Experiments on the *Chaperon* Effect in the Nitration of Aromatics†

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A nitro group may be effectively delivered to the *ortho* position of alkylbenzenes, provided that a suitable *chaperon* function is located in α-position and a dilute solution of HNO_3 in CH_2Cl_2 is used. The carbonyl function of an aldehyde or ketone is the best choice, but a carboxyl, alkoxycarbonyl, and amide groups all work well. The ether function showed a less pronounced *ortho* orientation effect, whereas the hydroxyl group was too prone to oxidation. Side reactions were minimal under the conditions employed. A *para chaperon* effect was seemingly at work in the CH_2Cl_2 nitration of benzenepropanenitrile. All the results were compared with the corresponding classical nitration in H_2SO_4.

Introduction

In addition to the general and hectic search for novel procedures of nitration of aromatics replacing the classical method employing HNO_3 in H_2SO_4, an active interest on the production of individual or less common and accessible isomers is also to be considered. Both replacement of the "solvent" system[2] and of the reagent[3] were recently presented. In some instances the end result amounted to a generally sharp increase of production of *o*-nitro derivatives,[4] but through different mechanistic pathways, that only in the case of some laterally functionalized compounds merged into the *chaperon* effect initially described by us.[2d] In view of the promising results in obtaining the much sought after[4b] *ortho* isomers in high yields, the avoidance of catalysts and obnoxious solvents, the straightforwardness of the procedure of facile implementation both in any chemical laboratory and in a perspective industrial application, as well as the absence of side reactions and polynitration, we have pursued the further study of the system.

Results and Discussion

In a previous report we have compared the results of the classical nitration in H_2SO_4 of benzeneacetic acid (**1**) and its methyl (**2**) and ethyl (**3**) esters with the results obtained in more or less concentrated solutions of 100% commercial HNO_3 in CH_2Cl_2.[2d] A comparison was also made between these experiments and those on alkylbenzenes with substituents of less or similar steric properties. No special effort was made to optimize yields or isomeric propensities in our reactions, but, anyhow, the following scenario was thus outlined: HNO_3 in CH_2Cl_2 is a more bland reagent in direct nitrations, a fact allowing the effective working of a fast preequilibration to intermediates[5] **5** and **6** in the case of substrates **1**−**4** (Scheme 1), uniquely suited to yield *ortho* products in a winning competition with the direct *para* (and *meta*) nitration of uncomplexed species. The α-carboxyl function could be regarded as the regiospecific *chaperon* of the nitronium ion into the ring. Interestingly enough, the bulkier ester functions (methyl and ethyl esters of benzeneacetic acid, **2** and **3**) appeared more efficacious in promoting *ortho* nitration than the carboxyl function of the corresponding free acid **1**.

We now observe that 1-methylethyl benzeneacetate (**4**) undergoes nitration to yield practically the same isomeric ratio as **2** and **3** (Table 1): the invariance with alkyl group bulkiness of the isomeric distribution seems to indicate that the site of O-precomplexation promoting the *ortho* nitration is the carbonyl oxygen (**6**). In this context, the alkyl group has most likely two favorable effects: its electron-releasing activity favors the formation of the adduct **6**, which, by and large, cannot undergo deactivation by a subsequent proton loss, yielding **7**. In keeping with the favorable six-member ring transition state assumption, moving the carboxyl function further away (β- or γ-carbon of the side chain), like in 3-benzenepropanoic (**8**) and 4-benzenebutanoic (**9**) acids, causes a complete loss of the effect. In fact, they undergo *ortho* nitration in much lesser proportions, which, when due

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(2) (a) Davis, G.; Cook, N. *CHEMTECH* **1977**, *7*, 626. (b) Bakke, J. M.; Hegbom, I. *Acta Chem. Scand.* **1994**, *48*, 181. (c) Bakke, J. M.; Hegbom, I.; Øvreeide, E.; Aaby, K. *Acta Chem. Scand.* **1994**, *48*, 1001. (d) Strazzolini, P.; Verardo, G.; Gorassini, F.; Giumanini, A. G. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1155.

(3) (a) Gigante, B.; Prazeres, A. O.; Marcelo-Curto, M. J.; Cornélis, A.; Laszlo, P. *J. Org. Chem.* **1995**, *60*, 3445. (b) Delaude, L.; Laszlo, P.; Smith, K. *Acc. Chem. Res.* **1993**, *26*, 607. (c) Riego, J. M.; Sedin, Z.; Zaldìvar, J. M.; Marziano, N. C.; Tortato, C. *Tetrahedron Lett.* **1996**, *37*, 513. (d) Suzuki, H.; Murashima, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 903. (e) Mori, T.; Suzuki, H. *Synlett* **1995**, 383. (f) Suzuki, H.; Mori, T. *J. Chem. Soc., Perkin Trans. 2* **1996**, 677.

(4) (a) Suzuki, H.; Tatsumi, A.; Ishibashi, T.; Mori, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 339. (b) Suzuki, H.; Takeuchi, T.; Mori, T. *J. Org. Chem.* **1996**, *61*, 5944.

(5) Eberson, L.; Hartshorn, M. P.; Radner, F. *Acta Chem. Scand.* **1994**, *48*, 937.

