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The Influence of *Ortho* Substituents on the Twisting Angle of a Nitro Group with Respect to Aromatic Six-Membered Carbon Rings*

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Abstract

Examples of aromatic six-membered carbon rings carrying a nitro group with (*a*) zero, (*b*) one and (*c*) two substituents in the *ortho* position have been retrieved from organic molecules in the Cambridge Structural Database. The 270 fragments of type (*a*), 392 fragments of type (*b*) and 82 fragments of type (*c*) have been used to examine the distributions of the rotation of the nitro group out of the aromatic plane, the nitro group bending out of the latter plane and the nitro group bending into this plane, resulting in different exocyclic angles. The analyses show that the out-of-plane rotation angle of a nitro group depends on the steric hindrance caused by one or two adjacent groups, the electronegativity of the adjacent group(s) and the crystal packing. The comparison of this angle for a number of nitrobenzene musk compounds with respect to the structure–activity theory of Beets indicates that this descriptor is not a determining factor for muskiness.

Introduction

Within the development of structure–activity relationships of muskiness, the compounds belonging to the nitro family have often been considered as a separate group. In the penetration and puncturing theory of Theimer & Davies (1967) both the mono- (*i.e.* benzenes) and bicyclic (*i.e.* indans and tetralins) nitro compounds are explicitly neglected. Using pattern-recognition techniques Jurs and co-workers developed a model for the monocyclic nitrobenzenes (Ham & Jurs, 1985) based on different descriptors to the model proposed for bicyclo- and tricyclobenzenoids (Narvaez, Lavine & Jurs, 1986). Curiously enough, the latter authors do not explain why only nitro-free compounds were taken into consideration.

Beets (1957, 1977) tried to involve all musks – exhibiting rather different chemical structures – in his profile–functional group theory. Paying less attention to the functional group and more to the overall molecular shape, it was easy to understand that replacement of an acetyl by a nitro group in the family of the so-called bicyclic *ortho*-musks only results in minor qualitative and quantitative odour changes. All indans and tetralins which make up this group have an aromatic ring with two bulky substituents on one side of the ring (in general, two quaternary C atoms in the *ortho* position) and an osmophoric group (acetyl, formyl, nitro) on the other side of it as a common characteristic

In contrast to the bicyclic nitromusks the monocyclic compounds have only one bulky quaternary C atom and two or three nitro groups attached to a benzene ring (only a few exceptions do not have these features). To tackle this problem Beets (1957, 1977) postulated that a nitro group could have two possible functions, namely that 'a nitro group in a sterically unhindered position, permitting its coplanarity with the benzene ring, may act, in the absence of more effective candidates, as a functional group analogous to an acetyl group' and further that 'a nitro group of which the usual coplanarity with the benzene ring is prevented by one or two adjacent bulky substituents and of which, consequently, the oxygens are forced out of the plane of the benzene ring, may function as a detail of the molecular profile in a way analogous to a tertiary butyl group of which two methyl groups are necessarily projecting out of the plane of the ring'.

The position and conformation of a nitro group with respect to the aromatic ring will have an essential role for the determination of its function. If this bifunctionality of nitro groups exists, there is reason to assume that the angle the NO_2 group makes with the aromatic ring will depend on its function. If odour perception is envisaged as an interaction between a complementary odorant molecule and a receptor, there is ground to believe that an optimum twisting-out-of-the-aromatic-plane angle for an osmophoric nitro group may exist.

In a free molecule a nitro group with two H atoms in the *ortho* position is expected to be coplanar with the benzene ring due to conjugation between the nitro group and the aromatic ring. When one or two substituents are introduced in *ortho* positions a number of energy-minimizing effects can deform the molecule: rotation of the NO_2 group out of the aromatic plane, the NO_2 group bending out of the benzene-ring plane (non-planar deformation) or the NO_2 group bending in this plane resulting in different exocyclic angles (distortion

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of the valence angles). These changes will depend on the electronic structure and the size of the substituent(s). In order to reduce strain, rotation of the nitro groups is the most effective method. To obtain quantitative data the rotation, the bending-in and the bending-out angle of the nitro group in aromatic compounds having two and one substituents, respectively (denoted hereafter NO-2 and NO-1), *ortho* to a nitro group, have been determined for a number of crystal structures in the Cambridge Structural Database (1989).

In a crystal the packing may influence the conformation of a molecule. In order to obtain an idea of the latter effect the angles the nitro group makes with the aromatic plane were also determined for compounds having two H atoms *ortho* to the nitro group (denoted hereafter NO-0).

In the discussion attention will be paid to the rotation angle of the nitro groups of the nitrobenzene musks and one of its isomers, of which the crystal structures have been established, with respect to Beets' theory. Next to this the rotation angle of the nitro group in the crystal structures of bicyclic nitromusks will be compared with the range found in this study.

