trans-2,2′-Dinitrostilbene as a precursor of *o*-nitrobenzaldehyde, a key intermediate for pharmaceuticals: reactivity and molecular structure studies

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A novel synthesis of *o*-nitrobenzaldehyde by means of the ozonolysis–reductive hydrolysis of symmetrical *trans*-2,2′-dinitrostilbene is reported, yielding only the *ortho* isomer of nitrobenzaldehyde. This new route reduces environmental hazards in the synthesis of *o*-nitrobenzaldehyde. The central ethylene bond of *trans*-2,2′-dinitrostilbene showed a high reactivity for the ozonolysis reaction. The molecular structures of 2-nitrobenzaldehyde and *trans*-2,2′-dinitrostilbene were studied theoretically by means of *ab initio* quantum mechanical calculations at the 6-31G*//6-31G* level. A non-coplanar conformer was found for *o*-nitrobenzaldehyde, where the carbonyl and nitro groups are slightly twisted with respect to the phenyl ring. Also, a non-coplanar minimal s-*trans*-*gauche*/s-*trans*-*gauche* conformer (NO_2-aryl-C=C-aryl-NO_2) was found for *trans*-2,2′-dinitrostilbene, where the aromatic groups are twisted with respect to the central double bond, and the nitro groups are also twisted out the planes of the aromatic rings. This structure is consistent with certain experimental physical–chemical properties of this molecule.

Introduction

The nitro derivatives of benzaldehyde have great importance as fine chemicals. They are intermediates for the synthesis of new cardiovascular drugs, specially for calcium antagonists, such as one group of the pharmaceutical market leaders, the dihydropyridine derivatives. In 1986, Nifedipine was the top-ranking drug of the German pharmaceutical market. The main raw material for the synthesis of Nifedipine and similar derivatives, *e.g.* Nisoldipine, is *o*-nitrobenzaldehyde. All these factors have pushed up the number of different patents[1–3] and papers[4,5] reporting new syntheses of *o*-nitrobenzaldehyde[6–8] published in recent years. This simple intermediate is the key to the economic cost of the synthesis of Nifedipine and similar drugs on an industrial scale.

The main problems in the direct synthesis of *o*-nitrobenzaldehyde are the safety hazards of the nitration reaction,[9] and separation of the final product from isomers and by-products.[10] The partial oxidation of 2-nitrotoluene gives low yields and selectivity,[11] especially for 2-nitrobenzaldehyde.[12,13] A useful intermediate for *o*-nitrobenzaldehyde synthesis is α-chloro-2-nitrotoluene. This intermediate can be obtained by means of aromatic nitration of benzyl chloride, yielding a mixture of mononitro isomers with an *ortho*/*meta*/*para* ratio of 30/15/55, respectively.[14] This method requires rigorous separation of the isomers, in order to obtain α-chloro-2-nitrotoluene in high purity. However, this route presents some safety problems due to the low thermal stability of these molecules. Several papers refer to the possible explosive decomposition of *o*-nitrobenzyl halides,[15,16] and a violent explosion during the drying of one of these compounds in a fine chemicals factory has been reported.[17] In particular, *o*-nitrobenzyl chloride decomposes exothermically and violently.[18] Besides, the direct chlorination of the side chain of 2-nitrotoluene with chlorine or PCl_5 does not give high selectivity due to the side reactions of ring chlorination and oxidation.[19] Chlorination in the side chain of toluene by means of an inorganic hypochlorite and a phase-transfer catalyst has been reported.[20] One of the aims of this work is the application of this method to the synthesis of α-chloro-2-nitrotoluene.

On the other hand, the chemistry of nitrostilbene derivatives has been developed because of its application in explosives chemistry. 2,2′,4,4′,6,6′-Hexanitrostilbene can be prepared directly from 2,4,6-trinitrotoluene with alkaline hypochlorite yielding the bibenzyl derivative as an important by-product.[21,22] A mixture of 2,2′-dinitrostilbene and 2,2′-dinitrobibenzyl was obtained directly from 2-nitrotoluene by means of base-catalysed (KOH and polyethylene glycol) autooxidation (with oxygen).[23] 2,2′-Dinitrostilbene can be obtained from the α-chloro-2-nitrotoluene by treatment with alkali in dioxane–water,[24] or with alcoholic KOH.[25]

A synthesis of *o*-nitrobenzaldehyde has been reported by means of the ozonolysis of an asymmetric alkene, *o*-nitrostyrene.[26] However, the use of symmetric stilbenes could minimise the number of ozonolysis by-products and overcome the separation and purification problems associated with the environmental effects of waste water. One of the aims of this work is the use of a symmetric nitrostilbene derivative to synthesise 2-nitrobenzaldehyde, in order to minimise by-products. Therefore, in this work, we report a novel synthesis which overcomes the safety hazards and environmental problems of previous methods, by means of α-chlorination of 2-nitrotoluene, "dimerization"–dehydrochlorination of the α-chloro derivative and partial ozonolysis of the symmetric *trans*-2,2′-dinitrostilbene (Fig. 1).