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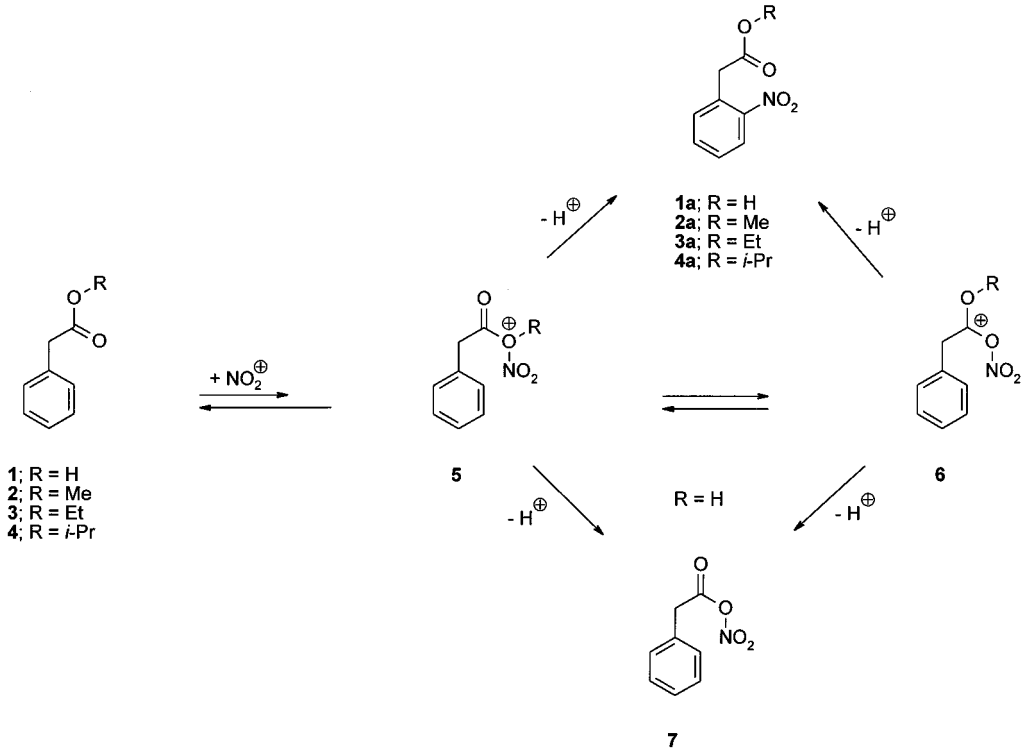
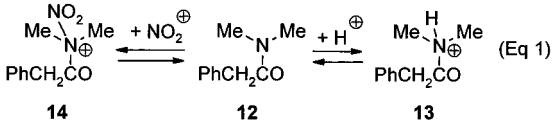
Scheme 1



consideration of the amounts of 2,4-dinitro derivatives produced in the classical nitration procedure is given, are practically coincidental with those in H_2SO_4, where these acids led to much less *ortho* nitration[6] than hydrocarbons with alkyl substituents of similar or lesser bulkiness.[7] Since this effect cannot be ascribed to an electron-withdrawing effect, as also confirmed by the smaller incursion of *meta* substitution, it is likely that the actual size of the lateral substituent in **8** and **9** in H_2SO_4 is much larger because of close association of solvent molecules. A methyl on the α-carbon of benzeneacetic acid (compound **10**) is also the cause of a decrease of the *chaperon* effect, which appears still marked in comparison with, e. g., alkylbenzenes such as isopropyl and *sec*-butyl.[8] This decrease could be related to some steric crowding near the center(s) coordinating the nitro group, contrasting the enhancing of the relevance of the most favorable conformation of the formed complex (Figure 1). Removal of the electron-withdrawing COOH group away from the α-position of the alkyl side chain causes an increase of the electron-releasing and *ortho,para*-orienting effect of the latter, as was evident also from the depressed production of the *meta*-isomer.

The steric hindrance to the *ortho* nitration is much stronger for benzeneacetic acid than for the model compound, i.e., the hydrocarbon (2-methylpropyl)benzene (**11**) in the classical nitration. Interestingly, chain lengthening as well as branching on site other than the α-carbon, has practically no effect on the distribution of isomers.[7] α-Branching on the ester alkyl group, like in **4**, leads to a decrease of the *ortho* substitution in H_2SO_4, being exactly the observation opposite to that of the experiments in CH_2Cl_2. The *chaperon* effect is noteworthy already in concentrated CH_2Cl_2 solutions, but reaches its high point in relatively dilute solution. Moreover, HNO_3 in CH_2Cl_2 is absolutely a much milder reagent at all concentrations: in fact, if a 100% conversion can be easily achieved in reasonable times, a second nitration is avoided at all under both sets of conditions.

A test on the *N*,*N*-dimethylamide group as α-*chaperon* shows that the reaction is slowed, but the *ortho* effect is still very strong. The more basic function of the *N*,*N*-dimethylbenzeneacetamide (**12**) most likely becomes at least partly protonated to **13** or nitrated to **14** (eq 1), and



this reaction detracts active concentration of free substrate for the *chaperon* effect. Also, these adducts would show some enhanced *meta* orientation and reasonably more so in H_2SO_4 or concentrated solutions of CH_2Cl_2, a fact, which indeed occurs in these experiments. A nitrile group located in the α- or β-position of an alkyl side chain, like in compounds **15** and **16**, does not appear to alter the electron-releasing properties of the alkyl substituent substantially; still the vicinity of the CN group to the aromatic ring (compound **15**) increases the occurrence of *meta* nitration. The orientation of the CN group is not amenable either to the *ortho* or *para chaperon* effect in the α-substituted compound **15**, and the enhanced relative amount of *para*-product can be ascribed to the steric bulk produced by solvation of the CN group by H_2SO_4 and HNO_3. When the CN group is removed by one more

(6) R. C. Gaudreault et al. *J. Pharm. Sci.* **1988**, *77*, 185, reported a 50% separated yield of 2-nitrobenzenebutanoic acid (**9a**) and a 22% separated yield of 4-nitrobenzenebutanoic acid (**9c**). There is an obvious erroneous assignment of the location of the nitro groups caused by their inversion, as also evidenced by the comparison with the melting points reported in the literature (see Experimental Section).

(7) Baas, J. M. A.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1081.

(8) Baas, J. M. A.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1089.