Data selection and retrieval

Crystallographic coordinates for NO-0, NO-1 and NO-2 nitro-aromatic compounds were retrieved from the Cambridge Structural Database (CSD; Allen, Kennard & Taylor, 1983). The data set was generated *via* the program *QUEST* (Allen & Davies, 1988; CSD *User Manual*, Part I, 1989) of the CSD System Version 3.4 as released on 1 January 1989. General search restrictions ensured that for all retrieved entries:

(*a*) CSD checks had shown no residual numerical errors.

(*b*) There was no disorder in the chemical structure.

(*c*) The entries contained no metal(s), *i.e.* only organic molecules were considered.

(*d*) The reported crystallographic R value was less than 0.100 (0.075 for the NO-0 compounds).

The large amount of data was reduced by imposing the following additional constraints to the NO-0 compounds:

(*e*) Only diffractometer data were allowed.

(*f*) The average estimated standard deviation for a C—C bond had to be less than 0.005 Å.

In total 797 crystal structures having an aromatic ring to which at least one NO_2 group was attached were retrieved from the CSD. For the three types (NO-0, NO-1 and NO-2) a nitro group was not selected for the calculations if the sum of the angles around the N atom was deviating more than 1° from 360°, thus avoiding strong intra- or intermolecular interactions of the nitro group. The different types are discussed below.

The database release was dated 1 July 1991 and contains 90 296 entries. All numerical calculations were carried out within the framework of the program *GSTAT* (CSD User Manual, Part II, 1989).

CSD reference codes for data sets NO-0, NO-1 and NO-2 and full citations have been deposited.*

Results

NO-0

From the data set 270 NO-0 fragments were matched in *GSTAT*. The parameters taken into consideration are visualized in Fig. 1. The statistics for 15 parameters are summarized in Table 1. No distinction can be made between NO1 and NO2, CNO1 and CNO2, CCCH1 and CCCH2, EXO1 and EXO2, the mean values for each pair, therefore, should be equal within the limits of accuracy.

From Table 1 it can be seen that the endocyclic angle of the aromatic ring which carries the nitro group (CCCN) is significantly larger than 120°, whereas the endocyclic angles which carry an H atom (CCCH1 and CCCH2) are significantly smaller than 120°. It has been observed that the enlarged C—C—C angle at the C atom attached to a nitro group is a common feature in nitro-aromatic compounds. Carter, McPhail & Sim (1966) suggested an explanation for this effect based on σ-bond hybridization, which would explain why the size of this endocyclic angle is independent of the rotation angle of the nitro group with respect to the aromatic ring (for the NO-0 fragments the correlation coefficient between CCCN and ANGLE is 0.26). Since the type of substituent at the other three endocyclic angles is unknown on the one hand and the behaviour of the endocyclic ring angles is beyond the scope of this work on the other hand, the interested reader is referred to the literature dealing with the nature of the deformations of the aromatic ring in substituted benzene derivatives which has been discussed *in extenso* by Domenicano and co-workers (*e.g.* Domenicano, Vaciago

* Lists of CSD reference codes for data sets NO-0, NO-1 and NO-2, and full citations have been deposited with the IUCr (Reference: SH0047). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

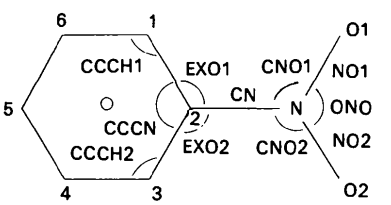


Fig. 1. Parameters taken into consideration, DIFF = 360.0° − (ONO + CNO1 + CNO2) (planarity of the NO_2 group), DEXO = EXO1 − EXO2, BEND = absolute value of the angle between the plane defined by the atoms C(1)—C(2)—C(3) and C(2)—N, ANGLE = angle of rotation of the NO_2 group about C(2)—N as defined by the angle between the plane defined by the atoms of the NO_2 group and the plane of the aromatic ring.

Table 1. NO-0 (*distances in* Å, *angles in* °)

Parameter	Mean (s.d.)	Minimum	Maximum
CN	1.466 (1)	1.433	1.500
NO1	1.219 (1)	1.179	1.242
NO2	1.218 (1)	1.187	1.242
ONO	123.57 (5)	121.46	127.33
CNO1	118.17 (4)	115.61	120.08
CNO2	118.25 (4)	115.13	120.34
CCCN	122.16 (5)	119.93	124.68
CCCH1	118.65 (6)	115.15	122.10
CCCH2	118.76 (5)	115.49	120.78
EXO1	118.91 (4)	117.42	121.58
EXO2	118.92 (4)	117.01	120.75
DEXO	−0.02 (6)	−2.39	3.32
ANGLE	7.3 (3)	0.0	28.2
BEND	0.94 (5)	0.0	3.70
DIFF	0.011 (1)	0.0	0.141

& Coulson, 1975*a*,*b*; Domenicano, Mazzeo & Vaciago, 1976; Domenicano & Murray-Rust, 1979).

