

A Novel Approach to the Evaluation of the Importance of Steric and Electronic Effects in S_NAr Reactions: A Computational, Thermodynamic and 1H and ^{13}C NMR Study of “Meisenheimer-Type” Adducts in the Benzo[*b*]thiophene Series

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The synthetically useful nucleophilic attack on nitrobenzo[*b*]thiophenes, a starting point for ring-opening/ring-closure pathways to different heterocyclic systems, has been investigated in detail. 3-Nitrobenzo[*b*]thiophene (**9**) and 2-nitrobenzo[*b*]thiophene (**10**) react with sodium methoxide in either DMSO or methanol to give the relevant “Meisenheimer-type” adducts **9'** and **10'**, identified by NMR spectroscopy. A UV study indicated that the equilibrium constants for the formation of **9'** at 293 K are 10.1 and 40 700 Lmol⁻¹ in methanol and in DMSO, respectively. Competition reactions showed that the stability constant of **10'** is lower than that of **9'**: accordingly, DFT [B3LYP/6-31+G(d,p)] calculations indicate that the formation of **9'** is thermodynamically more favoured than that of **10'** both in the gas phase and in DMSO. The reason for the opposite sequence in the stability constants previously found for the corresponding *gem*-dimethoxy Meisenheimer adducts **7'** and **8'** was therefore investigated in depth and appears to be a consequence of different steric interactions in the starting compounds, 2-methoxy-3-

nitro-**(7)** and 3-methoxy-2-nitrobenzo[*b*]thiophene (**8**), respectively. A study of ^{13}C NMR chemical shift changes accompanying the formation of adducts **9'** and **10'** confirms that the formation of the adduct exhibiting the larger stability constant is accompanied by a smaller π electron density redistribution, as we have previously found in other cases all governed by electronic effects. The opposite behaviour is observed in the formation of the *gem*-dimethoxy adducts **7'** and **8'**, which is a consequence of the predominance of steric effects. Further outcomes of more general interest deal with the aromatic character of benzo[*b*]thiophenes. NMR spectroscopic data and calculated bond lengths show that in the studied reactions the benzene ring, unlike the thiophene one, is scarcely affected by methoxide addition, retaining its nearly “full” aromatic character. Benzocondensation increases the stability constants of σ -adducts mainly because of a marked reduction in the aromatic character of the thiophene ring in the substrates.

Introduction

The flexible chemical behaviour of thiophene-based ring systems is an everlasting and fascinating research field.^[1] In particular, nucleophilic attack on nitro-activated thiophenes and benzo[*b*]thiophenes can lead to ring-opening/ring-closure processes affording different hetero- and homocycles with decorations hardly obtainable in a “straightforward” approach. Amine attack on 3,4-dinitrothiophene^[2a,2b] leads

to ring-opening products (with extrusion of hydrogen sulfide) exhibiting broad synthetic usefulness.^[2] Conversely, 2-nitrothiophene,^[2j] 3-nitrothiophene^[1g] and 3-nitrobenzo[*b*]thiophene^[1h] react with amines in the presence of silver nitrate to give ring-opening products with retention of the sulfur, which can easily be alkylated. In particular, the ring-opening product of 3-nitrobenzo[*b*]thiophene is an interesting building block for the synthesis of several different heterocyclic systems, such as thiochroman *S,S*-dioxides,^[2e] γ -lactams,^[2f] indoles^[2g] and pyrrolidinone oxazines.^[2h] Several of the above-mentioned compounds have revealed analgesic, anti-exudative, and anti-inflammatory activities,^[3a,3b] whereas in other cases their mutagenic^[3c–3e] or polarographic behaviour^[3f–3h] has been investigated in depth.

All the synthetically useful ring-opening/ring-closure protocols starting from 3-nitrobenzo[*b*]thiophene exhibit as their first steps a nucleophilic attack on the fused thiophene ring. We therefore decided to investigate nucleophilic attack on nitrobenzo[*b*]thiophenes, through a detailed study of the relevant “Meisenheimer-type” adducts.

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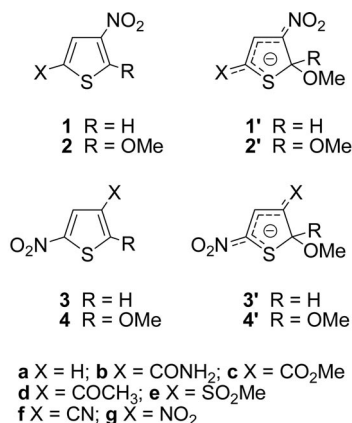
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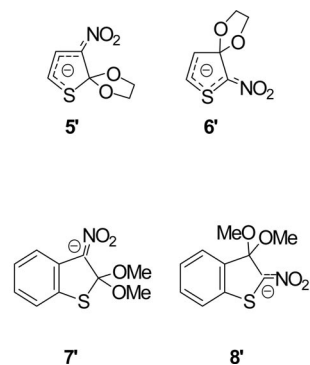
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These adducts have been studied as models of intermediates in nucleophilic aromatic substitutions occurring through the classic S_NAr mechanism.^[1a,4] In some earlier reports NMR spectroscopy was used only to identify the adducts, but some authors^[5] soon afterwards stressed that, for those carbons retaining their sp^2 hybridization during the formation of the adduct, ^{13}C chemical shift changes relative to the starting compounds can be good indicators of variation in their π electron densities. Although the first attempts^[5a,5b] to correlate sums of such chemical shift changes and stability constants in homogeneous series of Meisenheimer adducts met with some difficulties, we have shown^[6a] that such correlations do hold if restricted to substituents that exhibit the same kind of resonance effect (e.g., π -polarization rather than through-conjugation).

In this context we have carried out a comparative study^[6a–6d] of the reactions of sodium methoxide with some 4-nitro-2-*X*-thiophenes **1**, 2-methoxy-3-nitro-5-*X*-thiophenes **2**, 2-nitro-4-*X*-thiophenes **3** and 2-methoxy-5-nitro-3-*X*-thiophenes **4**, yielding the corresponding σ adducts **1'–4'**. In particular, we have found that in the sequence **1/1'**, **3/3'**, **2/2'**, **4/4'** for the same *X* group, the stability constants of the adducts increase as the sums of the ^{13}C chemical shift changes at C-3, C-4 and C-5 ($\Sigma\Delta\delta$) on going from **1–4** to the relevant adducts decrease. The explanation given^[6d] is that when ring carbons in the substrates are already markedly shielded because of the natures of substituents (e.g., OMe in **2** and **4**) or their relative locations, a lower π electron distribution change is necessary to form the adduct and so the relevant stability constant is then larger.

