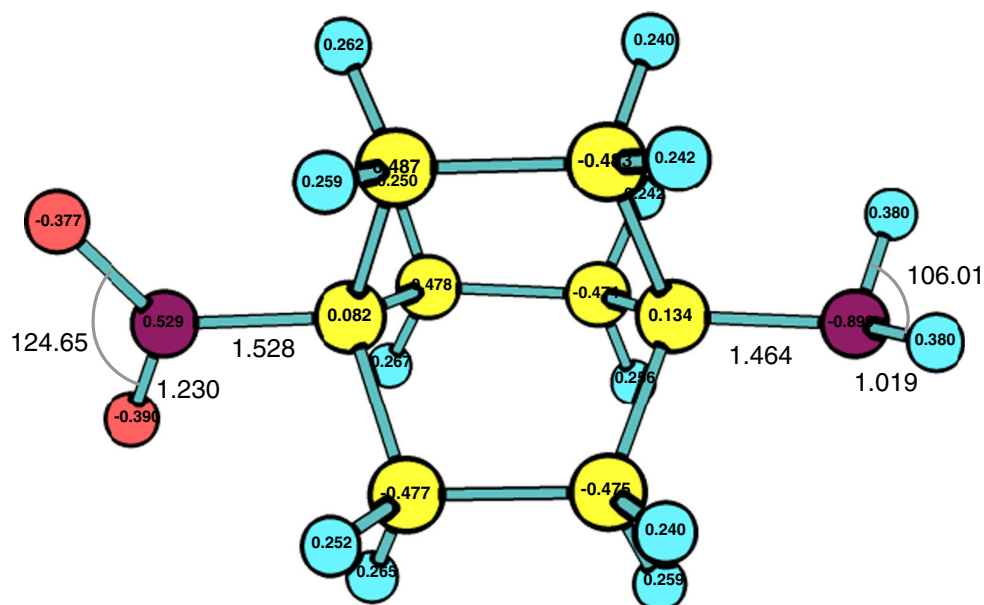
over another one to compare the ranges of the data. Statistically, dispersion of the data is characterized by variance [42], but a much more visual method is to examine the square root, i.e., the estimated standard deviation (ESD) since its values are of the same magnitude as the original data. In order to gain some information about the relationship of dispersion of the substituent characteristics P in the two series of data, we compared the ratio of ESD for these two series. In our case the ratios were defined as a fraction $P(\text{ESD for benzene derivative})/P(\text{ESD for bicyclo[2.2.2]octane derivatives})$, as presented in Table 1.

In the case of SESE, pEDA(NO_2), and cSAR(NO_2), the ratios for 1,4-substituted systems are always significantly greater for benzene derivatives than for bicyclo[2.2.2]octane

derivatives, i.e., ratios are >3.07 . A completely different picture is observed for 1,3-substituted species. For all of them the ratio is close to 1, in the range 0.908 and 1.506 except cSAR(NO_2) 1,3 where this is 2.361 and pEDA 1,3 where the ratio is 5.37. Note, however, that the ratios for 1,4-interactions are always significantly greater than those for 1,3-interactions.

A direct conclusion from the data of the Table 1 is that for 1,3-interactions the ratios are closer to 1 and do not differ much. Conversely, for 1,4-interactions, the ratios are much greater than 1 and much more differentiated. This may indicate that stronger interactions for 1,4-substituted species are associated with a significant contribution coming from the resonance interaction in the benzene series, whereas the

Fig. 10 Scheme of 1-nitro-4-amino-bicyclo[2.2.2]octane with total charges at atoms and showing some geometry parameters



through-space or field effects are similar in both series. In 1,3-interactions, however, in both series the interactions are of more comparable magnitude, and may be assumed to be due mostly to inductive/field effects.

Charges at carbon atoms analysis

The fundamental question related to the substituent effects in 1-(reaction site Y) to 4-substituted (by X)- bicyclo[2.2.2]octane derivatives concerns the character of intramolecular interactions between substituents X and reaction site Y. Is this an inductive effect or rather a field effect? An important discussion on this topic was presented in a review by Exner and Bohm [12]. In principle, the answer was that there is no fully reliable way to decide this. To solve this problem, at least in an approximate way, we decided to analyze the charges in carbon atoms in 1-nitro-4-aminobenzene and 1-nitro-4-amino-bicyclo[2.2.2]octane. Schemes of these molecules are presented in Figs. 9 and 10 together with NPA charges at the atoms indicated.

The charges at ipso-carbon atoms behave in a different way in these two systems. The difference between charges C1 and C4 in the case of benzene is 0.181 e whereas for bicyclo[2.2.2]octane is only 0.052; the ratio is 3.48. Thus, the direct interaction of the nitro group and the amino group on the substituted carbon atoms is significantly smaller in the case of bicyclo[2.2.2]octane system. The comparisons for charges at the remaining carbon atoms are more dramatic. The difference between atoms in positions 2 and 3 in par-nitroaniline is 0.092e whereas in the case of bicyclo[2.2.2]octane derivative, the greatest difference is 0.01e. This seems to show that the inductive effect is rather marginal, since if this was important, then these changes (differences) would be greater.

Conclusions

- (1) Linear regressions describing substituent effects with acceptable correlation coefficients were obtained for all substituent effect descriptors (SESE, sEDA/pEDA, cSAR) applied to 4-substituted 1-nitro-benzene and 1-nitrobicyclo[2.2.2]octane derivatives. The slopes for nitro-benzene derivatives were always much greater than for nitro-bicyclo[2.2.2]octane derivatives. This indicates much stronger interactions between substituents for benzene than for bicyclo[2.2.2]octane derivatives.
- (2) Analysis of ESD distribution of all characteristics under study showed that, in the case of pEDA, sEDA cSAR and SESE, the ratios of ESD for 1,4-substituted systems were always significantly greater for benzene derivatives than those for bicyclo[2.2.2]octane derivatives.

Conversely, a completely different picture appears for 1,3-substituted species. For all of them the ratio is much closer to 1. A general conclusion may be that interactions between Y and substituents for the 1,3-position for benzene and bicyclo[2.2.2]octane series are very similar, in contrast to those of the 1,4-series.

- (3) The difference between charges at C1 and C4 in the case of benzene is 0.181 e, whereas in bicyclo[2.2.2]octane it is only 0.052; the ratio is 3.48. Thus a direct interaction of the nitro group and the amino group on the substituted carbon atoms is significantly smaller in the latter. The difference between atoms in positions 2 and 3 in par-nitroaniline is 0.092e, whereas in the case of bicyclo[2.2.2]octane derivative, the greatest difference is 0.01e. From these small differences in charges it follows that the inductive effect is rather marginal. This result may be an important argument for the assumption that the substituent effect in 1,4 substituted bicyclo[2.2.2]octane derivatives occurs chiefly through a space interaction or field effect.

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