The sole distributions relevant to this work are those for the out-of-plane-rotation (ANGLE), the bending-out (BEND) and the difference between the exocyclic angles (DEXO) of the nitro group with respect to the aromatic plane, all given in Fig. 2. The parameters, the distributions of which are not shown, have no significantly aberrant behaviour from a normal distribution.

The distribution of DEXO is symmetrical around 0, as expected. The spread is small, since it can only be caused by packing effects.

Since the side of the ring to which the nitro group is deviating has no importance, the absolute value of BEND has been plotted in Fig. 2. Analogous, because no distinction is made between positive and negative rotations, ANGLE in the diagram represents positive and negative values. Therefore, the frequency for ANGLE = 0 and for BEND = 0 has to be doubled, or the rest of the frequencies halved in order to obtain the correct relative frequencies. If this is taken into consideration, the diagrams show half of a near-Gaussian distribution with a mean value for ANGLE and BEND of about 0. The value for the doubled frequency for ANGLE = 0 and for BEND = 0 has been indicated in Fig. 2.

Dashevskii, Struchkov & Akopyan (1966) reported the results of force-field calculations on the out-of-plane rotation of nitro groups in nitro-aromatic compounds. They found that an out-of-plane rotation of 18° requires only 2.51 kJ mol^{-1} (0.6 kcal mol^{-1}), a value which can easily be compensated if necessary by the energy of intermolecular interaction. 14 crystal structures have an out-of-plane NO_2 rotation angle larger than 18°. The respective publications have been checked for an explanation of this effect. In only three cases it has been attempted to explain the rotation angle (BICNUW: probably packing forces; HNIABZ11: intermolecular steric effects; MTNANL: intermolecular hydrogen bond). In seven cases the angle is mentioned in the text without further explanation (CIVVEI10, FANTBZ, FITPED,

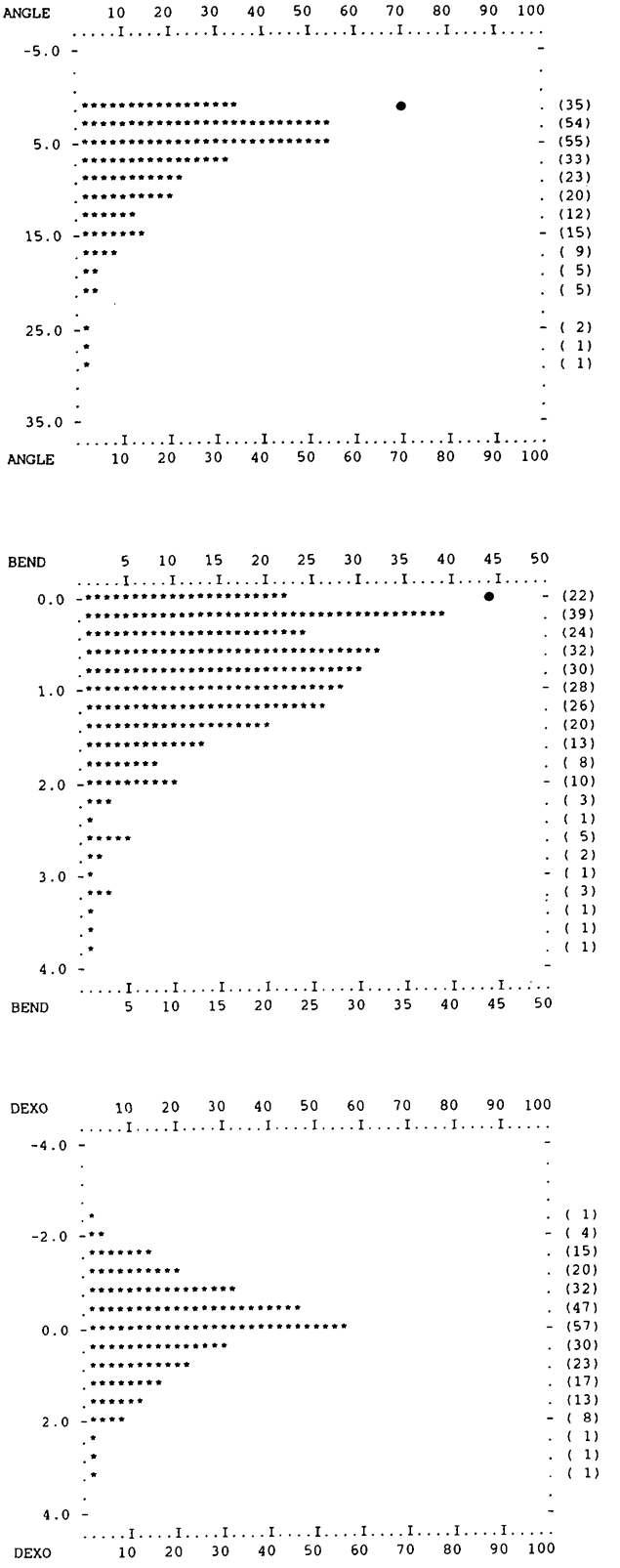


Fig. 2. Distributions of ANGLE, BEND and DEXO of the NO-0 compounds.