Results and discussion

Reactivity

Our previous investigations on the synthesis of 2,2′-dinitrostilbene, directly from 2-nitrotoluene by the Shipp method used in the synthesis of 2,2′,4,4′,6,6′-hexanitrostilbene,[22] gave negative results. Different reaction conditions were studied, including varying the temperature (0, 20 and 60 °C), reaction time (1, 4 and 24 h), solvent (THF–MeOH, acetonitrile), pH (8 and 13), and active chlorine concentration in the sodium hypochlorite solution (8 and 16%), but only the initial reactant was obtained. In the case of 2,4,6-trinitrotoluene, the electron-withdrawing effect of the three nitro groups together makes the methyl group active for chlorination.[22] However, the presence of only one nitro group in 2-nitrotoluene will probably not be

Table 1 The α-chlorination of 2-nitrotoluene by phase transfer catalysis (PTC)

Run	[NaOCl] (%)[a]	Molar rate (NaOCl/2NT)[b]	*t*/h	Catalyst	Molar rate (cat./2NT)	Conversion (%)	Selectivity (%)	Yield (%)
1	7.5	11	49	$Bu^n_4NHSO_4$	0.02	42	40.5	17[c]
2	16	11	48	$Bu^n_4NHSO_4$	0.02	60	30	18[d]
3	12	9	72	$Bu^n_4NHSO_4$	0.02	27	44	12[e]
4	4.5	1.2	64	$Bu^n_4NHSO_4$	0.02	23	26	6
5	4.5	2.0	47	$Bu^n_4NHSO_4$	0.02	23	17	4
6	8	1.3	24	$Bu^n_4NHSO_4$	0.02	20	40	8
7	8	2.4	48	$Bu^n_4NHSO_4$	0.02	32	38	12
8	17.5	1.0	24	$Bu^n_4NHSO_4$	0.02	19	37	7
9	17.5	2.4	72	$Bu^n_4NHSO_4$	0.02	30	37	11
10	17.5	3.86	48	$Bu^n_4NHSO_4$	0.01	35.5	32	11.3
11	17.5	3.25	48	$Bu^n_4NHSO_4$	0.08	34	33	11
12	8	2.5	48	RMe_3NCl[f]	0.04	39	24	9.5
13	17.5	3.25	48	Bu^n_4NCl	0.02	33.5	40	13.3
14	17.5	2.3	48	Me_4NCl	0.22	—	—	0
15	17.5	2.7	48	Et_3BzNCl	0.02	18	28	5

[a] Active chlorine (%). [b] Ratio NaOCl/2-nitrotoluene, taking into account the active chlorine content in the aqueous NaOCl solution. [c] Main by-product: 2-nitrobenzoic acid (yield 7%). [d] Yield of 2-nitrobenzoic acid = 9%. [e] Yield of 2-nitrobenzoic acid = 12%. [f] *n*-dodecyl(trimethyl)ammonium chloride.

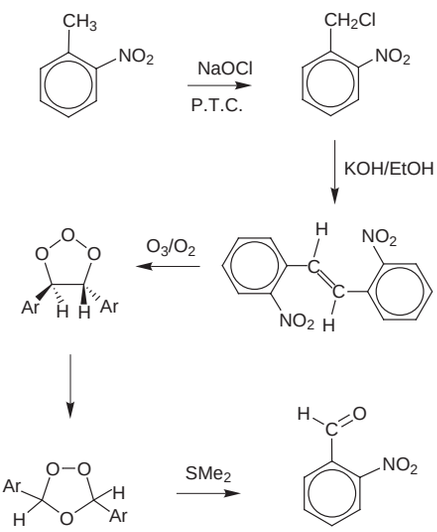

Fig. 1 Synthesis of *o*-nitrobenzaldehyde.

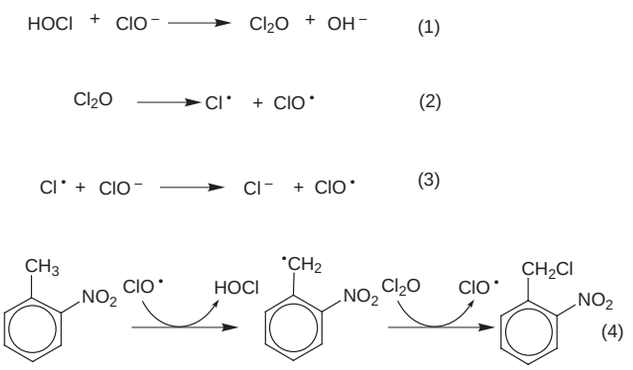

Fig. 2 Mechanism of the α-chlorination of 2-nitrotoluene with NaClO/PTC.

enough to activate the methyl group. Besides, the *ortho* disposition of the nitro group can disfavour the formation of 2,2′-dinitrostilbene due to steric effects.

Then, an alternative synthesis of the α-chloro-2-nitrotoluene intermediate was studied *via* α-chlorination of 2-nitrotoluene with sodium hypochlorite and a phase transfer catalyst (PTC). The yields were not high (18%), probably due to the electron-withdrawing effect of the nitro group. Previous studies of the relative reactivity of substituted toluene in this reaction[20] found a drastic decrease in the reactivity of the α-hydrogen with electron-withdrawing substituents in the aromatic ring. Several alkylammonium salts were tested as the PTC, and different conditions (Table 1) were studied (concentration of active chlorine in NaClO solutions, reaction time, catalyst, NaClO/substrate molar ratio, and catalyst/substrate ratio). The use of a catalyst/2-nitrotoluene molar ratio higher than 0.02 does not increase the yield nor selectivity for α-chloro-2-nitrotoluene. The main by-product obtained was *o*-nitrobenzoic acid. Taking into account the yields of α-chloro-2-nitrotoluene and *o*-nitrobenzoic acid, the selectivity for both products together can reach 89% with low conversion rates (run 3, Table 1). 2-Nitrobenzoic acid is easily separable in the basic pH of the aqueous phase, and 2-nitrotoluene (bp 118 °C/16 mmHg) and α-chloro-2-nitrotoluene (mp 50–52 °C) can be separated by standard methods. The unconverted 2-nitrotoluene could be recycled in the reaction. This fact could be interesting for possible industrial applications.