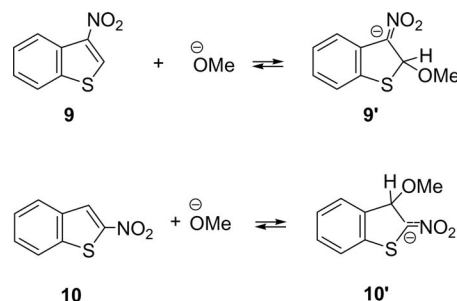


Attempts have been made to prepare Meisenheimer-type adducts at carbon atoms β to sulfur in nitro-activated thiophenes, but both 3-methoxy-2-nitrothiophene^[6e] and 2-nitrothiophene itself^[6f,6g] underwent methoxide attack at C-5. We therefore synthesized^[6h,6i] the spiro-Meisenheimer adducts **5'** and **6'** in $[D_6]DMSO$ by treatment of 2-(2-hydroxyethoxy)-3-nitrothiophene (**5**) or 3-(2-hydroxyethoxy)-2-nitrothiophene (**6**), respectively, with sodium methoxide and showed^[6i] that **6'** has a lower stability constant than **5'**, suggesting a similar sequence in the stability constants of the corresponding *gem*-dimethoxy adducts.



A pioneering study by De Santis and Stegel several years ago,^[7] however, showed that in the benzo[*b*]thiophene series both the 2-methoxy-3-nitro and the 3-methoxy-2-nitro derivatives (**7** and **8**, respectively) gave the corresponding Meisenheimer adducts **7'** and **8'** and that the latter even exhibits a slightly larger stability constant (6.0×10^2 vs. 3.7×10^2 L mol⁻¹ in methanol, as determined by UV spectroscopy).

At this stage, our current interest in S_NAr reactions of sulfur heterocycles,^[1a,2d,2i,2j,6] and particularly in those giving access to synthetically useful processes,^[2] prompted us to study the formation, stability, structures and π electron distributions of “Meisenheimer-type” adducts **9'** and **10'**, obtainable by sodium methoxide addition to 3-nitrobenzo[*b*]thiophene (**9**) or 2-nitrobenzo[*b*]thiophene (**10**), respectively, in either $[D_6]DMSO$ or $[D_4]MeOH$, with particular regard to the effect of the benzocondensation (Scheme 1).



Scheme 1.

Moreover, the previously studied formation of the adducts **7'** and **8'** has been revisited in the light of the current results for **9'** and **10'**. The conclusions overcome the specific problem of the relative reactivities of benzo[*b*]thiophene carbons α and β to the sulfur atom, because they provide new insight into the aromatic character and general reactivity of such fused ring systems and moreover they suggest a possible novel approach to the study of the relative importance of steric and electronic effects.

Table 1. ¹H and ¹³C NMR chemical shifts for 3-nitrobenzo[*b*]thiophene (**9**) and its corresponding methoxide adduct **9'** in [D₆]DMSO. The corresponding data in [D₄]MeOH are reported in parentheses. For comparison, NMR spectroscopic data for 3-nitrothiophene (**1a**) and its methoxide adduct **1'a** are also reported.

	δ 9 ^[a]	9'	$\Delta\delta$ (9' - 9)		δ 1a ^[b]	1'a ^[b]	$\Delta\delta$ (1'a - 1a) ^[b]
H-2	9.28 (8.94)	6.31 (6.42)	-2.97 (-2.52)	H-2	8.76	6.12	-2.64
H-4	8.47 (8.52)	7.07 (7.09)	-1.40 (-1.43)	H-4	7.65	6.30	-1.35
H-5	7.67 (7.60)	6.86 (7.09)	-0.81 (-0.51)	H-5	7.74	5.82	-1.92
H-6	7.59 (7.52)	6.97 (7.09)	-0.62 (-0.43)	-	-	-	-
H-7	8.21 (7.99)	8.09 (8.22)	-0.12 (0.23)	-	-	-	-
CH ₃	-	3.20 ^[c]	-	CH ₃	-	3.10	-
C-2	136.08 (134.91)	87.91 (87.94)	-48.17 ^[d] (-46.97) ^[d]	C-2	129.76	86.52	-43.24 ^[d]
C-3	141.36 (143.58)	118.08 (123.68)	-23.28 (-19.90)	C-3	148.01	122.97	-25.04
C-3a	129.48 (131.32)	133.50 (132.59)	4.02 (1.27)	C-4	122.15	119.37	-2.78
C-7a	138.41 (140.31)	134.33 (138.89)	-4.08 (-1.42)	C-5	128.90	114.50	-14.40
C-4	122.92 (124.56)	121.28 (122.81)	-1.64 (-1.75)	-	-	-	-
C-5	127.04 (128.03)	123.26 (127.70)	-3.78 (-0.33)	-	-	-	-
C-6	126.27 (127.46)	123.79 (125.26)	-2.48 (-2.20)	-	-	-	-
C-7	123.85 (124.38)	121.68 (125.48)	-2.17 (1.10)	-	-	-	-
CH ₃	-	52.90 (49.84)	-	CH ₃	-	51.84	-
$\Sigma\Delta\delta_{\text{th}}^{\text{[e]}}$	-	-	-23.3 (-20.1)	-	-	-	-42.2
$\Sigma\Delta\delta^{\text{[f]}}$	-	-	-33.4 (-23.3)	-	-	-	-

[a] [D₆]DMSO chemical shifts from ref.^[2k] [b] From ref.^[6d,6k] [c] Obscured in [D₄]MeOH. [d] Not included in the sums. [e] The sum includes thiophene ring carbon atoms retaining sp² hybridization. [f] The sum includes all ring carbons retaining sp² hybridization.

Results and Discussion

NMR Evidence of Adducts **9'** and **10'**

When 3-nitrobenzo[*b*]thiophene (**9**) in [D₆]DMSO or in [D₄]MeOH is treated with an equimolar amount of sodium methoxide (6 M in methanol), the adduct **9'** is formed, as shown by the general upfield shift in the ¹H and ¹³C NMR spectroscopic data (see Table 1) and the quantitative restoration of **9** on acidification with trifluoroacetic acid.