KAJVEW, KECTAN, NBFURX and TNIZMS). Finally, in four cases no attention has been paid to the relatively large twisting-out angle of the nitro group (CADCUF, CAGGOG, CPHNZP and FAHZUJ). It can be assumed that in the last two groups intermolecular steric effects, intermolecular hydrogen bonds or packing forces will be causing the non-coplanarity of the nitro group with the aromatic ring.

NO-1

In total 392 fragments, having the common feature of a nitro group with only one adjacent H atom, were matched in *GSTAT*. CCCH1 is the endocyclic angle of the aromatic C atom that carries the non-H substituent. The same statistics for the same parameters as calculated for NO-0 are given in Table 2 and the distributions of ANGLE, BEND, DEXO and CCCH1 are given in Fig. 3.

Table 2. NO-1 (*distances in* Å, *angles in* °)

Parameter	Mean (s.d.)	Minimum	Maximum
CN	1.463 (1)	1.413	1.518
NO1	1.217 (1)	1.118	1.283
NO2	1.215 (1)	1.071	1.287
ONO	123.21 (9)	117.10	127.42
CNO1	118.34 (6)	114.73	121.98
CNO2	118.39 (7)	114.43	124.71
CCCN	123.04 (8)	117.10	127.12
CCCH1	114.94 (14)	109.86	122.56
CCCH2	118.67 (6)	114.52	122.97
EXO1	120.70 (8)	115.13	125.47
EXO2	116.20 (6)	112.69	121.48
DEXO	4.5 (1)	−3.3	10.8
ANGLE	27 (1)	0.7	88.3
BEND	1.86 (9)	0.003	9.95
DIFF	0.053 (4)	0	0.648

Where distributions are not shown, the parameters have no significantly aberrant behaviour from a normal distribution.