According to earlier studies,[20] the reactions occurring in the hypochlorite–PTC system proceed by a free-radical mechanism rather than an electrophilic mechanism. The chloroxyl radical ($ClO^{\bullet}$) is the reactive reagent in the hypochlorite–PTC system. It is reasonable that this radical could be generated from Cl_2O,[27] which is formed in this system *via* reactions such as those shown in Fig. 2.[28] This reaction only proceeds significantly at pH 8–9, conditions under which a significant concentration of HOCl is present and Cl_2O can be formed [eqn. (1), Fig. 2]. Besides, this reaction only proceeds to any significant degree when a PTC is present. The tetrabutylammonium salts (chloride and bisulfate) were the catalysts which gave the best results. More hydrophilic catalysts, such as tetramethylammonium, and more hydrophobic catalysts with long chain alkyl groups, such as n-dodecyl-(trimethyl)ammonium, gave lower yields (Table 1). Although one cannot state definitively, given the present results, what the specific function of the PTC is, one can offer some suggestions on the basis of the proposed mechanism. The last two steps of the reaction, benzyl radical formation and chlorination, obviously occur in the organic phase. Thus, the organic phase must have a good supply of Cl_2O, which generates the chloroxyl radical ($ClO^{\bullet}$) for benzyl radical formation. Besides, the hypochlorite anion (ClO^-) should also be present in the organic phase for the electron transfer reaction capturing the $Cl^{\bullet}$ radical in order to regenerate $ClO^{\bullet}$ [eqn. (3) in Fig. 2]. It is well established[29] that quaternary ammonium ions frequently extract an adduct of an acid and its conjugate base into the organic phase. In this case, the PTC would increase the concentration of HOCl

and ClO^- as an adduct in the organic phase and, therefore, the Cl_2O could be generated inside the organic phase [eqn. (1), Fig. 2] and can produce $ClO^{\bullet}$. This radical reacts with the toluene derivative in the organic phase [eqn. (4), Fig. 2]. When the initial concentration of $HClO/ClO^-$ in the aqueous solution is low (molar ratio of NaClO/2-nitrotoluene lower than 2.4), the concentration of $HClO/ClO^-$ in the organic phase is too low and the yield of α-chloro-2-nitrotoluene is lower (runs 4–6 and 8, Table 1). In the last step [eqn. (4), Fig. 2] of the free-radical mechanism, the electron-withdrawing effect of the nitro substituent on the methyl group can disfavour homolytic cleavage of the C–H bond. This fact could explain the low yields of this reaction for toluenes with these substituents.

trans-2,2′-Dinitrostilbene was obtained by means of "dimerization"–dehydrochlorination of α-chloro-2-nitrotoluene with ethanolic KOH.[25] After studying different reaction conditions, we found two critical factors which affect the yield of 2,2′-dinitrostilbene: (i) the addition of the KOH solution to the α-chloro-2-nitrotoluene should be slow (15 min for 80 ml with high stirring), as high addition rates produce too high a concentration of KOH, which can promote different secondary reactions, such as formation of 2-nitrobenzyl alcohol, 2-nitrobenzyl ethyl ether, *etc.*; (ii) the total reaction time should be an intermediate compromise time (*e.g.* 30 min for 9.7 g of α-chloro-2-nitrotoluene), as shorter reaction times produce low conversion and low yield (entry 1, Table 2), while longer reaction times also produce low yields, probably due to decomposition of 2,2′-dinitrostilbene (entries 3 and 6, Table 2). Taking into account these factors, a yield of 67% for *trans*-2,2′-dinitrostilbene was obtained after only 30 min, which is a significant improvement of yield with a shorter reaction time compared to results previously described (41% after 3 h).[25] In all cases, only the *trans* isomer was detected *via* ^1H and ^{13}C NMR, showing a highly symmetrical structure.

This reaction was applied to α-bromo-2-nitrotoluene using the same conditions above described. No 2,2′-dinitrostilbene was detected. This reaction yielded mainly 2-nitrobenzyl ethyl ether. This fact can be explained by the excessively high reactivity of α-bromo-2-nitrotoluene, which reacts with a solvent molecule.[24]