Table 1. Nitrations of Monosubstituted Benzenes[a]

	nitration in H_2SO_4			concentrated nitration in CH_2Cl_2			diluted nitration in CH_2Cl_2		
substrates	conv (%)	mononitration (%, *o*-/*m*-/*p*- rel %)	dinitration (%)	conv (%)	mononitration (%, *o*-/*m*-/*p*- rel %)	dinitration (%)	conv (%)	mononitration (%, *o*-/*m*-/*p*- rel %)	dinitration (%)
hydrocarbons									
$PhCH_2CH(Me)_2$ (**11**)	89	83, 40/7/53	6	100	100, 44/5/51	0	100	100, 47/4/49	0
carboxylic acids									
$PhCH_2COOH$ (**1**)	100	100, 27/22/51	0	100	100, 47/14/39	0	100	100, 66/11/23	0
PhCH(Me)COOH (**10**)	100	100, 23/19/58	0	100	100, 40/15/45	0	100	100, 56/13/31	0
$Ph(CH_2)_2COOH$ (**8**)	100	92, 26/8/66	8	100	100, 39/5/56	0	100	100, 56/4/40	0
$Ph(CH_2)_3COOH$ (**9**)	100	90, 29/5/66	10	100	100, 36/5/59	0	100	100, 38/4/58	0
carboxylic esters									
$PhCH_2COOMe$ (**2**)	100	100, 40/15/45	0	100	100, 50/13/37	0	100	100, 75/8/17	0
$PhCH_2COOEt$ (**3**)	100	100, 41/14/45	0	100	100, 49/12/39	0	100	100, 75/8/17	0
$PhCH_2COO$*i*-Pr (**4**)	100	100, 31/17/52	0	100	100, 52/13/35	0	100	100, 75/7/18	0
$PhCH_2COO$*t*-Bu (**27**)	[b]			[b]			[b]		
carboxamides									
$PhCH_2CONMe_2$ (**12**)	89	89, 15/28/57	0	19	19, 43/17/40	0	80	80, 66/14/20	0
	100[c]	100, 14/28/58	0	100[c]	100, 32/20/48	0	—	—	—
nitriles									
$PhCH_2CN$ (**15**)	95	95, 12/19/69	0	96	96, 17/16/67	0	85	85, 15/14/71	0
	—	—	—	—	—	—	100[c]	100, 18/12/70	0
$Ph(CH_2)_2CN$ (**16**)	100	100, 23/14/63	0	100	100, 22/8/70	0	100	100, 19/6/75	0
aldehydes									
$PhCH_2CHO$ (**19**)	[d]			96[e]	87,[f] 75/8/17	0	100[g]	100, 82/5/13	0
ketones									
$PhCH_2COMe$ (**17**)	[d]			100	94,[h] 76/9/15	0	100[g]	96,[i] 85/5/10	0
$PhCH_2COPh$ (**18**)	[d]			100	85,[l] 72/8/20	—	100[g]	76,[m] 85/4/11	0
alcohols									
$PhCH_2CH_2OH$ (**24**)	[n]			[n]			[n]		
ethers									
PhOMe (**23**)	[d]			100	100, 67,[o] 37/<1/63	0	100	100, 68,[o] 36/<1/64	0
$PhCH_2OMe$ (**22**)	[p]			[p]			[p]		
$Ph(CH_2)_2OMe$ (**20**)	78	60, 33/9/58	18	100	100, 36/9/55	0	100	100, 52/7/41	0
$Ph(CH_2)_3OMe$ (**21**)	56	46, 34/7/59	10	100	100, 34/8/58	0	100	100, 37/10/53	0

[a] All percentile figures here reported refer to the whole intact reaction mixture after quenching with H_2O. [b] Complete cleavage of the ester was observed.[43] [c] After addition of 50% excess HNO_3. [d] Intractable mixture. [e] After 1 h at 0 °C; at rt extensive oxidation took place. [f] Oxidation products (13%, nitrobenzoic acids) were present. [g] After 2 h at room temperature; after 24 h extensive oxidation took place. [h] Some 6% of aldehydes was also detected in the quenched reaction mixture. [i] PhCHO (4%) was present. [l] 15% oxidation products. [m] 24% oxidation products. [n] Extensive oxidation. [o] Oxidation to 1,4-benzoquinone (3−8%), water soluble and polymeric products made up for the material balance. [p] Benzaldehyde was the only reaction product.

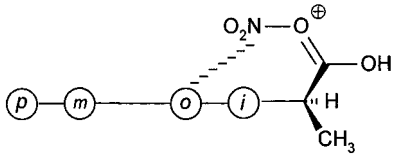
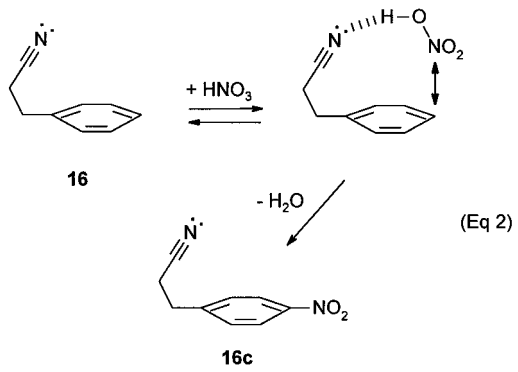


Figure 1. This conformation of the adduct **10**−NO_2^+ with the nitrogen of the nitro group hanging right over the *o*-carbon is favored by the presence of the α-methyl substituent.

CH_2 (compound **16**), the shielding of *ortho* positions seems not to increase but rather coordination of a NO_2^+ group or HNO_3 molecule by CN may induce a *para* nitration by a *para chaperon* effect (eq 2).

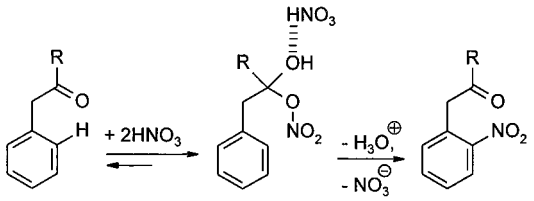


(Eq 2)