As further support for the structural assignment, in the ¹³C NMR spectrum in [D₆]DMSO, the C-2 appears as a sharp doublet of quartets, exhibiting a large decrease in ¹J(C,H) value with respect to the starting compound **9** (from 194.1 to 169.1 Hz, ratio 0.87), consistently with its reduced s character, whereas the new signal of the methoxy carbon appears, as would be expected, as a quartet of doublets (*J* = 141.4 and 5.0 Hz). The [D₄]MeOH spectrum is affected by overlapping of signals and deuteration at C-2, so its interpretation was assisted by spectra run in [D₆]DMSO/[D₄]MeOH mixtures to track the regular shift of each signal as the methanol fraction increases.

For purposes of comparison, Table 1 also reports ¹H and ¹³C NMR spectroscopic data for the previously discussed^[6d,6k] formation of the adduct **1'a** from 3-nitrothiophene (**1a**) in [D₆]DMSO, which was accompanied by a similar decrease in the chemical shifts of H-2, C-2 and C-3, with the ¹J(C-2,H-2) value decreasing from 195.5 to 172.8 Hz (ratio 0.88), but also with a noticeable decrease in the chemical shift of C-5 (corresponding to C-7a in the benzo[*b*]thiophene system).

When 2-nitrobenzo[*b*]thiophene (**10**) is treated with sodium methoxide either in [D₆]DMSO or in [D₄]MeOH, the NMR signals of the starting compound are still visible, together with the signals (much smaller in [D₄]MeOH) of a new species, which was identified as the adduct **10'** on the basis of general shielding with respect to the starting compound (see Table 2) and the recovery of **10** by simple acidification. In the [D₆]DMSO spectrum of **10'** the signal of C-3 appears, as would be expected, as a doublet of multiplets, with ¹J(C,H) reduced from 178.7 to 153.4 Hz (ratio 0.86), whereas the methoxy carbon exhibits a quartet of doublets (*J* = 140.8 and 5.5 Hz). Further details are reported in the Exp. Section.

Table 2. ^1H and ^{13}C NMR chemical shifts for 2-nitrobenzo[*b*]thiophene (**10**) and its methoxide adduct **10'** in $[\text{D}_6]\text{DMSO}$. The corresponding data in $[\text{D}_4]\text{MeOH}$ are reported in parentheses.

	δ 10	10'	$\Delta\delta$ (10' – 10)
3-H	8.61 (8.34)	5.80 (6.00)	–2.81 (–2.34)
4-H	8.15 (8.02)	7.36 (7.40)	–0.79 (–0.62)
5-H	7.68 (7.52)	7.10 (7.19)	–0.58 (–0.33)
6-H	7.58 (7.61)	7.25 (7.25)	–0.33 (–0.36)
7-H	8.13 (7.95)	7.25 (7.32)	–0.88 (–0.63)
CH_3	–	3.21 ^[a]	–
C-2	150.45 (152.37)	108.99 (119.91)	–41.46 (–32.46)
C-3	127.14 (127.03)	79.73 (80.77)	–47.41 ^[b] (–46.26) ^[b]
C-3a	136.11 (137.66)	137.13 (136.54)	1.02 (–1.12)
C-7a	139.79 (141.51)	139.50 (139.75)	–0.29 (–1.76)
C-4	126.26 (128.20)	123.94 (126.08)	–2.32 (–2.12)
C-5	129.52 (127.21)	126.53 (127.67)	–2.99 (0.46)
C-6	127.53 (130.29)	128.89 (130.92)	1.36 (0.63)
C-7	123.41 (123.97)	121.48 (122.90)	–1.93 (–1.07)
CH_3	–	53.87 (51.16)	–
$\Sigma\Delta\delta_{\text{th}}^{\text{[c]}}$	–	–	–40.7 (–35.3)
$\Sigma\Delta\delta^{\text{[d]}}$	–	–	–46.6 (–37.4)

[a] Obscured in $[\text{D}_4]\text{MeOH}$. [b] Not included in the sums. [c] The sum includes thiophene ring carbon atoms retaining sp^2 hybridization. [d] The sum includes all ring carbons retaining sp^2 hybridization.

UV Determination of the Equilibrium Constant of **9'**

The equilibrium constants for the formation of **9'** were measured at 298 K through UV/Vis spectral measurements on solutions of **9** in the presence of increasing amounts of sodium methoxide in several methanol/DMSO mixtures. The spectra of **9** and of **9'** in methanol show maxima at 339 and 346 nm, respectively. The unusual and small bathochromic shift now observed ($\Delta\lambda = 7$ nm) is comparable to those observed in the formation of the adducts **2a'**, **7'** and **8'** from the corresponding substrates **2a**, **7** and **8**.^[6d,6g,7]

The equilibrium constant (K_{c}) was found to increase with increasing sodium methoxide concentration. This effect had already been noted and related to ion-pair formation.^[8] Graphic extrapolation of the K_{c} versus $[\text{MeONa}]$ plot to zero concentration of sodium methoxide gave K_{c} values of 16.80, 26.93, 58.85, 74.55 and 215.5 L mol^{-1} for 9:1, 8:2, 7:3, 6:4, and 1:1 MeOH/DMSO solutions, respectively.

As would be expected, K_{c} significantly increases with the DMSO molar fraction (N_{DMSO}), much in keeping with the well-known different solvating abilities of aprotic and protic

dipolar solvents.^[4a] Here, as generally observed, $\log K_{\text{c}}$ linearly correlates with N_{DMSO} [$\log K_{\text{c}} = (1.01 \pm 0.05) + (3.61 \pm 0.21) N_{\text{DMSO}}$, $n = 5$, $r = 0.995$]. The good quality of the correlation allowed us to calculate the K_{c} values in pure methanol as well as in pure DMSO by extrapolation (10.1 and 40 738 L mol^{-1} , respectively). Further details are given in the Experimental Section.

From the calculated values of the equilibrium constants in methanol and in DMSO the relevant free energy changes at 298 K were determined as –1.37 and –6.28 kcal, respectively, thus indicating, particularly in DMSO, the higher stability of the reaction products with respect to the starting compounds. This is consistent with the NMR study, which also showed that this conclusion can be extended to the equilibrium involving **10** in $[\text{D}_6]\text{DMSO}$.