In the ozonolysis process a relatively stable intermediate ozonide was formed (Fig. 1) and detected by TLC (with toluene as eluent, $R_f = 0.3$, 0.4 and 0.7 for 2-nitrobenzaldehyde, intermediate ozonide and 2,2′-dinitrostilbene, respectively). This intermediate is transformed to *o*-nitrobenzaldehyde by means of reductive hydrolysis with dimethyl sulfide. This reagent is a mild reducing agent (cheap and easily available on an industrial scale) which does not attack the nitro group. Various reaction conditions are described in Table 3. The low temperature minimises the formation of other by-products. The total conversion of 2,2′-dinitrostilbene is observed in all cases. A large excess of dimethyl sulfide yields a high selectivity (95%) for a 2-nitrobenzaldehyde and 2-nitrobenzoic acid mixture. In all cases, 2-nitrobenzoic acid was detected as the main by-product and no other compound was present in significant amounts. The best selectivity was found by using an inert solvent such as methylene chloride. The formation of 2-nitrobenzoic acid is favoured by a long hydrolysis time, with the 2-nitrobenzaldehyde yield remaining constant (experiments 4 and 5, Table 3). However, when the intermediate ozonide solution was treated with oxygen at room temperature without any reduction agent, 2-nitrobenzoic acid was obtained as the main product. This fact seems to show that 2-nitrobenzaldehyde does not decompose to the carboxylic acid, however the intermediate ozonide can be directly oxidised to 2-nitrobenzoic acid by the oxygen in air after long reaction times. Finally the *o*-nitrobenzaldehyde was purified in a yield of 98%, while the 2-nitrobenzoic acid was recovered and purified with a yield of 90%.

The reactivity of the double bond of 2,2′-dinitrostilbene and the yield of *o*-nitrobenzaldehyde are surprisingly high, since this ozonolysis reaction is not favoured, due to the electron-withdrawing character[30] of the nitrophenyl moiety. On the other hand, a side reaction in the ozonolysis reaction is the conversion of the substrate to an epoxide derivative. This side reaction becomes important when bulky groups are present around the double bond.[31] However, we have not detected the epoxidation as a side reaction in our procedure and with this double bond, which is sterically hindered by two bulky *o*-nitrophenyl moieties.

Table 2 Synthesis of *trans*-2,2′-dinitrostilbene by dimerization–dehydrohalogenation of α-chloro-2-nitrotoluene

Entry	Addition time/ min	*t*/min	Yield (%)
1	15	10	36
2	15	30	67
3	15	120	51
4	2	60	40
5	2	182	42
6	80	280	47

Molecular structure

Our experimental results have posed several questions concerning the molecular structure of these molecules. The ^{13}C NMR chemical shifts of the aromatic carbons are described in Table 4. The values corresponding to *trans*-2,2′-dinitrostilbene are similar to those of the other molecules. This fact shows that the electronic delocalization of the π-system in this diaromatic structure is similar to that of the monoaromatic compounds. Thus, the delocalization effect between both phenyl rings and the central double bond appears low. On the other hand, the ^1H and ^{13}C NMR spectra of *trans*-2,2′-dinitrostilbene show a symmetric structure. For this compound, two symmetric coplanar conformers, with respect to the angles θ_1 and θ_1' (CCC_1C_2), are possible: s-*cis*/s-*cis* [$\theta_1 = \theta_1' = 0°$, Fig. 3(a)] or s-*trans*/s-*trans* [$\theta_1 = \theta_1' = 180°$, Fig. 3(b)]. The s-*cis*/s-*trans* [$\theta_1 = 0°$, $\theta_1' = 180°$, Fig. 3(c)] population can be neglected, since

Table 3 Synthesis of *o*-nitrobenzaldehyde by ozonolysis–reductive hydrolysis of *trans*-2,2′-dinitrostilbene

Entry	O_3/substrate[a]	*T*/°C (ozonolysis)	SMe_2/ substrate[b]	*t*/h[c] (hydrolysis)	η (%)[d] Aldehyde	Acid
1	9	−10	18	15	75	20
2	3.6	−17	18	1	74	10
3	3.6	−17	1.8	1	65	8
4	2	−8	4	15	67	20
5	3.6	−10	4	15	68	18

[a] Molar relation ozone/substrate. [b] Molar relation of dimethyl sulfide/substrate. [c] Reductive hydrolysis time at room temperature. [d] Aldehyde = *o*-nitrobenzaldehyde, mp = 40–42 °C (**CAUTION**: toxic and irritant product by inhalation); acid = *o*-nitrobenzoic acid, mp = 145 °C. η = Final yield with respect to the initial substrate, *trans*-2,2′-dinitrostilbene. Chromatographic (GC and HPLC) data.

Table 4 ^{13}C NMR chemical shifts of the aromatic carbons in the nitroderivatives studied (C_1 is joined to the alkyl or alkenyl chain, and the nitro group is joined to C_2)

	δ_C					
Compound	C_1	C_2	C_3	C_4	C_5	C_6
2-Nitrotoluene	133.6	149.6	124.6	126.9	133.1	132.8
α-Chloro-2-nitrotoluene	132.4	147.8	125.3	129.5	133.8	131.6
(2-Nitrobenzyl) ethyl ether	135.5	147.2	124.6	127.8	133.6	128.6
(*E*)-2,2′-Dinitrostilbene	132.7	147.9	125.0	129.1	133.8	129.2

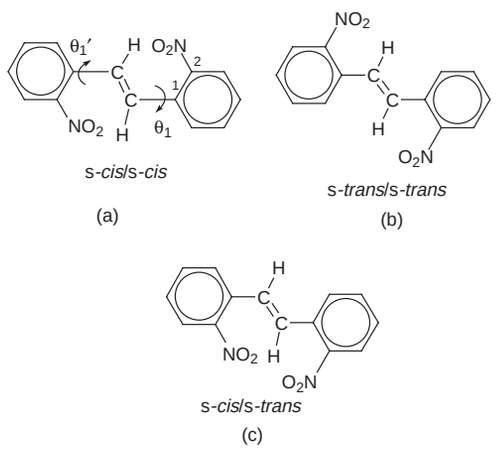

Fig. 3 Possible coplanar conformers of *trans*-2,2′-dinitrostilbene.

it will not give a symmetrical NMR spectrum. With only the experimental data, we cannot state which symmetric conformer is predominant. A high degree of electronic delocalization in this coplanar structure would provide relative stability, which does not seem to be consistent with the high reactivity of *trans*-2,2′-dinitrostilbene in the ozonolysis reaction. Thus, a theoretical study of the molecular structure of these compounds might help us understand the experimental results.

