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REGULAR ARTICLE

Computational evidence for back donation in an N → O group based on modes of transmission of substituent effects in 3-(4′-substituted) phenylfuroxans

S NATARAJAN BALASUBRAHMANYAM[a,*], BISHWAJIT GANGULY[b], RABINDRANATH LO[c], MUSIRI M BALAKRISHNA RAJAN[d], MOORKKANNUR N SREERAG[d], P C SHARAFUDEEN[d], R A OSHIYA[d] and NACHIAPPAN RAJENDRAN[e]

[a]Formerly of the Department of Organic Chemistry, Indian Institute of Science, Bangalore, Karnataka, India
[b]Central Salt and Marine Chemicals Research Institute, Bhavnagar, Gujarat, India
[c]Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic
[d]Chemical Information Sciences Laboratory, Department of Chemistry, Pondicherry University, Puducherry, India
[e]GTN Arts College, Dindigul, Tamil Nadu, India
E-mail: snobchem@hotmail.com

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Abstract. The N-oxide nitrogen in C-4′ substituted 3-phenyl furoxans occupies a position analogous to C-β in 4-substituted styrenes that have been examined for modes of transmission of substituent effects from the C-4 substituent to C-β. From geometry optimizations through high-level MO theory calculations, it was first ensured that the N-2–C-3 liaison in 3-(4′-substituted)phenyl furoxans retains as much double-bond character as it does in the case of furoxan bearing no substituents and that the *para*-substituted phenyl and furoxan rings maintain near uniplanarity. The calculations, carried out for such furoxans, chosen to represent a spectrum of effects from electron-donor to electron-acceptor, showed how the change in the 4′-substituent affects electron redistribution within N-oxide group in the way expected: while the residual positive charge at N increases the residual negative charge at O decreases. An increase in the N-oxide bond order (as measured by the Wiberg bond index), together with a small reduction in the N-2–O-6 bond length, was also found. That these effects were not artefacts of the calculation procedure was ensured when the calculations, repeated using a different functional, showed not only inverse dependence of positive N-2 and negative O-6 net charges on N-2–O-6 bond lengths but also confirmatory evidence from N-oxide bond dissociation and second-order perturbation energies. These results are interpreted as demonstrating graded back donation from O to N within the N → O group caused by a combined action of mesomerism and π-polarisation involving the substituent at the *para*-position of the phenyl group offering a spectrum of effects from electron-releasing to electron-withdrawing.

Keywords. 3(4′-substituted)phenylfuroxans; ranges of electron-releasing and electron-attracting substituents; substituent-dependent N-oxide bond lengths from B3LYP/6-311++G; inverse residual charge changes at N-2 and O-6; N-oxide bond dissociation and second-order perturbation energies from B3LYP/6-31++G and BLYP/6-31++G; back donation from O to N in N–O dative bond.

1. Introduction

In the early 1970s, Reynolds *et al.*,[1] reported that ^{13}C shifts of C-β in a series of 4-substituted styrenes **1** accord with the ability of substituent effects being transmitted through-space (field effects), *via* conjugative interactions (resonance effects) or by a polarization of the styrene π-electron system by the polar C–X bond (π-polarization effects) as seen from columns 2 & 3 of Table 1. The substituent effects that were

*For correspondence

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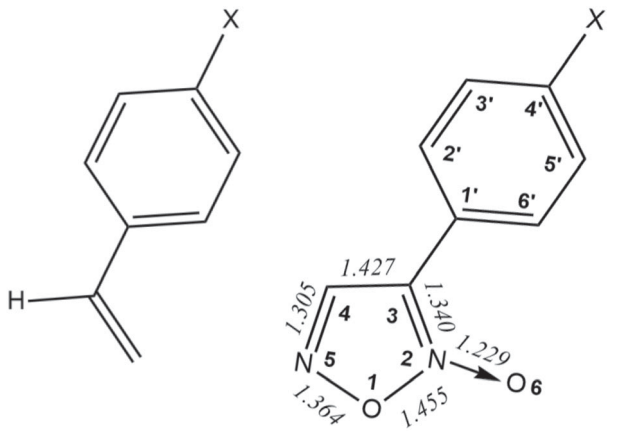
studied covered most of the spectrum from electron-releasing to electron-attracting groups among the gamut usually recommended for DSP correlations.[2] The trend of increasing deshielding of C-β (column 3, Table 1) is evident.