Interestingly enough, because of the effects of the benzocondensation on the aromaticity (see the discussion on this point in the Conclusions) we have been able, for the first time in a mononitro-substituted heterocycle not containing pyridine-like nitrogen atoms, to calculate the K_{c} value for the formation of the non-geminal “Meisenheimer-type” adduct from 3-nitrobenzo[*b*]thiophene both in methanol and in DMSO, by the above procedure.

Competition Reactions

The formation equilibria of the two adducts **9'** and **10'** both in $[\text{D}_6]\text{DMSO}$ and in $[\text{D}_4]\text{MeOH}$ were compared by mixing together solutions containing **9** and sodium methoxide (0.5 equiv.) and solutions containing **10** and sodium methoxide (0.5 equiv.). The subsequent trends to chemical equilibrium were monitored by ^1H NMR spectroscopy. The equilibrium constant of **9'** was found to be the larger in both solvents. See the Exp. Section for details.

DFT Calculations

a) Energies

The energies of **9**, **9'**, **10** and **10'** were determined both in the gas phase and in the presence of DMSO, simulated by means of the implicit method (CPCM-SCRF).^[9] The calculation level adopted (DFT/B3LYP),^[10] in conjunction with the accurate Pople-type basis set 6–31+G(d,p), is able both to take correlation energy into account and to describe intramolecular interactions. All of the calculations were performed with the Gaussian03 software.^[11]

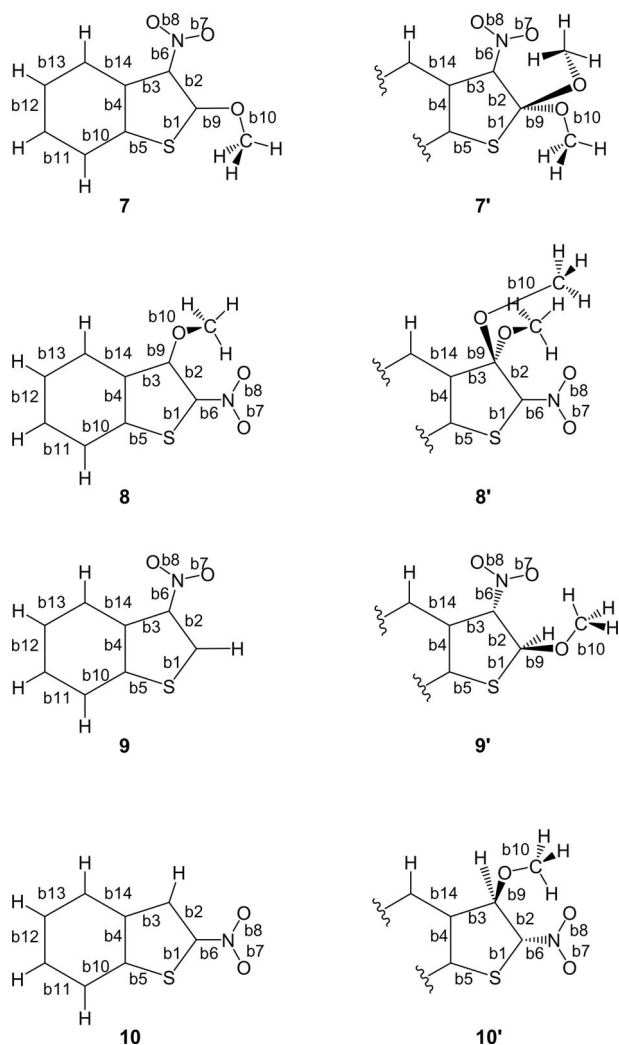
Table 3 reports some calculated energy differences indicating the relative stabilities of the products and the reactants. It stands out that the examined 3-nitro derivatives (**9** and **9'**) are more stable than the corresponding 2-nitro ones (**10** and **10'**) and that the difference between the adducts is greater than that between the starting compounds. The formation of the adduct **9'** is thus calculated to be significantly more favoured than that of **10'** (see $\Delta\Delta E$ values in Table 3), although DMSO as solvent exhibits some levelling effect with respect to the gas phase.

Table 3. Calculated energy differences (kcal mol⁻¹).

	Gas phase	DMSO
ΔE (10 – 9)	1.77	1.59
ΔE (10' – 9')	9.38	4.93
$\Delta\Delta E$	7.61	3.34

b) Geometries

In order to find an explanation for this greater stability constant of the “Meisenheimer-type” adduct **9'** with respect to **10'** and also for the opposite nature of the sequence in the stability constants previously found^[7] for the corresponding *gem*-dimethoxy adducts **7'** and **8'** we calculated the geometrical parameters of **7**–**10**, **7'**–**10'** and benzo[*b*]thiophene by the same method as described above. Selected results obtained for DMSO solutions are shown in Figure 1 and in Table 4, whereas more extensive data are given in the Supporting Information.

Figure 1. Calculated geometries for the substrates **7**–**10** and the adducts **7'**–**10'**.

The calculated geometries illustrate that the molecules of the nitrobenzo[*b*]thiophenes **9** and **10** are entirely planar. In 2-methoxy-3-nitrobenzo[*b*]thiophene (**7**) the methoxy group

Table 4. Calculated bond lengths [Å] and angles [°] for substrates **7**–**10**, adducts **7'**–**10'**, and benzo[*b*]thiophene (BT) in DMSO. Experimentally determined values for thiophene (TH) from the literature are reported for purposes of comparison.