The molecular structures of 2-nitrobenzaldehyde and *trans*-2,2′-dinitrostilbene were studied theoretically by *ab initio* quantum mechanical methods. The SCF-LCAO-MO *ab initio* calculations were performed using the GAUSSIAN-94 program,[32] using RHF wavefunctions at the 6-31G* level with analytical gradients. Full optimisation of the molecular geometry was carried out using the Berny method.[33] The critical points of the potential energy surface (PES) were detected taking into account minimal forces. For each critical point of the PES, a force constant analysis was performed in order to calculate the vibrational frequencies and the eigenvalues of the Hessian, and therefore to determine the nature of the critical point. Only those critical points that have no imaginary frequencies were considered as minima (conformers).

In 2-nitrobenzaldehyde, two equivalent conformers are found, M1 and M1′, where the aldehyde and nitro groups are not coplanar with the aromatic ring but both groups are slightly twisted from the phenyl ring [$\theta_1(HCC_1C_2) = 18$ and $-18°$ for M1 and M1′, respectively; and $\theta_2(ONC_2C_1) = -30$ and 30° for M1 and M1′, respectively] [see Fig. 4(a)]. In the conformers M1 and M1′, interactions such as intramolecular hydrogen bonds can be observed: (i) the interaction between the aldehyde hydrogen and one nitro oxygen; (ii) interaction between the aldehyde oxygen and the hydrogen of C_6; and (iii) interaction between one nitro oxygen and the hydrogen of C_3 [Fig. 4(a)]. Three additional critical points are found, T1, T2, and T3, which are 1.24, 3.73, and 5.38 kcal mol^{-1} less stable than M1, respectively. T1 corresponds to a planar structure where the aldehyde [$\theta_1(HCC_1C_2) = 0°$] and nitro [$\theta_2(ONC_2C_1) = 0°$] groups are coplanar with the aromatic ring. The force constant analysis shows two imaginary frequencies, one of them being very low in

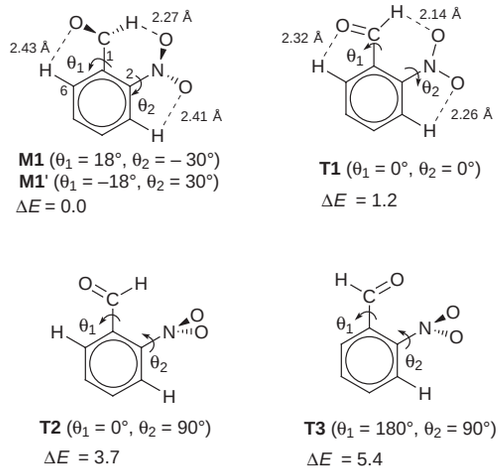

Fig. 4 Main conformations of 2-nitrobenzaldehyde found at the 6-31G*//6-31G* level, $\theta_1 = HCC_1C_2$, $\theta_2 = ONC_2C_1$ (ΔE in kcal mol^{-1}).

frequency (4 cm^{-1}) and intensity. The canonical analysis yields two negative curvatures, one of them being near zero (−0.0013 and −0.00001). At first sight, this critical point could be considered a second order saddle point. However, taking into account the relative energy with respect to other T*i* structures, and the low values of one of the negative frequencies and one of the negative eigenvalues, this critical point could be considered as a true transition structure, corresponding to the internal rotational angles θ_1 and θ_2 (transition vector: $\nu = 0.41\ \theta_1 + 0.91\ \theta_2$). The energy difference between T1 and M1/M1′ is not high, thus the transition from M1 to M1′, and *vice versa*, could easily be *via* T1. In T1 similar O···H distances to those in M1 were found, however steric factors could be more important than possible intramolecular H bonding, providing a slightly higher energy to T1 than M1. In the critical point T2, the nitro group is oriented in a plane perpendicular with respect to the phenyl ring [$\theta_2(ONC_2C_1) = 90°$] and the aldehyde is coplanar with the phenyl group [$\theta_1(HCC_1C_2) = 0°$]. The force constant analysis shows that T2 is a saddle point with a transition vector ($\nu = 0.99\ \theta_2$) in the transition from M1′ to the complementary conformer of M1 [$\theta_1(HCC_1C_2) = 18°$, $\theta_2(ONC_2C_1) = 150°$]. With respect to T3, the aldehyde group is coplanar with the aromatic ring [$\theta_1(HCC_1C_2) = 180°$] but the oxygen is positioned towards the nitro group, which is in a plane perpendicular with respect to the aromatic ring [$\theta_2(ONC_2C_1) = 90°$]. The high energy of this conformation T3 can be explained by the repulsion between the aldehyde oxygen and the nitro oxygens. The force constant analysis shows that T3 is a saddle point in the transition from M1 [$\theta_1(HCC_1C_2) = 18°$, $\theta_2(ONC_2C_1) = 150°$] to M1′ [$\theta_1(HCC_1C_2) = 342°$, $\theta_2(ONC_2C_1) = 30°$] with a transition vector ($\nu = -0.6\ \theta_1 + 0.8\ \theta_2$).