1 **2a:** X= NMe_2; **2b**: X= OMe; **2c**: X= Me; **2d**: X= F; **2e**: X= Cl; **2f**: X = H; **2g:** X= CF_2; **2h**: X = COMe; **2i**: X= CO_2Me; **2j**: X= CN; **2k**: X= NO_2
[Bond lengths (Å) averaged over **2a**–**2k**]

1.1 *The case of 3-(4-substituted)phenyl furoxans and the expectation of conveyance of substituent effects to N-2 on changing the substituent at C-4′ of the phenyl group*

The location of the N-oxide nitrogen (N-2) in 3-(4′-substituted)phenyl-1,2,5-oxadiazole-2-oxides **2** (3-phenyl furoxans) is similar to that of C-β in C-4 substituted styrenes **1**. The phenyl rings in the case of these monophenyl substituted furoxans were only too likely to maintain uniplanarity with isoxazole N-oxide ring or, to depart from it only to small extents. It seemed reasonable to expect that the effects of changes in the substituent at C-4′ of the phenyl group on N-2 of π-electron density may be similar to those seen in the case of C-β in styrenes **1**.[1]

1.2 *Change in the environment of N-2 accompanying the change from furoxans **2a** to **2k***

There may be many possible ways to examine changes in the environment of N-2 accompanying the change in the furoxan series **2a**–**2k**. One of them could be based on an expectation that ^{15}N chemical shifts would exhibit as a wide range of changes with a change of substituent at C-4′ as C-β does with a change of substituent at C-4 in styrenes **1**. Directly measuring the NMR line-shifts of the more abundant isotope ^{14}N would not be suitable in view of the known broadening in a high degree of these signals.[3] Getting information on the ^{15}N chemical shifts in the NMR spectra of the furoxan series **2a–2k** would

Table 1. Data for assessing the behaviour of the N-oxide moiety in furoxans **2a**–**2k** culled from Tables S1, S3 and S5 in the Supplementary Information.

Designations of substituents	C-4 substituent in styrenes **1** or C-4′ substituent in furoxans **2**	C-β ^{13}C shifts (ppm from TMS) in C-4 substituted styrenes **1a–1k***	Residual Positive charges (e) at N-2 in furoxans **2a–2k**‡	Residual negative charge (e) at O-6 in furoxans **2a–2k**‡	N-2–O-6 bond lengths (Å) in furoxans **2a–2k**‡	Wiberg bond indices (au) of N-2–O-6 bonds‡
a	NMe_2	108.93	0.33113	−0.42113	1.23337	1.4290
b	OMe	110.98	0.33689	−0.41207	1.23143	1.4374
c	Me	112.20	0.34066	−0.40671	1.23016	1.4428
d	F	113.43	0.34206	−0.40517	1.23006	1.4432
e	Cl	113.97	0.34373	−0.40191	1.22937	1.4464
f	H	113.20	0.34280	−0.40304	1.22937	1.4463
g	CF_3	116.02	0.34877	−0.39424	1.22788	1.4535
h	$COCH_3$	115.91	0.34776	−0.39637	1.22832	1.4516
i	CO_2R	–†	0.34753	−0.39593	1.22820	1.4522
j	CN	117.05	0.34965	−0.39139	1.22740	1.4557
k	NO_2	117.90	0.35248	−0.38707	1.22671	1.4592

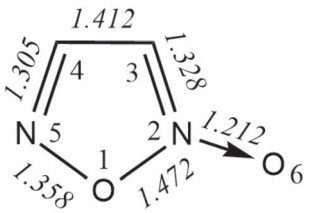
*Taken from reference 1. †Not reported in reference 1. ‡Values in columns 4–6 are from calculations at B3LYP/6-311++G** level of theory.

involve not only the synthesis of ^{15}N enriched samples but also gaining access to the needed NMR instrumentation. Also, a problem that may arise with furoxans **2** is that some or all of the synthetic procedures may yield only mixtures of furoxans **2** and their tautomers that have the N-oxide group at N-5. Separation and purification could be highly problematic.