	TH ^[a]	BT	7	8	9	10	7'	8'	9'	10'
<i>b1</i>	1.71	1.754	1.750	1.762	1.715	1.754	1.937	1.778	1.843	1.779
<i>b2</i>	1.37	1.361	1.399	1.394	1.373	1.370	1.520	1.532	1.507	1.504
<i>b3</i>	1.42	1.444	1.457	1.439	1.452	1.428	1.453	1.527	1.454	1.512
<i>b4</i>	1.37	1.420	1.414	1.415	1.419	1.425	1.421	1.398	1.419	1.405
<i>b5</i>	1.71	1.760	1.765	1.754	1.763	1.756	1.770	1.777	1.783	1.783
<i>b6</i>	–	–	1.412	1.408	1.432	1.422	1.349	1.324	1.343	1.324
<i>b7</i>	–	–	1.246	1.249	1.242	1.244	1.284	1.307	1.293	1.303
<i>b8</i>	–	–	1.249	1.245	1.241	1.240	1.290	1.293	1.290	1.298
<i>b9</i>	–	–	1.318	1.341	–	–	1.394	1.423	–	–
<i>b9'</i>	–	–	–	–	–	–	1.395	1.423	1.439	1.452
<i>b1-b6</i>	–	–	–	117.0	–	119.5	–	116.4	–	119.4
<i>b2-b6</i>	–	–	122.4	128.8	120.2	125.5	119.0	128.5	120.2	126.0
<i>b3-b6</i>	–	–	124.4	–	125.4	–	125.0	–	125.5	–
<i>b6-b7</i>	–	–	119.8	117.4	118.9	117.7	121.1	118.5	120.6	119.6
<i>b6-b8</i>	–	–	118.2	119.7	118.3	118.8	120.4	122.5	120.7	121.3
<i>b1-b9</i>	–	–	121.9	–	–	–	108.1	–	105.4	–
<i>b2-b9</i>	–	–	125.8	129.9	–	–	118.4	114.2	114.8	114.3
<i>b3-b9</i>	–	–	–	119.0	–	–	109.1	114.5	–	–
<i>b9-b10</i>	–	–	119.3	120.0	–	–	116.9	116.9	114.5	114.4
							117.0	117.0		

[a] See ref.^[1a], p. 309.

can orient itself further from the nitro group (see Figure 1), the molecule still being planar, with the full nitro group and the methoxy carbon in the ring plane and only two methyl protons out of it. Little steric hindrance is evident: the *b2-b6* and *b6-b7* bond angles are not far from standard values and only *b2-b9* reaches 125.8° (see Figure 1 and Table 4). In 3-methoxy-2-nitrobenzo[*b*]thiophene (**8**), in contrast, the methoxy group cannot orientate itself towards the *peri* hydrogen 4-H and tends to point towards the nitro group but conflicts with it (see Figure 1). The methoxy carbon is therefore well out of the ring plane (*b3-b9-b10* dihedral –125.8°) and even the nitrogen of the nitro group is slightly but significantly bent out of it (*b3-b2-b6* dihedral –171.4°), although the C–NO₂ moiety as a whole is still planar. The very large *b2-b6* and *b2-b9* bond angles (see Table 4), as well as the short nonbonding distance (2.181 Å) between an oxygen of the nitro group and a methoxy proton, are evidence of the particularly marked steric hindrance in this molecule.

With regard to the studied Meisenheimer adducts, the calculations indicate that in **7'** and **9'** the tetrahedral carbon C-2 is bent with respect to the general molecular plane (the *b4-b3-b2* values being 6.7 and 14.4°, respectively). We can note that the dihedral value is lower for the *gem*-dimethoxy adduct **7'**, in which the overall steric crowding is greater but balanced between the two sides of the ring plane, consistently with previous findings from X-ray diffraction studies of Meisenheimer adducts in the benzene series.^[12] Conversely, adducts **8'** and **10'** each exhibit a tetrahedral carbon (i.e., C-3), which is *α* to the benzene ring and therefore somewhat forced to be coplanar to it. This results in a

nearly coplanar location of all the ring atoms of the *gem*-dimethoxy adduct **8'**, whereas in **10'** C-3 and C-2 exhibit small and opposite deviations from the general plane of the molecule. We can also note that in each of the monomethoxy adducts **9'** and **10'** the methoxy substituent points towards the nitro group (see Figure 1), which avoids the conflict through a marked bending of the nitrogen of the nitro group out of the general plane (*b4–b3–b6* 160.4° in **9'**, *b3–b2–b6* 152.6° in **10'**), resulting in a marked pyramidalization of the corresponding nitrated ring carbon, whereas the C–NO₂ moiety, as a whole, is still planar. In each of the *gem*-dimethoxy adducts **7'** and **8'** the nitrogen of the nitro group is bent to a much smaller extent (*b4–b3–b6* 177.6° in **7'**, *b3–b2–b6* 174.8° in **8'**) and the pyramidalization of the nitrated carbon is much smaller, because the nitro group is in conflict with a methoxy group on each side of the ring.

Interestingly, in the parent benzo[*b*]thiophene and in its neutral derivatives **7–10** the calculated bond lengths in the benzene ring (from *b10* to *b14*, not shown in Table 4) are very close to the 1.397 Å value of benzene itself, showing differences generally within ±0.01 Å, with only slightly larger variations for *b4* (see Table 4), the bond common to the two rings. With regard to the other bonds of the thiophene ring, *b1* and *b5* are usually 0.04–0.05 Å longer in neutral benzo[*b*]thiophenes than in thiophene itself. Thus, unlike the benzene moiety, the thiophene ring does not seem to retain much of its aromatic character as a consequence of benzo[*b*]condensation. In this context we can note that in benzo[*b*]thiophene the length of *b4* (1.42 Å) is more similar to the benzene value than to the thiophene one. Only small bond length changes are observed as a consequence of nitration of benzo[*b*]thiophene, with the exception of *b1* in **9**: this is calculated to be appreciably shorter than *b5*, as a possible consequence of a preferential resonance interaction between the heterocyclic sulfur and the coplanar 3-nitro group.

Remarkably, the calculated bond lengths of the benzene ring, including *b4*, show even smaller variations on going to the anions **7'–10'**. Methoxide attack at C-2 does not produce any change even in the *b3* bond length of **7'** and **9'** with respect to **7** and **9**, showing that the additional negative charge is effectively confined on C-3 and the nitro group. Correspondently, methoxide attack at C-3 does not produce any shortening of the *b1* values in **8'** and **10'** with respect to **8** and **10**, indicating that the additional negative charge is confined on C-2 and the nitro group.

In all the adducts the nitro group bond lengths exhibit the expected pattern: a ca. 0.08 Å shortening for the *b6* value and a ca. 0.05 Å elongation for *b7* and *b8*. The methoxy groups in **7'** and **8'** each show a 0.08 Å increase in *b9*, as the expected consequence of the release of conjugative interactions with the ring operative in the corresponding substrates **7** and **8**. It seems particularly interesting to note the marked elongations of *b1* in **7'** and **9'** ($\Delta\lambda = 0.187$ and 0.128 Å, respectively). Now the *b1* lengths (1.937 and 1.843 Å, respectively) are even greater than literature tetrahydrothiophene values (1.821 Å^[13a] and 1.840 Å^[13b]). This dramatic weakening of *b1*, even larger than expected, shows

the direction of further reactivity, providing an explanation for, for example, the previous observation^[1h] that 3-nitrobenzo[*b*]thiophene can react with secondary aliphatic amines through cleavage of the *b1* bond, yielding ring-opening products that give access to the syntheses of several different heterocyclic systems^[2e–2h] (see the Introduction). In contrast, *b5* shows only a small elongation (0.02 Å), and correspondently the ring cleavage was found to occur with sulfur retention (see the Introduction).