Two conformers (M1 and M2) are found for *trans*-2,2′-dinitrostilbene, which correspond to non-coplanar structures (s-*trans*-*gauche*/s-*trans*-*gauche*), where the nitro groups are slightly out of the plane of the aromatic ring [$\theta_2(ONCC) = -26°$ and $\theta_2 = 31°$ for M1 and M2, respectively] and the central C=C double bond is not coplanar with the aromatic rings [$\theta_1(C{=}CC_1C_2) = 142°$, $\theta_1'(C{=}CC_1'C_2' = -146°$ for M1, and $\theta_1 = \theta_1' = 136.6°$ for M2] (Fig. 5). Nevertheless, both conformers correspond to a symmetrical structure and this is consistent with the experimental NMR results described above. The force constant analysis of both conformers gives no imaginary frequencies. In these conformers, possible hydrogen bonding interactions can be observed between the nitro oxygens and the central C=C double bond hydrogens [$d(O\cdots H) = 2.26$–2.37 Å] and the vicinal aromatic hydrogens [$d(O\cdots H) = 2.35$–2.4 Å]. The minimal energy conformer is M1, where the phenyl rings are in parallel but in different planes. The secondary conformer

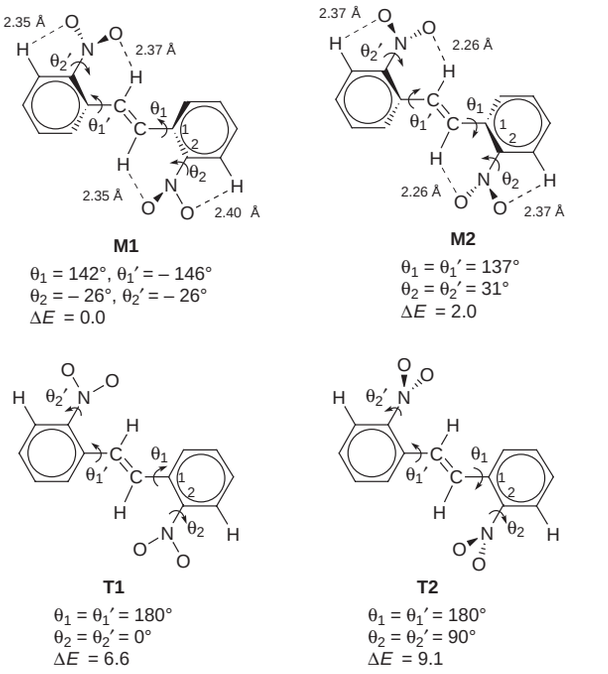

Fig. 5 Main conformations of *trans*-2,2′-dinitrostilbene found at the 6-31G*//6-31G* level, $\theta_1 = (C{=}CC_1C_2)$, $\theta_1' = (C{=}CC_1'C_2')$, $\theta_2 = (ONC_2C_1)$, $\theta_2' = (ONC_2'C_1')$ (ΔE in kcal mol^{-1}).

M2 is 2.0 kcal mol^{-1} less stable than M1, and its phenyl rings in crossed (nearly perpendicular, 87°) planes.

The completely coplanar s-*trans*/s-*trans* conformation (T1) of *trans*-2,2′-dinitrostilbene is found to be a critical point with an energy 6.6 kcal mol^{-1} higher than M1, where the C=C double bond and the nitro groups are in the same plane as both aromatic rings [$\theta_1(C{=}CC_1C_2) = \theta_1'(C{=}CC_1'C_2' = 180°$, and $\theta_2(ONC_1C_2) = \theta_2'(ONC_1'C_2') = 0°$]. The force constant analysis of T1 shows that it is not a conformer. One additional critical point (T2) is found in this s-*trans*/s-*trans* conformation, which has an energy 9.1 kcal mol^{-1} higher than M1. In T2 the C=C double bond is coplanar to both aromatic rings [$\theta(C{=}CC_1C_2) = \theta'(C{=}CC_1'C_2') = 180°$], and the nitro groups are in a plane perpendicular to the aromatic rings [$\theta(ONC_1C_2) = \theta'(ONC_1'C_2') = 90°$]. The frequency analysis of this critical point showed imaginary frequencies, indicating that it is not a minimum point of the PES. The eigenvalues of the Hessian showed that it is a second order saddle point corresponding to the internal rotation angles $\theta_1(C{=}CC_1C_2)$, $\theta_1'(C{=}CC_1'C'_2)$, $\theta_2(ONC_2C_1)$ and $\theta_2'(ONC_2'C_1')$.

The conformation s-*cis*/s-*cis*, where the nitro groups are positioned towards the central C=C double bond [$\theta_1(C{=}CC_1C_2) = 0°$], is much more unstable than the s-*trans*/s-*trans* conformation [$\theta_1(C{=}CC_1C_2) = 180°$]. For the s-*cis*/s-*cis* conformation, one critical point was detected where the aromatic rings and the central C=C double bond are coplanar with each other and both nitro groups are in planes perpendicular to the aromatic ring [Fig. 5, $\theta_2(ONC_2C_1) = 90°$]. This structure has an energy 12.4 kcal mol^{-1} higher than M1.