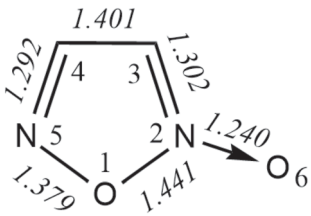
Another possible mode of investigation could be to use high-level computational methods in order to gain knowledge of what happens to the environment of N-2 when the property of the C-4′ substituent changes from electron-repellant to electron-attractant.

2. Computational methods

Pasinszky *et al.,*[4] have reported that parameters from the optimized geometry of the unsubstituted furoxan ring calculated employing the GAUSSIAN package at the B3LYP/6-311++G(2d,2p) level (together with those from certain other procedures) agreed well with those determined by X-ray crystallography.[5] Taking precaution to check whether we had the right approximations in view of cautionary statements advanced by Pasinsky *et al.,*[4] especially with reference to furoxans, we repeated the calculations. Bond lengths taken from our results and experimental ones from X-ray crystallography[5] are, respectively, presented in structures **3A** & **3B** (bond angles are included in Table S1, Supplementary Information). There were differences among the three sets but they were considered immaterial to the subject of this paper.



3A. Furoxan molecule showing bond lengths (Å) calculated at B3LYP/6-31++G** level of theory[4]



3B. Furoxan molecule showing experimentally found bond lengths (Å) by X-ray diffraction[5]

2.1 *Tasks*

Geometry optimizations for the furoxans **2a–2k** were carried out (at the B3LYP/6-311++G** level) starting with the parameters for the furoxan and the phenyl ring at C-3 taken from published X-crystallographic data[6] on 3,4-diphenylfuroxan, taking the C-4 phenyl group as having been replaced by a hydrogen. The calculated geometry-minimized values of the inter-ring dihedral angle (C-4-C-3-C-1′-C-2′ dihedral angles) ranged just between −4.148° and +0.018° (Table S2, Supplementary Information), regarded as low enough to allow passage of information between the C-4′-substituted phenyl and furoxan rings.

The averages of calculated bond lengths of the furoxan moiety in systems **2a–2k** (shown in structure **2**, and included in Table S3 (Supplementary Information), were close to those reported for the parent furoxan **3**, indicating that the former maintain the degree of aromaticity as well as bond localizations attributed to the latter.[4] Drawing an analogy of structures **2a–2k** with styrenes **1** while changing the substitution at position C-4′ of the phenyl group in the furoxans appeared justified under this circumstance. There was one significant difference: the C-3–C-4 bonds, longest at 1.43 Å on the average (Table S3, column 5), were longer than in system **3** (1.406 Å). However, the N-2–O-6 bonds (1.24 Å on average) were closely similar in length to that in system **3** (1.24 Å).

A point noteworthy for the discussion to follow is that, based on natural population analysis (NPA), Pasinszky *et al.*[4] had reported that the residual charge at N-2 is moderately positive (+0.36 e) while that at the connected O-6 is negative (−0.39 e) in the unsubstituted furoxan **3**.

Since it was not possible to take into account in the calculations, rotation of either the phenyl rings with respect to the furoxan ring or of independent rotations of substituents that are non-symmetric to rotation about the *ipso* axis (e.g. –COMe, –CO_2Me), the C-2′–C-3′ and C-5'–C-6' bond pairs in the phenyl moieties were not expected to appear equivalent. This element of non-symmetry acts in addition to the one inherent to the N-oxide oxygen being nearer one side of the phenyl ring in the optimized geometry of a 3-phenylfuroxan.

3. Results and Discussion

3.1 *Expected changes in the NPA residual charges at N-2 and O-6 and N–O bond lengths*

Tabulation of data from the GAUSSIAN calculations carried out at the B3LYP/6-31++G** level, disclosed interesting trends in N-2–O-6 bond lengths and changes in net charge distributions (by NPA) down the series from **2a** to **2k**. However, it was

found that these trends could be made visually evident only when the net positive charges at N-2 or net negative charges at O-6 were magnified by multiplication by 1000 before plotting against the bond length changes, as diagrammed in Figures 1A and 1B, reproduced in columns 4 & 5 in Table 1 from data taken from Table S4, Supplementary Information. The positive charge at N-2 showed an *increasing* trend aligned with *decreasing* electron-releasing capacity of the substituent at C-4′. While this trend was what was to be expected wholly unexpected was a *decreasing* trend in the residual negative charge at O-6.