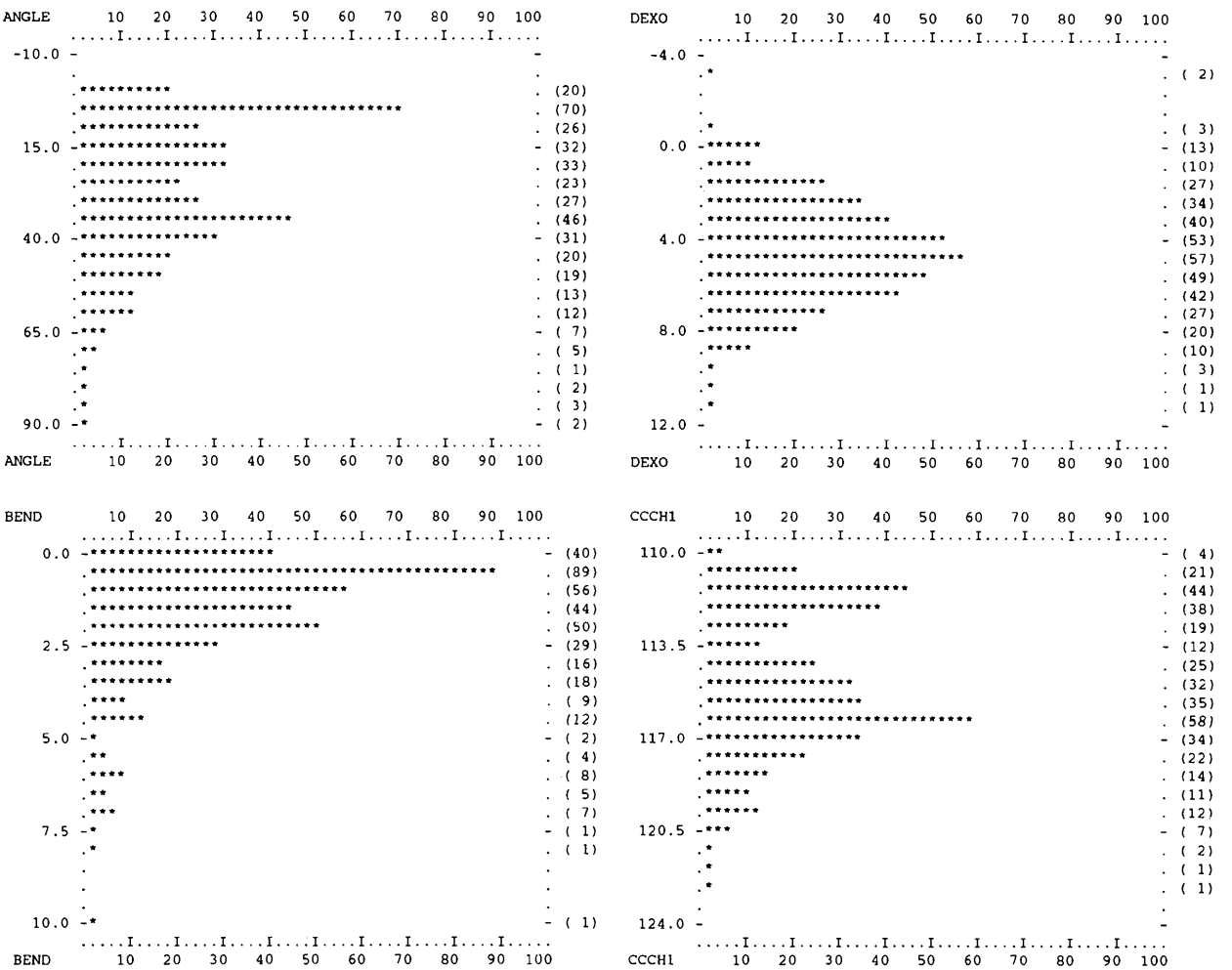


Fig. 3: Distributions of ANGLE, BEND, DEXO and CCCH1 of the NO-1 compounds.

Table 3. NO-1 (*angles in* °)

Type	No. of fragments	ANGLE Mean (s.d.)	ANGLE Range	BEND Mean (s.d.)	BEND Range	DEXO Mean (s.d.)	DEXO Range
All fragments	392	27 (1)	0–88	1.86 (9)	0.003–9.95	4.5 (1)	−3.3–10.8
C atoms	83	35 (2)	2–88	2.3 (2)	0.03–7.4	5.5 (3)	−0.2–10.6
—CH_2—*R* [*R* = C, H]	21	29 (3)	5–49	1.1 (2)	0.03–3.3	5.1 (3)	1.3–7.8
—CO—*R* [*R* = OH, NH_2]	10	25 (7)	7–86	1.6 (4)	0.6–4.5	3.7 (6)	1.6–7.8
—C_{ar} (fused)	32	38 (2)	7–66	3.9 (4)	0.09–7.4	9 (3)	1.0–10.6
N atoms	123	25 (2)	1–86	2.1 (2)	0.06–7.8	5.3 (2)	−1.0–9.9
—NO_2	15	39 (4)	13–66	4.0 (3)	2.6–6.1	4.2 (5)	1.5–8.5
—NH_2	6	8 (3)	2–23	0.9 (4)	0.1–2.8	5.0 (4)	4.0–6.1
—NH*R*	66	13 (2)	1–64	1.6 (2)	0.06–7.8	5.8 (2)	−1.0–8.5
—NR_2	23	45 (3)	16–75	2.4 (4)	0.1–7.0	5.6 (4)	1.8–9.9
O atoms	157	24 (1)	1–70	1.50 (11)	0.003–9.95	3.1 (2)	−3.3–9.9
O^-	120	24 (1)	3–66	1.56 (12)	0.003–5.77	3.0 (2)	−3.3–9.9
OH	19	12 (3)	2–51	1.3 (5)	0.1–9.9	3.2 (3)	0.3–5.2
O—(C=O)—*R* or O—(P=O)—R_2	4	17 (5)	1–25	1.9 (5)	0.7–3.2	5.7 (2)	5.2–6.4
S atoms	20	30 (6)	1–78	1.3 (2)	0.08–3.1	5.9 (2)	4.5–8.3
—S—N—	2	2.8 (4)	2.4–3.1	1.8 (8)	1.0–2.7	5.1 (6)	4.5–5.7
—S—C—	10	12 (3)	1–28	1.1 (3)	0.08–3.1	5.6 (4)	4.8–7.2
Sulfonyl	1	21	—	1.9	—	8.3	—
Sulfonate	7	65 (3)	59–69	1.4 (4)	0.2–3.0	6.1 (3)	4.8–7.5
Halogen atoms	9	27 (5)	2–43	1.8 (3)	0.4–3.9	5.9 (9)	3.2–10.8
F	1	13	—	0.4	—	3.2	—
Cl	5	34 (5)	14–43	1.6 (2)	0.7–2.0	4.42 (7)	4.11–4.53
Br	3	18 (10)	2–37	2.4 (8)	1.3–3.9	9.2 (7)	7.8–10.8

The ANGLE distribution is a composite one. The conspicuous peak at about 5° is mainly because of hydrogen-bond formation of the nitro group with NH_2, NH*R* or OH substituents.