While the present advancement of our studies do not allow to decide the relative importance of adducts **5** and **6** in the *ortho* nitration reaction, an independent evidence for the exceptional *ortho chaperon* effect of a carbonyl group in α-position of a side chain is offered by the results of the CH_2Cl_2 nitration of 1-phenyl-2-propanone (**17**) and 1,2-diphenylethanone (**18**). The very clean reaction of the former gives a spectacular conversion to its *o*-nitro derivative **17a** (85% with no attempt at optimization of the conditions ever made); the latter produces 65% of the *ortho*-derivative **18a**. The figures for the actual regiospecificity are practically identical and even more impressive, because the side products are neither nitro derivatives nor derived from the products of mononitration of either **17** or **18**. Interestingly, whereas in our comparative experiments in H_2SO_4 only an intractable number of oxidation and nitration products result by the action of HNO_3 on ketones **17**, **18**, and aldehyde **19**, in contrast with earlier reports[9] from which some propensity toward *ortho* nitration could be inferred, even our CH_2Cl_2 reactions in concentrated conditions give exceptionally high conversions and yields in the *ortho*-derivatives. This behavior may be due to the possible intervention of a different nitrating intermediate, as shown in Scheme 2. Aldehydes are known to be very sensitive compounds: surprisingly enough our experiments on benzeneacetaldehyde (**19**) in CH_2Cl_2 result in an unex-

(9) (a) List, O. *Chem. Ber.* **1893**, *26*, 2451. (b) Neber, P. W.; Hartung, K.; Ruopp, W. *Chem. Ber.* **1925**, *58*, 1234. (c) Womack, E. B.; Campbell, N.; Dodds, G. B. *J. Chem. Soc.* **1938**, 1402. (d) Sugii, M.; Nakai, R. *J. Org. Chem.* **1957**, *22*, 288.

Scheme 2



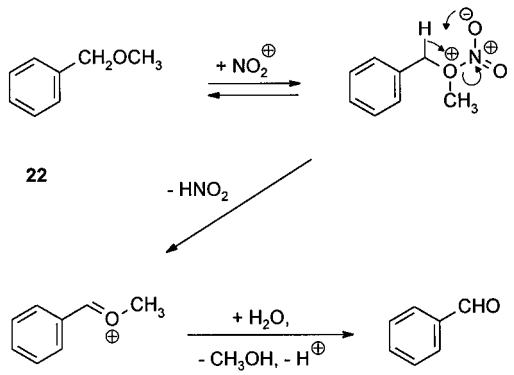
17; R = Me
18; R = Ph
19; R = H

17a; R = Me
18a; R = Ph
19a; R = H

pectedly clean nitration reaction, yielding 82% of the *o*-nitro product, i.e., 2-nitrobenzeneacetaldehyde (**19a**), accompanied solely by the other two isomers **19b** and **19c**. Oxidation is therefore minimal under these conditions, and once more polynitration does not occur.

(2-Methoxyethyl)benzene (**20**) was found to yield anomalously high proportions of *ortho*-product (ca. 60%), when neither pure HNO_3 nor its solution in H_2SO_4 were used, but some form of low acidity nitrating agent or N_2O_5.[10] Precomplexation of NO_2^+ by the heteroatom was invoked in order to rationalize the observation on the account that the homologue (3-methoxypropyl)benzene (**21**) did not show such behavior. Coming to our work on methoxyalkylbenzenes we observe that using a 1:1 ratio HNO_3 vs organic substrate in H_2SO_4 gives a mixture containing only mono and dinitro isomers both with (2-methoxyethyl)benzene (**20**) and (3-methoxypropyl)benzene (**21**), the latter reacting a bit slower. The inability of effecting dinitration by HNO_3 in CH_2Cl_2 shows up already in concentrated solution, which brings about full conversion of the substrate to mononitro derivatives in 1 h: the ratios of mononitro isomers being practically identical for both substrates and types of experiments. Some *ortho* effect is apparent in the CH_2Cl_2 dilute system with **20** where the *ortho*-product formation is raised to 52%. The smaller effectiveness of the β-oxygen in promoting *ortho* nitration seems to be ascribed especially to a decreased attitude to release the coordinated nitro group to the *ortho*-position, because of the increased basicity of the ether oxygen in comparison with the carbonyl oxygen of ketones as well as of esters. In contrast to the behavior of **20** and **21**, methoxymethylbenzene (**22**) gives invariantly benzaldehyde as the sole reaction product, the oxidation reaction resulting faster than *any* expected nitration. In fact, HNO_3, neat or in H_2SO_4, is considered a nitrating agent for **22**,[11] but an oxidant to benzaldehyde when in diluted aqueous solution, where the mechanism was studied[12] and compound **22** found to undergo oxidation induced by small concentrations of HNO_2, which upon reaction with HNO_3 delivers NO_2. The latter is then protonated to the radical cation species responsible for the abstraction of a benzyl hydrogen. We do not routinely purify our 100% commercial HNO_3 from nitrogen oxides, and therefore such an oxidative mechanism could also be operative here. Alternatively, since electron transfer to NO_2^+ or, *a fortiori*, to HNO_3 seems unlikely, we assume that NO_2^+ first is quickly delivered to the

Scheme 3



oxygen, and then HNO_2 is eliminated from the adduct, followed by O-demethylation (Scheme 3). The sequence Ar−CH−O is the key factor for this end result, which shows that delivery of NO_2^+ to the ring from that position is impossible.

To obtain a further confirmation to our *chaperon* hypothesis, although largely substantiated by our experiments, we rule out a "simple" solvent effect, a very weak effect of which was reported in the nitration of chlorobenzene with acyl nitrates,[13] in an ad hoc set of experiments on anisole (**23**). There has been a number of reports on the sulfonitration[14] and the nitration under special conditions[2c,3a,10,15] of this substrate. Practically all works referred to an "initial" behavior, *i.e.*, far away from high conversions; moreover, analytical procedures as well as stringent material balances were commonly not rigorous. We find that a clean, although marred by oxidation to water-soluble byproducts in a substantial extent, mononitration only occurs on **23** with HNO_3 in a more or less concentrated CH_2Cl_2 solution, affording similar results. Whereas the desirable comparison with the reaction of **23** with NO_2^+ (from $HNO_3-H_2SO_4$) is not feasible, because this reaction results in an intractable tarry material,[3c] it can be hardly substained that the observed isomeric ratio (1:1.74, *ortho*:*para*) evidences any working of any solvent effect in *ortho* orientation by CH_2Cl_2. These *ortho* conversions are worse even of those obtained on ethylbenzene (1:1.14, *ortho*:*para*);[2d] by and large, they cannot imply any linear coordination effect[15b] under these conditions.