Two other features were also noticeable. The first, as can be made out from Table S4, is what appears to be a general drift of negative charge within the furoxan ring, from the C-4 - N-5 - O-1 side towards the C-3 - N-2 side towards the increasingly positive N-2 down the **2a**-**2k** series. There are small general readjustments, by way of bond length changes down the series, most noticeably as a shortening of the O-1 - N-2 bond (Table S3).

The second feature is the commonly found close or even jumbled positioning of the halogens and halogen-containing substituents relative to hydrogen as a substituent. This appears attributable to a shifting balance between their two opposing dual capabilities, one of eletropositivity that is electron-attractive and the other of electron-releasing mesomeric effect.

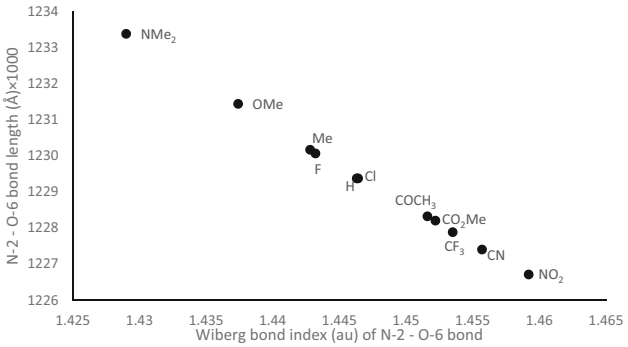


Figure 2. Plot of N-2–O-6 bond lengths (Å) against Wiberg Bond Indices (au) in furoxans **2a**–**2k**.

3.2 *Unexpected changes in and N–O bond lengths*

There is also clear evidence, as seen in column 6 of Table 1, that the N-2–O-6 bond length *decreases* attending the change from **2a** to **2k**. This decrease was unexpected, and somewhat counterintuitive, in that the change of the C-4′ substituent from the electron-releasing $–NMe_2$ to the electron-withdrawing $–NO_2$ would lead one to expect both a *lengthening* and an associated *weakening* (lessening of bond order), of the N-oxide bond. But, as is apparent from Figure 2 (constructed from GAUSSIAN outputs assembled in Table 1 column 7), the opposite effects, N–O bond *shortening* and a concomitant *increase* in the Wiberg bond indices are seen. The linear correlation was judged to be 'good,' with least-squares fit having a correlation coefficient of 0.9845.