The mean value of BEND and DEXO is significantly higher and their spread is larger than in the NO-0 structures, undoubtedly the effect of steric hindrance.

Compared with the NO-0 structures, the ONO miminum value is more than 4° lower. The low values are observed with the picrates where the nitro group is adjacent to an O^- group. Cady (1967) observed smaller ONO angles in compounds having either steric problems associated with two *ortho* substituents which have intramolecular forces strong enough to hold the nitro group in the plane of the aromatic ring, or two adjacent negatively charged groups (remark that these are compounds of the NO-2 type). It is observed that also NO-1 compounds with a nitro group adjacent to only one substituent can have smaller ONO angles.

CCCH1 can be considered as the superposition of two distributions, one with a mean CCCH1 = 111.5° and the other with a mean CCCH1 = 116°. The first belongs to the picrates, the second relates to the rest of the compounds. Domenicano, Vaciago & Coulson (1975*a*,*b*) already observed that the endocyclic angle of a benzene ring is contracted when conjugation may occur between a substituent and the ring whenever the former has filled or unfilled orbitals of suitable size and symmetry available for mixing with the π-orbitals of the ring.

The highest negative correlation coefficient is found between CCCN and CCCH1 (–0.79), which can be explained by the fact that the sum of the endocyclic angles in the aromatic ring is fixed (720°). ANGLE shows a correlation (0.62) with ONO. The adjacent non-H-atom substituents can be divided into five groups: C atoms (83 fragments), N atoms (123), O atoms (157), S atoms (20) and halogens (9). The results for ANGLE, BEND and DEXO of these groups and their respective subgroups are collected in Table 3.

C *atoms*

The mean value of ANGLE, BEND and DEXO is larger than the corresponding mean values of the whole NO-1 distribution. The other parameters have the same distribution as the overall NO-1.

The mean value of BEND increases upon going from fragments having an adjacent —CH_2—*R* group to fragments having an adjacent —CO—*R* group, which corroborates with an increase in intramolecular hindrance. The higher value for a neighbouring C_{ar} can be explained by the fact that the latter cannot compensate for intramolecular steric hindrance by a concerted rotation of the nitro group and its adjacent group as in the case of the two other types.

In the 21 fragments with a NO_2 group having an adjacent —CH_2—*R* group the lower values of ANGLE are generally observed when the adjacent substituent is a methyl group. CCCH1 is 4° less than in NO-0.

In the group CO—*R* large CN distances correlate strongly with large CCCN angles (correlation coefficient = 0.92). The difference between the out-of-plane rotation angle of the nitro group in the 2-position in 2,4-dinitrobenzoic acid (19°, BIPJUF10) and 2,5-

dinitrobenzoic acid (86°, DAJXUH) is of interest. Possibly the strong electron-withdrawing character of the nitro group in the 5-position plays a role in the significantly larger angle of the latter compound. This explanation was also suggested in a series of *p*-nitrobenzene derivatives by Wallis & Watkin (1982).

The highest values of ANGLE are observed in two dinitrodihydroxyanthraquinones (BOLPEX and NHANTQ): 62–88°, mean value of ANGLE = 81°.

In one case (DEJWIY) a short NO distance of 1.118 Å is observed. In this compound there is also a significant difference between CNO1 and CNO2 (7°), whereas ANGLE is 78°. The other *ortho* nitro group in the molecule has normal distances and angles around the N atom and ANGLE is only 28°. This difference can be accredited to steric hindrance.

N *atoms*

For the discussion the 123 fragments have been divided into four subgroups

N *in an adjacent* NO_2 *group*. The mean value of BEND for this subgroup is the highest observed of all subgroup types which can be explained by the strong intramolecular forces acting between the neighbouring nitro groups.

Compared with NO-0, the CCCN angle is reduced by 1.5° whereas the endocyclic angle, to which the second nitro group is attached (*i.e.* CCCH1), is increased by 1.6°. An increase of ONO of 1.2° is observed. There exists a correlation (coefficient = 0.71) between CN and ONO.

N *in* NH_2 *group*. The amino group keeps the nitro group in the plane of the aromatic ring by an intramolecular hydrogen bond: the average ANGLE = 8 (3)° has only one outlier of 22.5° [2,4,6-trinitroaniline (TNIOAN)]. This is also the only compound in which the amino group is positioned between two nitro groups. Compared with NO-0, the mean CCCH1 (C atom which carries the amino group) is reduced by 4° and ONO is 1° smaller. The intramolecular hydrogen bond does not lead to extreme values for BEND and DEXO. The correlation coefficient between CCCN and CN is 0.95.

N *in N-monosubstituted amines*. Substitution of one of the H atoms of the amino group increases both ANGLE and BEND.