When benzeneethanol (**24**) is submitted to the action of HNO_3 at high concentration in CH_2Cl_2, no product of ring nitration is detected by GC-MS analysis, the major product observed being benzeneacetic acid (**1**), the second largest being benzaldehyde. The two oxidative pathways must be so fast as to disrupt the nitration capabilities of the solution, possibly because of the formation of H_2O. Minor amounts of benzeneacetaldehyde (**19**) and of two compounds, both showing the highest peak of their mass spectra at 104 *m*/*z*, identified tentatively as benzeneethyl

(10) Norman, R. O. C.; Radda, G. K. *J. Chem. Soc.* **1961**, 3030.

(11) It is surprising to read in in some earlier reports (see: Knowles, J. R.; Norman, R. O. C. *J. Chem. Soc.* **1961**, 2938. Reference 10. Hartshorn, S. R.; Moodie, R. B.; Schofield, K. *J. Chem. Soc. B* **1971**, 2454.) that **22** would undergo only (?) mononitration to the three nitrophenyl derivatives under conditions (H_2SO_4) strictly comparable to ours.

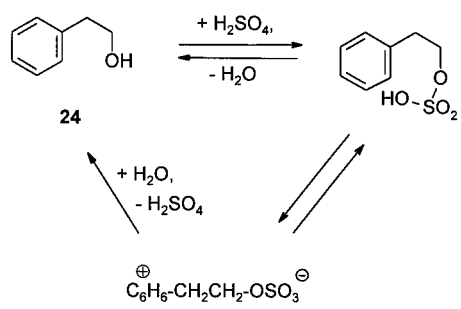
(12) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1966**, *88*, 5832.

(13) Sparks, A. K. *J. Org. Chem.* **1966**, *31*, 2299.

(14) (a) Griffiths, P. H.; Walkey, W. A.; Watson, H. B. *J. Chem. Soc.* **1934**, 631. (b) Bunton, C. A.; Minkoff, G. J.; Reed, G. J. *J. Chem. Soc.* **1947**, 1416. (c) Hoggett, J. G.; Moodie, R. B.; Schofield, K. *J. Chem. Soc., Chem. Commun.* **1969**, 605. (d) Barnett, J. W.; Moodie, R. B.; Schofield, K.; Weston, J. B.; Coombes, R. G.; Golding, J. G.; Tobin, G. D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 248.

(15) (a) Halvarson, K.; Melander, L. *Arkiv. Kemi* **1957**, *11*, 77. (b) Kovacic, P.; Hiller, J. J., Jr. *J. Org. Chem.* **1965**, *30*, 2871. (c) Brandt, L.; Verbesselt, R. *Tetrahedron* **1972**, *28*, 89. (d) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans 1* **1974**, 369. (e) Suzuki, H.; Murashima, T.; Mori, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1443.

Scheme 4



nitrite (**25**) and benzeneethyl nitrate (**26**), are also present. The reason why the nitration of the initial substrate is completely frustrated lies most likely in the extremely fast competing oxidative reaction sequences. This is shown to be the case in a more dilute solution: after 24 h the starting material is all used up to yield the oxidation product benzaldehyde and the precursor **26** only. It is noteworthy that the usually more reactive system $HNO_3-H_2SO_4$ also is ineffective to yield nitration products, leaving most of the starting material unchanged and only causing partial oxidation to **19**. It is quite likely that the inactivation of the system is due to the reactions outlined in Scheme 4.

A thorough examination of Table 1 shows that when no *chaperon* effect may be invoked, the results in the three nitrating mixtures, and more significantly in the two using CH_2Cl_2, are very similar. On the other hand, the effect of many functions strategically located in the α-position of an alkyl side chain of a benzene ring in giving a strong *ortho* regioselectivity in the nitration reactions (α-*chaperon* effect) is definitively established. Side reactions, oxidations and polynitrations, are practically absent. The use of dilute solutions of HNO_3 in CH_2Cl_2 is usually mandatory in order to obtain *ortho* orientation: more concentrated solutions behave in a fashion similar to classic H_2SO_4 nitrations, although they show some obvious advantages, above everything being a more controllable system. HNO_3 in CH_2Cl_2, besides allowing the operation of the *chaperon* mechanism, exhibits, therefore, a much blander nature than alone or in H_2SO_4, perhaps because it is present in clusters, where the NO_2^+ donor is some adduct of lower reactivity than naked NO_2^+ itself.

Experimental Section[16]

General Methods. Unless otherwise specified, reagents and solvents were commercially available (Aldrich Italia, Milano, Italy) and used as received. Commercial 100% HNO_3 was kindly supplied by Pravisani S. p. A. (Udine, Italy) and used without further purification. The other reagents employed were prepared with conventional methods (see below). The course of all the reactions described was monitored by GC and GC-MS, after a preliminary quenching of the reaction mixtures with ice cold 10% aqueous Na_2SO_4, drying over Na_2SO_4 and treatment with CH_2N_2, when suitable. After careful elimination of the solvent, the whole mixture was analyzed also by ^{1}H NMR. Elemental analyses were obtained for all isolated compounds and were satisfactory. GC analyses were carried out using a 0.25 mm i.d. × 30 m SPB5 fused silica capillary column (Supelchem, Milano, Italy). We have observed that a number of different GC stationary phases, which were found absolutely suitable both for their retention properties, resolution, and analysis time, showed relatively high discriminatory behavior toward the *p*-nitro isomers, which were strongly retained in a substantial proportion such to affect the peak area ratios of the isomers within a very large range of suitable concentrations, as shown by a parallel accurate ^{1}H NMR quantitative evaluation.