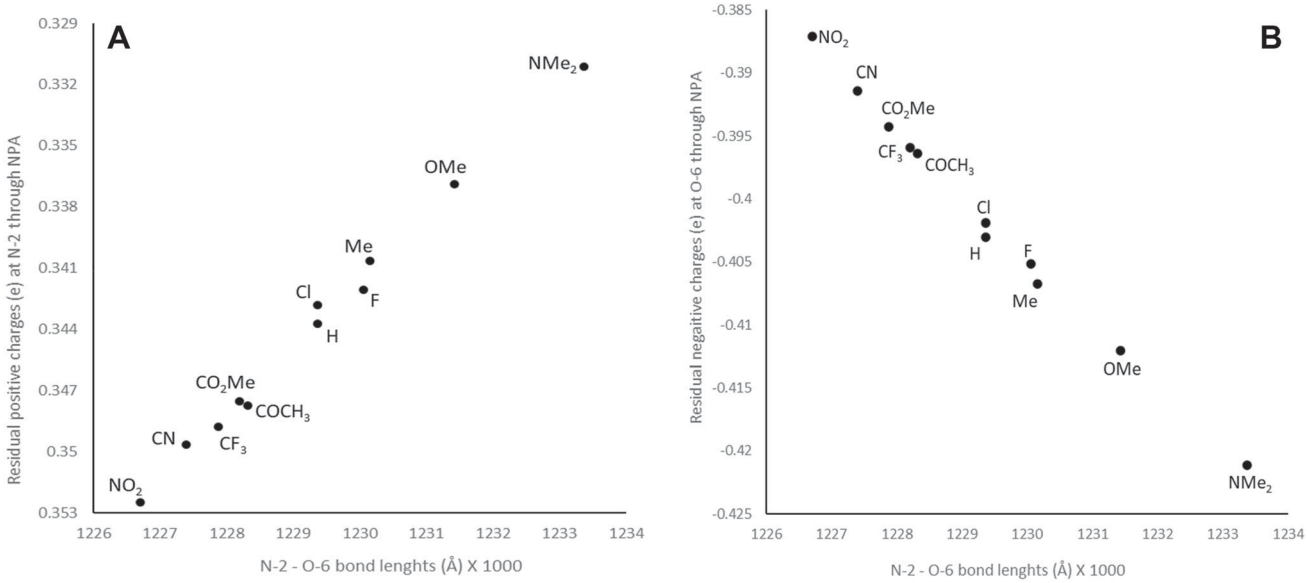


Figure 1. **A**. Plot of NPA residual positive charges at N-2 *versus* N-2–O-6 bond lengths. **B**. Plot of NPA residual negative charges at O-6 *versus* N-2–O-6 bond lengths.

Since the changes in net charges, both at N-2 and O-2 were small there was cause for concern in that we could be dealing with artefacts of the calculation procedure. Any attempt at interpretation would then amount to building a superstructure on flimsy foundations. We sought confirmation of the observed trends by carrying out further calculations using a different functional (e.g. GGA functional, BLYP) than hybrid-functional B3LYP/. Given our past experiences, we considered it impractical to employ the reputedly highly accurate methods (like CCSD or CCSD(T)) used by Pasinszky *et al.,* besides B3LYP/6-311++G(2d,2p)[4] not only because of the large size of the substituted furoxans but also because of the long time expected to be taken. The desired parameters using BLYP/6-31++G** are placed in Table S5 (Supplementary Information). The calculated results with BLYP functional follow the same trends as observed with B3LYP functional. From Table 2 (with information taken from Table S6) it is clearly seen that both the N-2 and O-6 NBO interactions and bond dissociation energies increase down the **2a**–**2k** series.

The order of correlation, the spectrum of changes from mesomerically electron-releasing to mesomerically electron-withdrawing, has remained remarkably consistent with what has been seen in myriad studies of the correlation of various properties under different conditions, ranging from dissociation constants of substituted benzoic acids to ^{13}C NMR chemical shifts in many series.[7] The intra-furoxan ring bond length re-adjustments were negligibly small (Table S3) with the exception of shortening of the O-1–N-2 and N-2–O-6 bonds. Since the latter changes were themselves small, it seemed prudent to test separately for a possible trend in the (calculated) net negative charge at O-6 and relate them to bond dissociation energies (BDE). The inverse dependence is apparent in the plot in Figure 3 that shows a least-squares correlation coefficient of 0.9574 even while preserving the known order of the spectrum of mesomeric change from electron-releasing to electron-attracting.

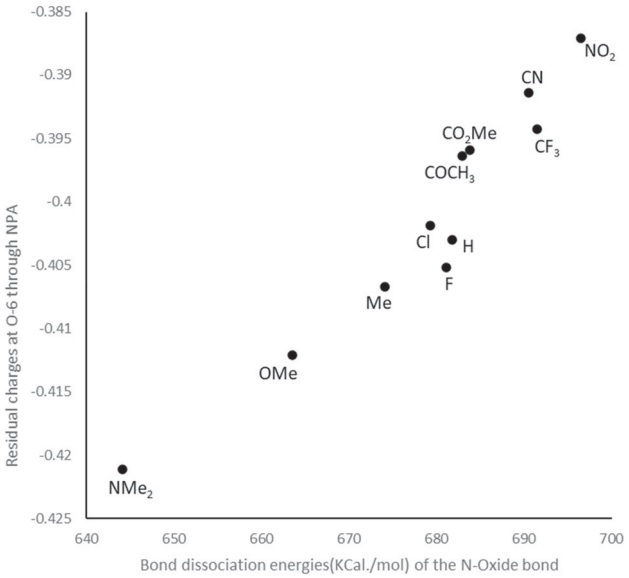


Figure 3. Plot of residual negative charges (e) at O-6 against bond dissociation energies of the N-oxide bond in furoxans **2a**–**2k**.