The distribution of ANGLE clearly shows two separate curves [Fig. 4(*a*)]. This parameter correlates with ONO [0.83, Fig. 4(*b*)].

Compared with NO-0, the reduction of CCCH1 is smaller (3°) than in the previous subgroup, whereas the reduction of ONO has the same value. In 54 fragments with ANGLE less than 19° the H atom of the monosubstituted amine lies near the nitro group; this value is larger in two cases (KEJGIP: 39°, TAFCAE: 27°) due to steric intramolecular hindrance with other substituents. If the nitro group is situated near the non-H-atom group of the amine, ANGLE lies within the range 44–64°.

N *in N-disubstituted amines*. The same trend (increase of ANGLE and BEND) is observed upon further substitution of the second H atom of the amino group.

Because of steric hindrance the mean value of ANGLE is higher than in the other compounds having an adjacent N atom. The value of 75° is observed with a *N*-fluorosubstituted compound (FBATNB): the NO_2 group undergoes a significant repulsion from the strong electronegative halogen, which is also expressed in the large difference in exocyclic angles (DEXO = 9.9°). Compared with NO-0, a number of angles undergo changes: ONO and CCCN are increased by 1.1 and 0.8°, respectively, whereas CCCH1 and CCCH2 are reduced

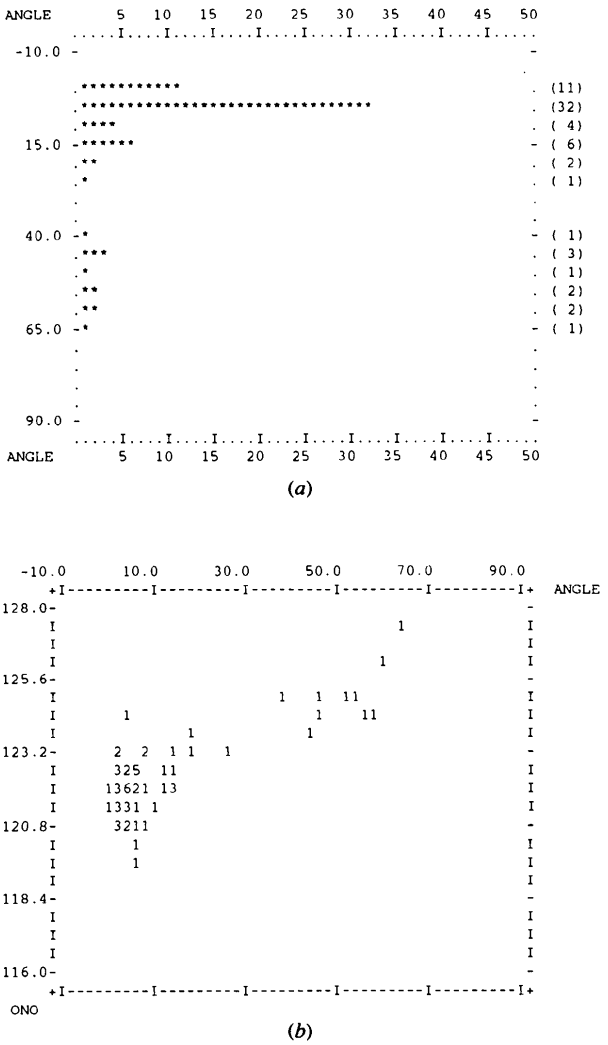


Fig. 4. (*a*) Distribution of ANGLE for the *N*-monosubstituted amines and (*b*) Scatter diagram of ANGLE *versus* ONO for the *N*-monosubstituted amines (NO-1).

by 2.4 and 1.3°, respectively. DEXO is not significantly higher than in the other compounds.

In one compound (KAJVEW) the nitro group has an ONO angle of 118.6° and a short NO distance of 1.163 Å. This is probably caused by the steric hindrance of the bulky group.

In the series of the N-disubstituted compounds there are no significant correlations.

O *atoms*

Compared with NO-0 a decrease for ONO of 1° and an increase for CCCN of 1.6° is observed. The mean value of DEXO is significantly smaller and the mean value of BEND is smaller than for the whole NO-1 distribution. In the group of the O^- substituents (picrates) two significantly high negative values of DEXO are observed, presumably due to the strong ring distortion that is observed within these compounds (KASVIJ and PROPIC10). No significant correlations are noticed.

For the 157 fragments the distribution of CCCH1 (Fig. 5) clearly shows two distinct curves. In the curve with the lowest mean value only compounds with an O^- substituent attached to the ring are found.

The mean value of ANGLE and BEND for the 19 hydroxyl fragments (OH) is somewhat smaller than for the 120 O^- fragments; this can be attributed to a higher repulsion by a negatively charged O atom than by an OH group.

In the 14 cases not listed in the table, where bulky substituents cause considerable steric hindrance, ANGLE lies between 32 and 70° with a mean of 52 (3)°.