Our theoretical results for *trans*-2,2′-dinitrostilbene show that the predominant conformers have non-coplanar structures. In these structures, the electron delocalization across the π-systems will be low. This fact explains some experimental behaviour, such as the ^{13}C NMR spectrum and the high reactivity of the central ethylenic group in the ozonolysis reaction. Besides, this structure could also explain the experimental singlet ground-state electronic absorption spectrum of this molecule, which has a maximum at 255 nm with a small band at 335 nm. This result contrasts with the absorption spectrum of the non-sterically hindered *trans*-4,4′-dinitrostilbene, which has a maximum at 357 nm.[34] The steric crowding of the *ortho* nitro groups in *trans*-2,2′-dinitrostilbene enforces the twisted configuration with very little conjugation between the aromatic rings and the central double bond. This structure is also consistent with the X-ray diffraction studies of 2,2′,4,4′,6,6′-hexanitrostilbene, where the aromatic rings are severely twisted with respect to the plane of the central double bond, at angles of 104 and 98°.[35] On the other hand, the disposition of the nitro groups twisted out of the aromatic ring planes is consistent with the experimental excited triplet-state absorption spectra of *trans*-2,2′-dinitrostilbene, where the triplet state lifetime is significantly shorter than that of *trans*-4,4′-dinitrostilbene. Smit[34] suggested that this result is due to an absence of resonance effects due to the nitro groups on the triplet lifetime of this molecule. Our theoretical calculations find that the steric hindrance of the *ortho* nitro moieties forces a twisting of these nitro groups out of the aromatic ring plane, thereby reducing π-orbital conjugation with the aromatic ring π-orbital.[36]

Conclusions

An alternative synthesis of 2-nitrobenzaldehyde is established in this work. This route avoids the safety and environmental hazards of previous methods. This new synthesis of 2-nitrobenzaldehyde yields a mixture of two products, which can easily be separated. Both products, 2-nitrobenzaldehyde and 2-nitrobenzoic acid, are used as intermediates for dyes and pharmaceuticals. The synthesis of *trans*-2,2′-dinitrostilbene from α-chloro-2-nitrotoluene has been improved significantly, providing a higher yield in a shorter time than that previously described. This method appears amenable to scale-up on an industrial level and can be extrapolated to other benzaldehydes with different substitution patterns, such as 3- and 4-nitrobenzaldehydes. Nevertheless, our best results were not obtained under optimised conditions. Further research should result in a systematic optimisation of all parameters, especially for scaling-up purposes.

The NMR results indicate a highly symmetrical structure for *trans*-2,2′-dinitrostilbene. Besides, a low level of electronic delocalization across the π-systems (phenyl rings, central ethylenic bond, and nitro groups) was observed in this molecule. This fact corresponds to a non-coplanar structure. Our *ab initio* quantum mechanical studies on these molecules show us a non-coplanar structure as the predominant conformer, where the phenyl groups are twisted with respect to the central ethylenic bond and the nitro groups are also twisted out of the aromatic ring planes. The non-coplanar and non-conjugated structure of this conformer could explain the high reactivity of the central C=C double bond in the ozonolysis reaction, as the ethylenic π-system is not delocalized across both aromatic rings. This structure also explains some of the spectroscopic features of this molecule, such as the variations in its electronic absorption spectrum with respect to that of *trans*-4,4′-dinitrostilbene. This twisted structure is also consistent with X-ray studies of 2,2′,4,4′,6,6′-hexanitrostilbene.

Experimental

Materials

Unless otherwise noted, high quality commercial materials and solvents shown by GLC to be free of impurities were used as received. The commercial bleach used was donated by Ercros S.A. in concentrated form (17% of active chlorine), with subsequent corresponding dilutions.

Analytical methods

NMR spectra were measured at 200 MHz (for ^{1}H NMR) and 50.3 MHz (for ^{13}C NMR) with a Varian VXR 200 spectrometer, using TMS as internal reference; *J* values are in Hz. A DEPT pulse sequence was used for elucidation, distinguishing

different CH_x species ($x = 0$–3) in the NMR studies. The MS analyses were performed using a Hewlett Packard 5985B spectrometer. TLC analysis was conducted on 0.25 mm E. Merck silica gel plates (60F-254) using UV light (254 nm) as developing agent, and toluene or benzene–cyclohexane (1 : 1) as the mobile phase. In the GLC analytical studies a Perkin-Elmer 8500 chromatograph was used with a flame ionisation detector, and a 2 m × ¼ inch column with a stationary phase of QF (15%) + DC.200 (20%). The quantitative analysis was performed using pentadecane as an internal standard. Concerning the HPLC analysis, a Hewlett-Packard HP-1090-m chromatograph was used with an UV-V diode-array spectrometer as detector. A reverse phase column Spherisorb ODS-2, C-18 (250 mm × 4.6 mm × 5 μm) was used with an eluent flux of 1 ml min^{-1}. This eluent consisted of acetonitrile–monopotassium phosphate buffer (pH = 2.3) (15 : 85). All reactions were monitored by TLC, GLC, and HPLC analysis.