To confirm further the presence of the trends described so far we calculated the second-order perturbation energy (E^2) data within NBO analysis in the furoxan series **2a**–**2k** calculated at B3LYP/6-31++G** level of theory. The most significant perturbation, seen from the 5th column of Table 2, appears as a donation of the lone-pair on oxygen (O6)

Table 2. Second-Order Perturbation Energy data within NBO analysis, taken from Table S5, and bond dissociation energy values in furoxans **2a**–**2k** calculated at B3LYP/6-31++G** level of theory.

Substituent designation	NBO (au) of the N-2–O-6 bond	Bond dissociation energy (kcal/mol)	E2 (kcal/mole)	
			LP (O6) → σ*(N2-O1)	LP (O6) → σ*(N2-C3)
NMe_2	0.988595	644.1	1.1, 45.3	7.5, 7.0, 64.9
OCH_3	0.988650	663.5	1.1, 45.4	7.5, 7.3, 67.3
Me	0.988665	674.1	1.1, 45.4	7.5, 7.3, 68.5
F	0.988685	681.1	1.1, 45.2	7.5, 7.4, 69.1
Cl	0.988705	679.3	1.1, 45.3	7.5, 7.4, 69.7
H	0.988695	681.8	1.0, 45.5	7.5, 7.4, 69.4
CF_3	0.988745	691.5	1.1, 45.2	7.5, 7.5, 71.6
COMe	0.988715	682.9	1.1, 45.1	7.5, 7.5, 70.7
CO_2R	0.988725	683.8	1.1, 45.2	7.5, 7.5, 71.0
CN	0.988775	690.5	1.1, 45.2	7.5, 7.5, 72.1
NO_2	0.988790	696.5	1.1, 45.0	7.5, 7.6, 73.1