¹³C NMR Chemical Shift Differences

A further contribution to the study of the formation of “Meisenheimer-like” adducts can come from study of the ¹³C chemical shift changes accompanying their formation. In Tables 1, 2, 5 and 6 the ¹³C chemical shifts of the adducts **7'–10'** are compared with those of the corresponding substrates **7–10**. For purposes of comparison, the available data for the corresponding adducts in the thiophene series are also reported. In our previous extensive studies of Meisenheimer adducts^[6a–6d,6h,6j,6k] we have stressed that a reasonable and self-consistent picture can be obtained by regarding the ¹³C chemical shift differences between the adducts and the corresponding substrates as mainly related to *i*) hybridization change for the carbon undergoing methoxide attack, and *ii*) π electron density variations for the ring carbons retaining their sp² hybridization.

Table 5. ¹³C NMR spectroscopic data for 2-methoxy-3-nitrobenzo[*b*]thiophene (**7**) and the relevant Meisenheimer adduct **7'** in [D₆]DMSO. For comparison, NMR spectroscopic data^[6a] for 2-methoxy-3-nitrothiophene (**2**) and the relevant adduct **2'** are also reported.

	δ	δ	$\Delta\delta$	δ	δ	$\Delta\delta$	
	7	7'	(7'–7)	2	2'	(2'–2)	
C-2	172.24	126.55	–45.69 ^[a]	C-2	168.42	126.26	–42.16 ^[a]
C-3	122.46	112.40	–10.06	C-3	128.49	117.07	–11.42
C-3a	129.89	134.19	4.30	C-4	121.61	120.50	–1.11
C-7a	124.70	129.35	4.65	C-5	110.17	109.86	–0.31
C-4	121.72	121.39	–0.33	–	–	–	
C-5	126.99	123.55	–3.44	–	–	–	
C-6	124.83	122.86	–1.97	–	–	–	
C-7	122.87	120.53	–2.34	–	–	–	
CH ₃	63.53	51.62	–11.91 ^[a]	CH ₃	63.16	51.76	–11.40
$\Sigma\Delta\delta_{\text{th}}^{[b]}$	–	–	–1.1	$\Sigma\Delta\delta_{\text{th}}^{[b]}$	–	–	–12.8
$\Sigma\Delta\delta^{[c]}$	–	–	–9.2	–	–	–	–

[a] Not included in the sums. [b] The sum includes thiophene ring carbons retaining sp² hybridization. [c] The sum includes all ring carbons retaining sp² hybridization.

In this context we can explain the very marked change exhibited by the chemical shift of C-2 on going from **9** to **9'** or from **7** to **7'** and of C-3 on going from **10** to **10'** or from **8** to **8'** mainly on the basis of the hybridization change from sp² to sp³. This compares with the chemical shift changes shown by the corresponding carbons in Meisenheimer adducts in the thiophene series.

More interestingly, the other chemical shift differences shown in Tables 1, 2, 5 and 6, when large enough to be interpreted, can mainly be related to π electron density

Table 6. ^{13}C NMR spectroscopic data for 3-methoxy-2-nitrobenzo-thiophene (**8**) and the relevant Meisenheimer adduct **8'** in $[D_6]-DMSO$. For comparison, NMR spectroscopic data^[6i] for **5** and the relevant spiro adduct **5'** are also reported.

	δ		$\Delta\delta$		δ		$\Delta\delta$
	8	8'	(8'-8)		5	5'	(5'-5)
C-2	134.28	104.83	-29.45	C-2	129.3	108.7	-20.6
C-3	151.91	107.29	-44.62 ^[a]	C-3	157.2	112.5	-44.7 ^[a]
C-3a	131.31	135.92	4.61	C-4	118.0	123.4	5.5
C-7a	134.68	136.85	2.17	C-5	133.1	124.5	-8.6
C-4	124.54	124.27	-0.27	-	-	-	-
C-5	125.97	124.78	-1.19	-	-	-	-
C-6	130.69	129.93	-0.76	-	-	-	-
C-7	123.67	121.74	-1.93	-	-	-	-
CH ₃	63.00	51.33	-11.67	-	-	-	-
$\Sigma\Delta\delta_{th}^{[b]}$	-	-	-22.7	$\Sigma\Delta\delta_{th}^{[b]}$	-	-	-23.7
$\Sigma\Delta\delta^{[c]}$	-	-	-26.8	-	-	-	-

[a] Not included in the sums. [b] The sum includes thiophene ring carbons retaining sp^2 hybridization. [c] The sum includes all ring carbons retaining sp^2 hybridization.

changes accompanying the formation of the adducts, so we can investigate how the shielding caused by the full negative charge is distributed over the ring carbons. As would be expected, the observed chemical shift differences are lower for the *gem*-dimethoxy adducts **7'** and **8'**, because the shielding introduced by the negative charge is partially balanced by the release of the +*R* effect that the methoxy group can exhibit in the starting substrates.

It stands out that the main shielding effect is observed for the nitro-substituted carbon atoms (i.e., C-3 on comparison of **9'** and **9**, or **7'** and **7**, and C-2 on comparison of **10'** and **10**, or **8** and **8'**), the effect being particularly large when the nitrated carbon is C-2 (methoxide attack at C-3). It can be noted that in all these benzo[*b*]thiophene adducts all the other sp^2 carbons exhibit only small changes relative to the corresponding starting compounds, because even C-7a in **9'** does not exhibit the great shielding with respect to the starting compound conversely shown by C-4 in **1a'** with respect to **1a**. Interestingly, all the carbons of the benzene ring exhibit small chemical shift differences. These findings are in close agreement with the results of the analysis of bond lengths showing that the negative charges of the adducts **7'-10'** are confined to their nitrated carbons and the nitro groups.