1-Methylethyl benzeneacetate (**4**)[17] and 1,1-dimethylethyl benzeneacetate (**27**)[18] were obtained according to a described procedure.[19] *N*,*N*-Dimethylbenzeneacetamide (**12**)[20] was prepared by treating benzeneacetyl chloride with liquid $(CH_3)_2NH$ in Et_2O and purified by distillation: 65% yield; bp 96 °C/20 Pa; mp 40 °C. 1-Phenyl-2-propanone (**17**)[21] was prepared by a known procedure.[22] Methoxymethylbenzene (**22**: 89% yield; bp 75 °C/2933 Pa),[23] (2-methoxyethyl)benzene (**20**: 87% yield; bp 86 °C/2933 Pa),[24] and (3-methoxypropyl)-benzene (**21**: 92% yield; bp 97 °C/2933 Pa)[24,25] were obtained by adding the corresponding alcohols into a suspension of NaH (80% dispersion in mineral oil) in $(CH_3OCH_2CH_2)_2O$ and heating the mixture for 30 min at 60 °C, followed by treating with Me_2SO_4 (60 °C for 3 h), conventional workup, and final distillation.

Nitrations in H_2SO_4. All these nitrations were carried out according to a single procedure, although it might not be the most suitable for an individual substrate, to make comparison more homogeneous. A chilled solution of 100% commercial HNO_3 (5.4 mmol) in H_2SO_4 (0.37 mL) was added in one lot to the aromatic substrate (5.0 mmol, Table 1) at 0 °C under vigorous stirring. The obtained mixture was allowed to reach room temperature during 1 h, when the reaction was invariably quenched by pouring it into a chilled 10% aqueous solution of Na_2SO_4, immediately thoroughly extracted with CH_2Cl_2, and finally dried over anhydrous Na_2SO_4. An aliquot was analyzed by ^{1}H NMR after solvent replacement with $CDCl_3$. GC and GC-MS analyses were also always secured on the intact CH_2Cl_2 mixture, as well as after treatment with ethereal CH_2N_2. The material balance was always determined by weighing the intact extract after complete solvent removal. In the case of neutral substrates a subsequent extraction of the whole organic mixture with 5% aqueous $NaHCO_3$ was performed, and the analyses were repeated for data consistency. Acidic material was always also analyzed by GC and GC-MS after methylation with CH_2N_2. Separations of individual products were eventually carried out with suitable procedures, whenever deemed necessary.

Nitrations in CH_2Cl_2. (a) Concentrated System. A solution of 100% commercial HNO_3 (25 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise to a solution of the aromatic substrate (5.0 mmol, Table 1) in CH_2Cl_2 (1.0 mL) under vigorous stirring at 0 °C. The mixture was left to reach room temperature during 1 h and, after this time, was diluted with CH_2Cl_2 (30 mL), washed three times with 10% aqueous Na_2SO_4, and then prepared for analyses and separations as described above.

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(b) Diluted System. A solution of 100% commercial HNO_3 (50 mmol) in CH_2Cl_2 (7.7 mL) was added dropwise to a solution of the aromatic substrate (5.0 mmol, Table 1) in CH_2Cl_2 (25 mL) under vigorous stirring at 0 °C. The mixture was then stirred 24 h at room temperature and, after this time, washed with 10% aqueous Na_2SO_4 and treated in the usual way.

Methyl 2-nitrobenzeneacetate (2a), methyl 4-nitrobenzeneacetate (2c), ethyl 2-nitrobenzeneacetate (3a), and **ethyl 4-nitrobenzeneacetate (3c)** have been described previously.[2d]

1-(2-Methylpropyl)-2-nitrobenzene (11a). Yellow oil: bp 129 °C/2400 Pa;[26a] IR (film) 2960s, 2870m, 1609w, 1577w, 1527s, 1467m, 1386w, 1348s, 1165w, 862m, 785m, 735s, 702w, 668m cm^{-1}; ^1H NMR δ 0.92 (d, J = 6.6 Hz, 6H), 1.91 (*app* nn, 1H), 2.79 (d, J = 7.1 Hz, 2H), 7.26−7.39 (m, 2H), 7.50 (*pseudo* td, $J_o = J_{o'}$ = 7.5 Hz, J_m = 1.4 Hz, 1H), 7.86 (dd, J_o = 7.9 Hz, J_m = 1.3 Hz, 1H); ^{13}C NMR δ 149.81, 136.28, 132.64, 132.30, 126.88, 124.52, 41.65, 29.48, 22.39; MS *m*/*z* 120 (100), 92 (80), 43 (75), 65 (57), 41 (45), 179 (M^+, <1).

1-(2-Methylpropyl)-4-nitrobenzene (11c). Pale yellow oil: bp 141 °C/2400 Pa;[26] IR (film) 2959s, 2871w, 1606m, 1599m, 1519s, 1467w, 1346s, 1110w, 858m, 799w, 743m, 698w cm^{-1}; ^1H NMR δ 0.92 (d, J = 6.6 Hz, 6H), 1.92 (*app* nn, 1H), 2.59 (d, J = 7.2 Hz, 2H), 7.24−7.35 (m, 2H), 8.09−8.20 (m, 2H); ^{13}C NMR δ 149.60, 133.97, 129.78, 123.39, 45.16, 30.11, 22.22; MS *m*/*z* 43 (100), 137 (99), 41 (67), 90 (54), 107 (51), 179 (M^+, 49).

α-Methyl-2-nitrobenzeneacetic Acid (10a). White solid: mp 108 °C;[27] IR and ^1H NMR;[28] ^{13}C NMR δ 179.35, 148.66, 134.45, 133.45, 129.93, 128.28, 124.96, 41.43, 17.39; MS *m*/*z* 77 (100), 43 (91), 150 (54), 103 (53), 149 (50), 195 (M^+, 4).

2-Nitrobenzenepropanoic Acid (8a). Pale yellow crystals: mp 113 °C;[29] IR (pellet) 2923s (broad), 1701s, 1520s, 1436m, 1342s, 1273w, 1221m, 934w, 861m, 792w, 729m, 699w cm^{-1}; ^1H NMR δ 2.80 (t, J = 7.7 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 7.38−7.46 (m, 2H), 7.50−7.62 (m, 1H), 7.91−7.99 (m, 1H), 11.09 (broad s, 1H); ^{13}C NMR δ 178.78, 149.14, 135.16, 133.30, 132.07, 127.72, 124.95, 34.54, 27.96; MS *m*/*z* 149 (100), 77 (88), 135 (66), 91 (43), 79 (42), 195 (M^+, 16).