α-Chlorination of 2-nitrotoluene

A solution of 2-nitrotoluene (11 g) in methylene chloride was added to an aqueous solution of sodium hypochlorite. The reaction mixture was adjusted to pH 9 with HCl and the phase transition catalyst (PTC) was added. The reaction was carried out with strong stirring at room temperature. At the end of the reaction, the mixture was acidified to pH 1, separating the two phases. The aqueous phase was extracted with methylene chloride. All organic phases were collected and partially concentrated to a determined volume for GLC and HPLC analysis. This organic phase was washed with an aqueous solution of NaOH (10%), and concentrated under reduced pressure to give a yellow liquid, from which α-chloro-2-nitrotoluene and 2-nitrotoluene were separated by TLC. 2-Nitrotoluene: $\delta_H(CDCl_3)$ 2.63 (s, 3H, CH_3), 7.1–8.1 (m, 4H, aromatic); $\delta_C(CDCl_3)$ 20.5 (CH_3), 124.6 (C_3), 126.9 (C_4), 132.8 (C_6), 133.1 (C_5), 133.6 (C_1), 149.6 (C-NO_2); *m*/*z* 137 (M^+, 16%), 120 (100), 92 (63), 91 (59), 77 (33). α-Chloro-2-nitrotoluene: $\delta_H(CDCl_3)$ 4.98 (s, 3H, CH_3), 7.1–8.1 (m, 4H, aromatic); $\delta_C(CDCl_3)$ 42.9 (CH_2), 125.3 (C_3), 129.5 (C_4), 131.6 (C_6), 133.8 (C_5), 132.4 (C_1), 147.8 (C-NO_2). The alkaline washing solution was acidified, extracted with methylene chloride, and concentrated to give a white solid analysed as pure 2-nitrobenzoic acid (mp 145 °C).

2,2′-Dinitrostilbene

An ethanolic solution (80 mL) of KOH (10 g) (85%) was added to another ethanolic solution of freshly prepared α-chloro-2-nitrotoluene (9.7 g). The reaction was carried out at room temperature and at the end an insoluble solid was formed. The reaction mixture was filtered and the solid was washed with ethanol (90%) and hot water obtaining a solid of mp 193–195 °C, which was recrystallised with acetone (67%); (mp 195–195.5 °C (lit.,[37] 196 °C); $\delta_H(CDCl_3)$ 7.50 (t, 2H, $^3J = 7.3$, H *para*), 7.58 (s, 2H, CH alkene), 7.70 (t, 2H, $^3J = 7.3$, H *meta*), 7.83 (dt, 2H, $^3J = 7.9$, $^5J = 1.2$, H *ortho*), 8.06 (dt, 2H, $^3J = 7.3$, $^5J = 1.2$, H *meta* vicinal to NO_2); $\delta_C(CDCl_3)$ 125.0 (C_3), 129.04 (CH alkene), 129.07 (C_4), 129.2 (C_6), 132.7 (C_1 without H), 133.8 (C_5), 147.9 (C-NO_2).

Dehydrohalogenation–dimerization reaction of α-bromo-2-nitrotoluene

Commercial α-bromo-2-nitrotoluene was used as received (**CAUTION**: volatile and irritant product by skin and face contact). The procedure described above for α-chloro-2-nitrotoluene was followed in this case. Instantaneously the precipitation of a solid was detected. After 10 min the conversion was total, and only one product was detected, identified as (2-nitrobenzyl) ethyl ether; $\delta_H(CDCl_3)$ 1.29 (t, 3H, $^3J = 6.9$, CH_3), 3.63 (q, 2H, $^3J = 6.9$, CH_2, Et), 4.87 (s, 2H, benzylic), 7.41 (dd, 1H, $^3J = 8.1$, $^3J' = 7.8$, H *para*), 7.65 (d, 1H, $^3J = 7.8$, H *meta*), 7.81 (d, 1H, $^3J = 7.8$, H *ortho*), 8.05 (d, 1H, $^3J = 7.8$, H *meta* vicinal to NO_2); $\delta_C(CDCl_3)$ 15.2 (CH_3), 66.7 (CH_2, Et), 69.1 (C benzylic), 124.6 (C_3), 127.8 (C_4), 128.6 (C_6), 133.6 (C_5), 135.5 (C_1), 147.2 (C-NO_2).

Ozonolysis of 2,2′-dinitrostilbene

An Ultradynamics MDL 1500B ozone generator was used (**CAUTION**: ozone is highly toxic above 0.5 ppm in air). Oxygen gas freshly enriched with ozone (*ca*. 1.5%) was bubbled (flow rate = 80–200 L h^{-1}) through a solution of 2,2′-dinitrostilbene (0.2 g, 0.74 mol) in methylene chloride at low temperature (−10 °C). The reaction was monitored by TLC until total conversion. Methyl sulfide (2 ml) was added to the reaction mixture, and gentle stirring was applied at room temperature. The final reaction mixture was concentrated under reduced pressure to eliminate the remaining SMe_2. The concentrated mixture was diluted with ethyl acetate and analysed by GLC and HPLC (Table 3). This organic solution was washed with an alkaline solution, concentrated, and purified by preparative TLC yielding (see Table 3) pure (GLC) 2-nitrobenzaldehyde (mp 40–42 °C, purification yield 98%, **CAUTION**: toxic and irritant product by inhalation); *m*/*z* 151 (M^+, 97%), 150 (75), 105 (43), 104 (18), 77 (100), 76 (32), 51 (95). The alkaline washing solution was acidified with HCl and extracted with methylene chloride. The organic solution was concentrated, and the residue was recrystallised ($CHCl_3$) to give a white solid, analysis of which showed it to be 2-nitrobenzoic acid (mp 145 °C, purification yield 90%).

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