The sums of the chemical shift changes including all of the carbons retaining their sp^2 hybridization are heavily affected by the shieldings of the nitrated carbons and are therefore more negative for the formation of the adduct **10'** than for **9'** and for the formation of the adduct **8'** than for **7'**. The results obtained for the monomethoxy adducts **9'** and **10'** show that, once more, in a comparison of "Meisenheimer-like" adducts with the same substituents in different relative positions, the adduct exhibiting the larger stability constant is that showing the smaller π electron density change with respect to the starting compound.

Previously we have found the same behaviour in the thiophene series when comparing the spiro-Meisenheimer adducts **5'** with **6'**^[6h,6i] and when comparing the adducts **1'**, **2'**, **3'**, and **4'**:^[6a-6d] that is, when we have compared adducts

bearing the same substituents in different relative positions, and also when comparing non-geminal and geminal Meisenheimer adducts.

The benzo[*b*]thiophene *gem*-dimethoxy adducts **7'** and **8'** exhibit the opposite behaviour, with the larger stability constant being exhibited by **8'**, the formation of which is accompanied by larger shielding of ring carbons. However, our previous analysis of calculated geometries indicate that this can be reasonably explained on the basis of the prevalence of steric effects over the electronic ones.

Conclusions

Both experimentally measured NMR chemical shifts and calculated bond lengths show that the benzene ring carbon atoms in the substrates **7-10** are scarcely affected by methoxide attack, providing evidence that the benzene ring retains its full aromatic character and is therefore the only "really aromatic" ring.

Accordingly, the Bird's aromatic indexes^[14] of benzene (I_A 100) and thiophene (I_A 81.5) in comparison with that of benzo[*b*]thiophene (I_A 119) suggest a very modest contribution of the thiophene system to the global aromaticity of benzo[*b*]thiophene.

Overall, these data also appear highly consistent with the possible "non-aromatic" reactivity of the thiophene ring in benzo[*b*]thiophenes (e.g., with nucleophiles). With some amines, for instance, **10** gives Michael-type addition on the *b2* double bond that can be followed by an oxidative process (i.e., globally a ONSH reaction),^[1h] whereas in contrast **9** undergoes ring-opening by cleavage of the *b1* bond with some amines and silver nitrate.^[1h]

In conclusion, we may call into question the assumption that the reactions between nitrobenzo[*b*]thiophenes and nucleophiles represent the first steps of S_NAr reactions or rather Michael additions. We think that the nitrobenzo[*b*]thiophenes studied, because of the very low aromatic characters of the thiophene rings in these systems, furnish an interesting instance of borderline behaviour well in line with their global reactivity. As a matter of fact, for instance, 3-bromo-2-nitrobenzo[*b*]thiophene can give either normal S_NAr substitution with nucleophiles or S_NAr substitution accompanied by a nitro group rearrangement,^[2k-2n] whereas in contrast, **9** and **10** give ring-opening^[1h] or ONSH reactions,^[1h] respectively, with amines. Moreover, with sodium methoxide the same **9** and **10** give products that can be regarded both as "Meisenheimer-like" adducts and as Michael addition products. In our opinion this borderline behaviour represents one of the most intriguing aspects of the reactivity of nitrobenzo[*b*]thiophenes.

Benzocondensation allowed the stability constant of **9'** in methanol to be evaluated, as a direct consequence of the reduced aromaticity of the thiophene ring in **9**, in which, in contrast, the resonance interaction between the heterocyclic sulfur and the 3-nitro group is of some importance.

On comparing adducts **9'** and **10'**, obtained from substrates with the same substituents at different relative loca-

tions, we have once more found that the larger stability constant is exhibited by the adduct of which the formation is accompanied by the lower π electron density reorganization, as evaluated on the basis of ^{13}C NMR chemical shifts (the so-called $\Sigma\Delta\delta$ values; see Tables 1, 2, 5 and 6).

Interestingly enough, the opposite is found for the corresponding *gem*-dimethoxy adducts, in which steric hindrance can overcome electronic effects, thus causing an only “apparent” exception to the rule linking ^{13}C chemical shifts changes accompanying the formation of Meisenheimer-like adducts to their stabilities.

To the best of our knowledge this is the first example of this unexpected behaviour. The above ^{13}C NMR patterns have their counterparts in the shape of the UV/Vis spectra, for which only a “small” shift of the maximum on going from **9** to **9'** has been observed ($\Delta\lambda = 7$ nm). This gives further support to some of our previous comments^[6d] on the Meisenheimer adduct formation from **2a**, indicating that the situation can also be extended to benzo[*b*]thiophenes, as also suggested by De Santis and Stegel.^[7]

Experimental Section

Synthesis and Purification of Compounds: 3-Nitrobenzo[*b*]thiophene (**9**) and 2-nitrobenzo[*b*]thiophene (**10**) were synthesized and purified according to literature procedures.^[15]

NMR Studies: ^1H NMR spectra were run at 200 MHz and ^{13}C NMR spectra at 50 MHz, always at 298 K. Chemical shifts are reported in ppm (δ) downfield from internal TMS. The INADEQUATE experiment was run at 75 MHz. Assignments for 3-nitrobenzo[*b*]thiophene (**9**) in $[\text{D}_6]\text{DMSO}$ are taken from ref.^[2k], but were further checked by a 2D-INADEQUATE experiment showing, in particular, correlation of C-3a with both C-3 and C-4. Assignments for **9** in $[\text{D}_4]\text{MeOH}$ were assisted by spectra run in $[\text{D}_6]\text{DMSO}/[\text{D}_4]\text{MeOH}$ 3:1 and 1:1 mixtures. With regard to the assignments of 2-nitrobenzo[*b*]thiophene (**10**), the weak signals of the unprotonated C-3a and C-7a could be better studied in $[\text{D}_6]\text{DMSO}$ spectra for solubility reasons: they both appeared as multiplets, exhibiting the primary structures of a quartet and a triplet, and were safely assigned to C-7a and C-3a, respectively, on the basis of the different numbers of their $^3J(\text{C,H})$ couplings. The assignments in $[\text{D}_6]\text{DMSO}$ could then be translated to $[\text{D}_4]\text{MeOH}$ with the assistance of spectra run in mixtures of the two solvents. The procedure was reversed for the assignments of 4-H and 7-H, because in $[\text{D}_4]\text{MeOH}$ the 4-H and 7-H doublets are not overlapping and 4-H could be more safely identified by irradiation of 3-H in a NOEDIF experiment. The adduct **9'** was obtained by treating a solution of **9** (0.2 M) in $[\text{D}_6]\text{DMSO}$ or in $[\text{D}_4]\text{MeOH}$ with an equimolar amount of sodium methoxide (freshly prepared 6 M solution in methanol). When a solution of **10** (0.2 M) in $[\text{D}_6]\text{DMSO}$ was treated with an equimolar amount of sodium methoxide the extent of formation of **10'** was about 65% in the readily acquired ^1H NMR spectrum, fading to about 43% after 1 h. When the reaction between **10** (saturated solution, 8 mg/0.7 mL) and sodium methoxide (1 equiv.) was carried out in $[\text{D}_4]\text{MeOH}$, only weak signals of a new species could be detected together with those of the starting 2-nitrobenzo[*b*]thiophene. With 3 equiv. of sodium methoxide the new species was formed at a level of about 20% and with 10 equiv. at a level of 65%. With regard to the assignments of the signals of the adducts **9'** and **10'**, the sp^3 ring carbon could in each