4-Nitrobenzenepropanoic Acid (8c). White needles: mp 165 °C;[29] IR (pellet) 2920s (broad), 1701s, 1605w, 1596w, 1517s, 1436m, 1344s, 1220m, 1188w, 1111w, 934w, 859m, 732m, 693w cm^{-1}; ^1H NMR ($CDCl_3$/CD_3COCD_3 7/3 v/v) δ 2.72 (t, J = 7.5 Hz, 2H), 3.09 (t, J = 7.5 Hz, 2H), 7.41−7.52 (m, 2H), 8.09−8.21 (m, 2H); ^{13}C NMR ($CDCl_3$/CD_3COCD_3 7/3 v/v) δ 172.93, 148.15, 146.02, 128.80, 122.98, 33.90, 29.94; MS[30] *m*/*z* 149 (100), 77 (46), 195 (M^+, 45), 106 (30), 107 (29).

2-Nitrobenzenebutanoic Acid (9a). Pale yellow crystals: mp 70 °C;[31] IR (pellet) 2962s (broad), 1705s, 1608w, 1575w, 1523s, 1420w, 1346s, 1292m, 1267m, 1220m, 918w, 858m, 789w, 761m, 723m, 668w cm^{-1}; ^1H NMR δ 2.02 (m, 2H), 2.47 (t, J = 7.3 Hz, 2H), 2.96 (t, J = 7.8 Hz, 2H), 7.30−7.43 (m, 2H), 7.48−7.59 (m, 1H), 7.87−7.95 (m, 1H), 10.57 (broad s, 1H); ^{13}C NMR δ 179.52, 149.27, 136.24, 133.01, 131.94, 127.29, 124.78, 33.43, 32.03, 25.40; MS *m*/*z* 132 (100), 162 (99), 92 (90), 146 (72), 91 (62), 209 (M^+, <1).

1-Methylethyl 2-Nitrobenzeneacetate (4a). Pale yellow liquid: bp 124 °C/67 Pa; IR (neat) 2983m, 2937w, 1732s, 1614w, 1581w, 1528s, 1467w, 1414w, 1349s, 1289w, 1255w, 1220m, 1181m, 1146w, 1108s, 958w, 842m, 789m, 718s cm^{-1}; ^1H NMR δ 1.22 (d, J = 6.3 Hz, 6H), 3.98 (s, 2H), 5.02 (sp, J = 6.3 Hz, 1H), 7.31−7.38 (m, 1H), 7.39−7.49 (m, 1H), 7.58 (*pseudo* td, $J_o = J_{o'}$ = 7.5 Hz, J_m = 1.5 Hz, 1H), 8.07 (ddd, J_o = 8.0 Hz, J_m = 1.5 Hz, J_p = 0.3 Hz, 1H); ^{13}C NMR δ 169.21, 148.60, 133.33, 133.14, 129.81, 128.29, 124.92, 68.58, 39.87, 21.45; MS *m*/*z* 43 (100), 120 (78), 41 (58), 92 (37), 78 (36), 223 (M^+, <1).

1-Methylethyl 4-Nitrobenzeneacetate (4c). Pale yellow crystals: mp 36 °C;[32] IR (pellet) 2987w, 1730s, 1607w, 1518s, 1467w, 1351s, 1229m, 1189m, 1104s, 905w, 856w, 836w, 798w, 723s cm^{-1}; ^1H NMR δ 1.24 (d, J = 6.3 Hz, 6H), 3.70 (s, 2H), 5.03 (sp, J = 6.3 Hz, 1H), 7.42−7.51 (m, 2H), 8.15−8.23 (m, 2H); ^{13}C NMR δ 169.65, 147.14, 141.63, 130.20, 123.69, 68.92, 41.38, 21.70; MS *m*/*z* 43 (100), 137 (21), 136 (15), 41 (13), 89 (11), 223 (M^+, <1).

***N*,*N*-Dimethyl-2-nitrobenzeneacetamide (12a).** Pale yellow crystals: mp 73 °C;[33] IR (pellet) 2935m, 1655s, 1612w, 1578w, 1522s, 1389m, 1345s, 1134s, 864m, 794m, 739s, 696w, 593m, 493w cm^{-1}; ^1H NMR δ 2.98 (s, 3H), 3.14 (s, 3H), 4.06 (s, 2H), 7.32 (*app* d, J_{app} = 7.5 Hz, 1H), 7.43 (*pseudo* td, $J_o = J_{o'}$ = 7.7 Hz, J_m = 1.6 Hz, 1H), 7.57 (*pseudo* td, $J_o = J_{o'}$ = 7.5 Hz, J_m = 1.4 Hz, 1H), 8.08 (dd, J_o = 8.0 Hz, J_m = 1.3 Hz, 1H); ^{13}C NMR δ 168.98, 149.00, 133.19 (2C), 131.39, 127.97, 124.96, 38.71, 37.29, 35.57; MS.[33b]

***N*,*N*-Dimethyl-4-nitrobenzeneacetamide (12c).** Pale yellow crystals: mp 87 °C;[33c] IR (pellet) 2933w, 1649s, 1604w, 1513s, 1396w, 1350s, 1264w, 1135m, 1110w, 858w, 818m, 799w, 740s, 694w cm^{-1}; ^1H NMR δ 2.99 (s, 3H), 3.07 (s, 3H), 3.82 (s, 2H), 7.38−7.50 (m, 2H), 8.12−8.23 (m, 2H); ^{13}C NMR δ 169.35, 146.79, 142.74, 130.02, 123.56, 40.15, 37.51, 35.60; MS.[34]

2-Nitrobenzenepropanenitrile (16a). Yellowish crystals: mp 39 °C;[35] IR (neat) 2249w, 1611w, 1577w, 1525s, 1349s, 1077w, 858m, 813w, 791m, 743s, 700m, 664w, 605w, 530m cm^{-1}; ^1H NMR δ 2.85 (t, J = 7.1 Hz, 2H), 3.24 (t, J = 7.1 Hz, 2H), 7.44−7.55 (m, 2H), 7.65 (*pseudo* td, $J_o = J_{o'}$ = 7.5 Hz, J_m = 1.4 Hz, 1H), 8.04 (dd, J_o = 8.1 Hz, J_m = 1.6 Hz, 1H); ^{13}C NMR δ 148.55, 133.68, 132.84, 132.46, 128.53, 125.14, 118.55, 29.16, 18.20; MS *m*/*z* 77 (100), 78 (88), 92 (59), 103 (53), 51 (49), 176 (M^+, 2).