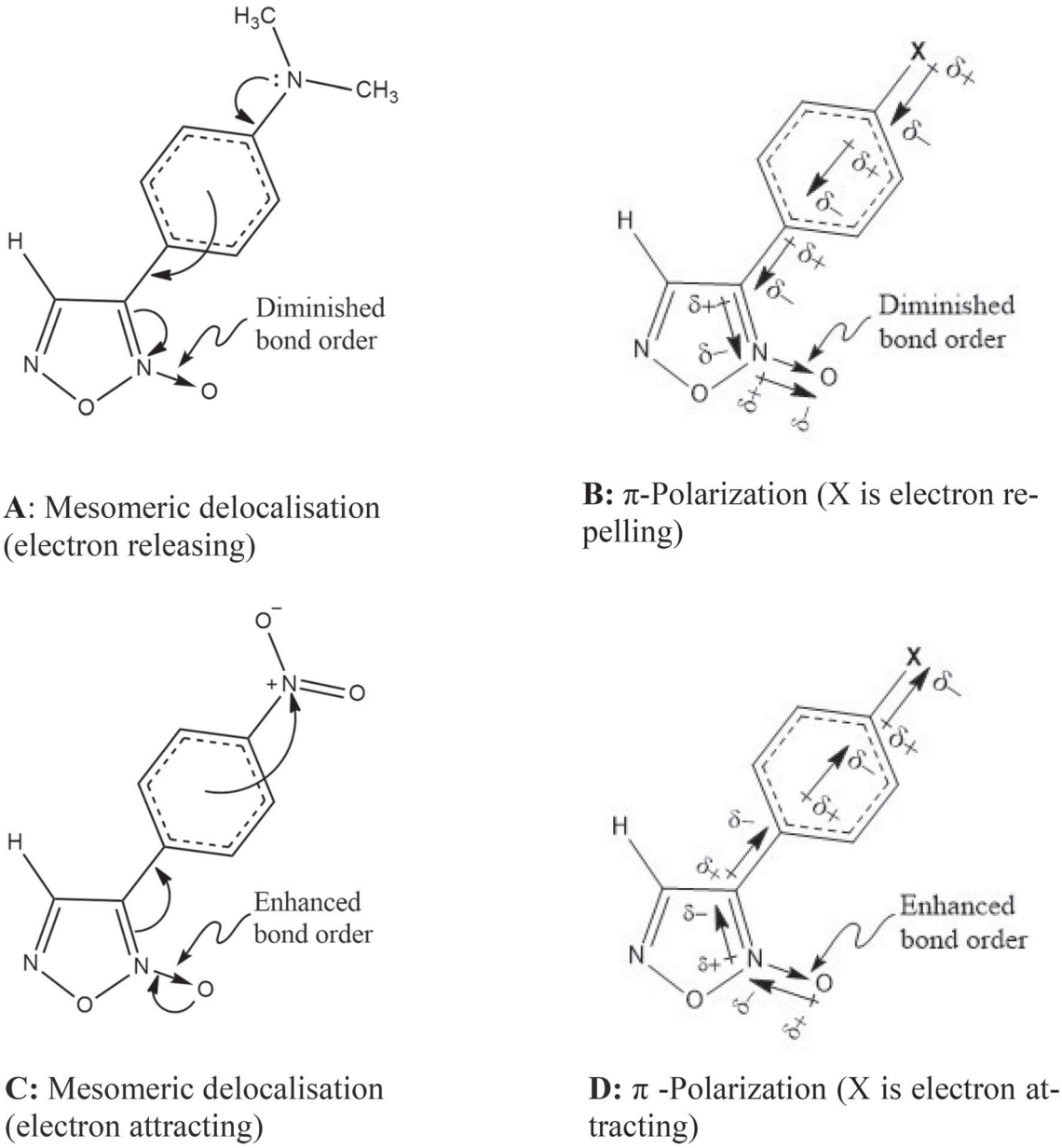


Figure 4. Modes of conveyance of effects **A** and **C** *via* mesomeric delocalisation and **B** and **D** *via* π-polarisation.

to the N-2–C-3 anti-bonding σ* orbital possibly because of favourable orientation. The implied delocalization is also consistent with a tightening of the N-oxide bond with an increasing electron-withdrawal property of the C-4′ substituent.

3.3 *Discussion*

We believe that we now have sufficient proof that the unusual effect of increasing BDE attending increasing electron withdrawal from nitrogen N-2 is caused by two factors. The *initial* situation is describable by a mesomeric drift of negative charge towards N-2, reinforced by π-polarization, as illustrated for the case of the electron-releasing substituent $–NMe_2$ at C-4′, as depicted in Figures 4A and 4B. This flooding of negative charge causes a withdrawal of negative charge towards O-6, as is to be expected due to electron–electron repulsion causing π-polarization within the N-oxide group, an effect that includes *lessening* of N-2–O-6 bond order. This position is modified to its opposite, as electron-release changes into electron-withdrawal. In that case, with an electron-withdrawing substituent, illustrated with $–NO_2$ at C-4′ (Figures 4C and 4D), electron-withdrawal causes N-2 to become more positive. The consequent change in π-polarization results in the exocyclic oxygen O-6 to back

donate.[8] This happens to increase extents with N-2, enhancing the N-oxide bond order as electron-release changes to electron-withdrawal. The N-oxide group can, thus, be seen as having a form of buffering ability.

It is interesting to speculate in this context that the decrease in N-O bond length down the **2a**–**2k** series can be ascribed to an increase in positive charge at N-2 with a simultaneous increase in the negative charge at O-6, bringing the N and O centers nearer.

4. Conclusions

The increase in the Wiberg bond index of the N-oxide bond as electron-donation from the phenyl C-4′ substituent gets lower (column 7 Table 1 and as implied in Figure 2) is counterintuitive and would not be normally expected. We believe that our finding that the N → O dative bond gets strengthened by a back donation from O to N through our calculations based on bonding theoretical methods may be unique to the N-oxide group in the particular situation found in furoxans **2a**–**2k**. We believe this finding is among the few to provide a theoretical basis for the transmission of mesomeric substituent effects. It is important to note that, in the methods of calculation we have used, through-space inductive effects, likely to be exerted by the C-4′ substituent on the centre of electron distribution within the N-oxide bond, needed for dual substituent parameter (DSP) correlations, are not taken into account. An interesting related question of whether there is an 'overreaction' on the part of the N-oxide oxygen remains open.

Supplementary Information (SI)

Tables S1-S6 are available at www.ias.ac.in/chemsci.

Acknowledgement

The authors thank the reviewer for constructively suggesting how to confirm the small change observed of the calculated N-oxide bond lengths with a change in C-4′ substituent in the furoxan series is not merely an artefact of the calculation procedure. We have included confirmatory calculations and discussed the results.

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