case be easily identified on the basis of its particularly large decrease in chemical shift value with respect to the starting compound and, in $[\text{D}_6]\text{DMSO}$, on the basis of its expected fine structure and *J* values (see Results and Discussion). The nitrated carbon could be identified because of its singlet structure and its large decrease in chemical shift. The individual carbons in the pairs C-3a and C-7a, C-4 and C-7, and C-5 and C-6 were assigned by chemical reasoning, although their assignment does not affect the conclusions of this work.

Competition Reactions: Several competition reactions were carried out under different conditions. In particular, when a solution of 3-nitrobenzo[*b*]thiophene (**9**) in $[\text{D}_6]\text{DMSO}$ (0.17 M) was treated with MeONa (5.68 M in MeOH, 0.5 equiv.), the ^1H NMR spectrum showed the formation of the adduct **9'** at a level of ca. 47%. When an analogous solution of 2-nitrobenzo[*b*]thiophene (**10**) was treated with MeONa (0.5 equiv.) the sharp multiplets of **10'** could be detected, but the very heavy broadening of the absorptions of the starting compound did not allow the real extent of the Meisenheimer adduct formation to be determined. When the two solutions were mixed, the peaks due to **9**, **9'** and **10'**, together with the humps due to **10**, could be detected. At first, the level of formation of **9'** was ca. 60%, but it increased with time, becoming practically quantitative. At the same time the absorptions due to **10'** faded, but it was not possible to follow the fate of **10** because of the heavy broadening of its signals. After 2 h acidification with trifluoroacetic acid allowed us to obtain, after 4 h of further delay, a ^1H NMR spectrum showing the superposition of the patterns of the signals of **9** and **10**. The quantitative restoration of both of the starting compounds shows that **10'** did not decompose when the relevant signals faded. We can therefore conclude that the equilibrium constant of methoxide addition in $[\text{D}_6]\text{DMSO}$ is larger for 3-nitrobenzo[*b*]thiophene (**9**) than for 2-nitrobenzo[*b*]thiophene (**10**). When a solution of 3-nitrobenzo[*b*]thiophene (**9**) in $[\text{D}_4]\text{MeOH}$ (0.06 M) was treated with MeONa (5.68 M in MeOH, 0.5 equiv.), the ^1H NMR spectrum showed the formation of the adduct **9'** at level of ca. 45%. When an analogous solution of 2-nitrobenzo[*b*]thiophene (**10**) was treated with MeONa (0.5 equiv.) the level of the formation of **10'** was about 5%. Further MeONa was then added (to a total of 3.25 equiv.) and **10'** increased to nearly 20%. Mixing of the two solutions produced a ^1H NMR spectrum at first showing more than 70% of **9'** with respect to **9**, together with a decrease in **10'**. After 1 h the percentages of the two adducts had changed, with a significant increase in **9'**. Acidification with trifluoroacetic acid then produced a ^1H NMR spectrum showing the superposition of the patterns of the starting compounds **9** and **10** (the H-2 singlet of **9** was smaller than at the start of the experiment because of some deuteration). This experiment definitely shows that the equilibrium constant of the methoxide addition is also larger for 3-nitrobenzo[*b*]thiophene (**9**) than for 2-nitrobenzo[*b*]thiophene (**10**) in $[\text{D}_4]\text{MeOH}$. All of the experiments were carried out at 298 K.

UV Determination of the Equilibrium Constant of 9': The equilibrium constants for the formation of **9'** can be determined from spectral measurements on methanolic solutions of **9** and sodium methoxide containing variable amounts of DMSO, provided that the extinction coefficients of substrate (ϵ_s) and of adduct (ϵ_a) are known. In fact:

$$[\mathbf{9}'] = \frac{D_e/l - \epsilon_s C_s}{\epsilon_a - \epsilon_s} \quad \text{and} \quad [\mathbf{9}] = C_s - [\mathbf{9}']$$

where D_e represents the optical density of the solution at equilibrium, C_s the total substrate concentration (the sodium methoxide

concentration, being in large excess over that of **9**, is assumed to be constant), and *l* the thickness of the cuvettes in cm. Measurements were carried out with a Cary 1E spectrophotometer. The UV/Vis (200–500 nm) spectrum of **9** in methanol shows an absorption maximum at 339 nm; the formation of the complex **9'** causes a definite although minor spectral change with a bathochromic shift. Addition of increasing amounts of sodium methoxide causes an increase in absorption with a change in the shape of the spectrum. At a sodium methoxide concentration close to 0.5 M, the substrate is completely converted into the corresponding adduct, the absorption maximum being at 346 nm, and further increase in base concentration causes no further spectral change. The spectra for different methanol/DMSO mixtures were recorded at 298 K. Samples were prepared by addition of a solution of the substrate and increasing amounts of sodium methoxide to DMSO. All solutions were thermostatted at 298 K. The concentrations used were 9.0×10^{-5} M for the substrate and from 5.0×10^{-4} to 8.0×10^{-1} M for sodium methoxide.

Supporting Information (see also the footnote on the first page of this article): ¹H and ¹³C NMR spectra of compounds **9'** and **10'**. Additional DFT-calculated geometrical parameters of **7–10**, of **7'–10'**, of thiophene in DMSO.

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