4-Nitrobenzenepropanenitrile (16c). White crystals: mp 79 °C;[36] IR (pellet) 2243w, 1599w, 1515s, 1344s, 1178w, 1104m, 1015w, 937w, 858s, 806m, 748m, 699m, 653w, 518m, 499s cm^{-1}; ^1H NMR δ 2.72 (t, J = 7.1 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H) 7.40−7.48 (m, 2H), 8.17−8.25 (m, 2H); ^{13}C NMR δ 147.16, 145.22, 129.28, 124.02, 118.28, 31.09, 18.74; MS *m*/*z* 136 (100), 77 (40), 106 (39), 103 (36), 176 (M^+, 34).

1-(2-Nitrophenyl)-2-propanone (17a). Pale yellow crystals: mp 27 °C;[37] IR (neat, melted) 1723s, 1613w, 1579w, 1525s, 1411m, 1348s, 1162m, 869w, 789m, 732m, 699w, 673w, 631w cm^{-1}; ^1H NMR δ 2.30 (s, 3H), 4.13 (s, 2H), 7.27 (dd, J_o = 7.5 Hz, J_m = 1.2 Hz, 1H), 7.43 (*pseudo* td, $J_o = J_{o'}$ = 7.7 Hz, J_m = 1.5 Hz, 1H), 7.58 (*pseudo* td, $J_o = J_{o'}$ = 7.5 Hz, J_m = 1.4 Hz, 1H), 8.08 (dd, J_o = 8.1 Hz, J_m = 1.2 Hz, 1H); ^{13}C NMR δ 203.51, 148.37, 133.48, 133.37, 130.18, 128.22, 124.93, 48.34, 29.76; MS.[38]

2-(2-Nitrophenyl)-1-phenylethanone (18a). Yellow crystals: mp 72 °C; IR;[39] ^1H NMR δ 4.69 (s, 2H), 7.33 (dd, J_o = 7.5 Hz, J_m = 1.4 Hz, 1H), 7.41−7.65 (m, 5H), 7.97−8.07 (m, 2H), 8.13 (dd, J_o = 8.0 Hz, J_m = 1.4 Hz, 1H); ^{13}C NMR δ 195.29, 148.95, 136.37, 133.58, 133.46, 133.41, 130.57, 128.66, 128.32, 128.15, 125.17, 44.07; MS *m*/*z* 105 (100), 77 (64), 106 (15), 51 (8), 78 (7).

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2-Nitrobenzeneacetaldehyde (19a). Orange oil: bp 115 °C/47 Pa; a well-known compound.[40]

1-(2-Methoxyethyl)-2-nitrobenzene (20a). Pale yellow liquid: bp 70 °C/10 Pa;[41] IR (film) 2931w, 2874w, 1526s, 1349s, 1115s, 858m, 787w, 744m, 703w, 668m cm^{-1}; ^1H NMR and ^{13}C NMR;[41] MS *m*/*z* 45 (100), 120 (42), 77 (40), 65 (36), 51 (32).

1-(2-Methoxyethyl)-4-nitrobenzene (20c). White crystals: mp 64 °C;[10,42] IR (pellet) 2936w, 2882w, 1608w, 1599w, 1510s, 1388w, 1344s, 1194w, 1108s, 966m, 859s, 807m, 754m, 702m, 525s cm^{-1}; ^1H NMR δ 2.98 (t, J = 6.5 Hz, 2H), 3.35 (s, 3H), 3.65 (t, J = 6.5 Hz, 2H), 7.34−7.46 (m, 2H), 8.09−8.21 (m, 2H); ^{13}C NMR δ 147.17, 146.56, 129.65, 123.52, 72.38, 58.73, 36.01; MS *m*/*z* 45 (100), 77 (33), 151 (31), 89 (30), 51 (27), 181 (M^+, 25).

1-(3-Methoxypropyl)-2-nitrobenzene (21a). Yellow liquid: bp 96 °C/53 Pa; IR (film) 2927m, 2873m, 1610w, 1578w, 1527s, 1459m, 1350s, 1118s, 856m, 787m, 741m, 704w, 666w cm^{-1}; ^1H NMR δ 1.75−1.92 (*sym* m, 2H), 2.87 (t, J = 7.7 Hz, 2H), 3.25 (s, 3H), 3.32 (t, J = 6.2 Hz, 2H), 7.19−7.32 (m, 2H), 7.38−7.48 (m, 1H), 7.75−7.82 (m, 1H); ^{13}C NMR δ 149.33, 136.79, 132.73, 131.94, 126.89, 124.50, 71.53, 58.36, 30.30, 29.44; MS *m*/*z* 45 (100), 91 (43), 77 (34), 65 (27), 118 (26).

1-(3-Methoxypropyl)-4-nitrobenzene (21c). Pale yellow crystals: mp 44 °C; IR (film) 2928m, 2874m, 1610m, 1521s, 1385w, 1344s, 1204w, 1180w, 1110s, 1054m, 1016w, 863w, 849m, 804w, 745m, 668m cm^{-1}; ^1H NMR δ 1.83−2.00 (*sym* m, 2H), 2.82 (t, J = 7.7 Hz, 2H), 3.35 (s, 3H), 3.39 (t, J = 6.2 Hz, 2H), 7.30−7.40 (m, 2H), 8.09−8.19 (m, 2H); ^{13}C NMR δ 149.93, 146.33, 129.22, 123.59, 71.29, 58.59, 32.24, 30.76; MS *m*/*z* 163 (100), 45 (89), 91 (34), 115 (30), 117 (26), 195 (M^+, <1).

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