In four compounds [BAPPCT, BENHUX, CIHXUM and FIJSOG (all picrates)] an NO distance in the nitro group less than 1.15 Å was observed. None of the authors noticed this feature, but it can be assumed that strong intra- and/or intermolecular effects play an important role.

S *atoms*

Four different types of substituent occur in the distribution of ANGLE (Fig. 6). The lowest values are observed in two thio-amino (—S—N—) compounds. The highest values are found in seven sulfonate compounds [range = 59–69°, mean = 65 (3)°], where both steric hindrance and a negative charge are important factors.

Compared with NO-0 an average increase of 1° for both ONO and CCCN is observed, together with a decrease for CCCH1 and CCCH2 of 3.3 and 1°, respectively. As seen from the table BEND is smaller than for the other NO-1 structures. The rather poorly populated subsets preclude an adequate analysis, but there is some indication that BEND is larger when the atom bonded to sulfur is an N or O atom than when it is attached to a C atom.

Halogen atoms

The values of BEND and DEXO increase when going from the F to the Br compounds.

Four Cl compounds have an ANGLE between 37 and 43°, but a fifth compound shows an ANGLE of only 13.7° (SAVFOK). A possible explanation for this lower value may be the shorter NO distances of 1.130 and 1.145 Å and an ONO angle of 119° in the nitro group. The values of ANGLE for the three Br compounds are 2, 16 and 37°. Dashevskii, Struchkov & Akopyan (1966) calculated the values for ANGLE for a number of *ortho*-halonitrobenzenes: 20.2, 26.0 and 34.5° for Cl, Br and I, respectively. These different values compared with the crystal structures are not only to be explained in terms of the absence of packing forces but possibly also by the

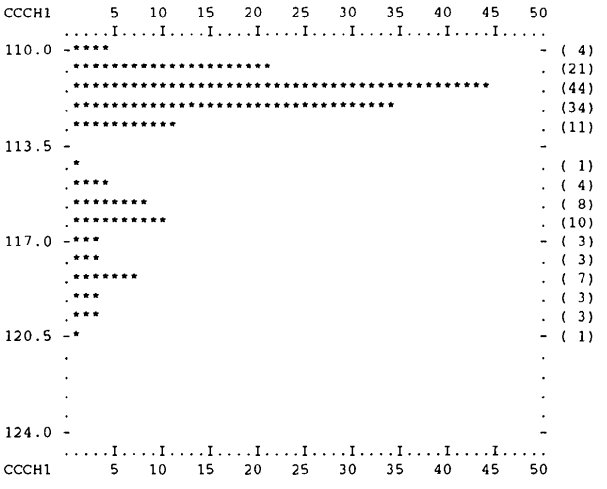


Fig. 5. Distribution of CCCH1 for the O atoms (NO-1).

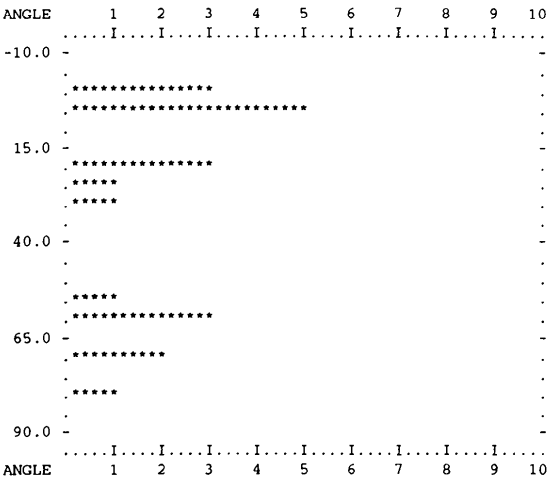


Fig. 6. Distribution of ANGLE for the S atoms (NO-1).

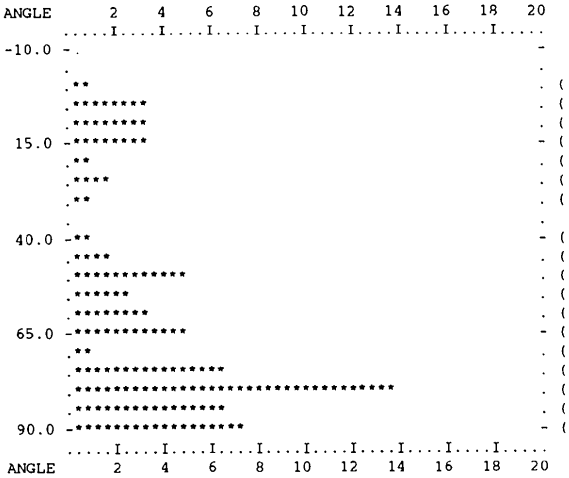
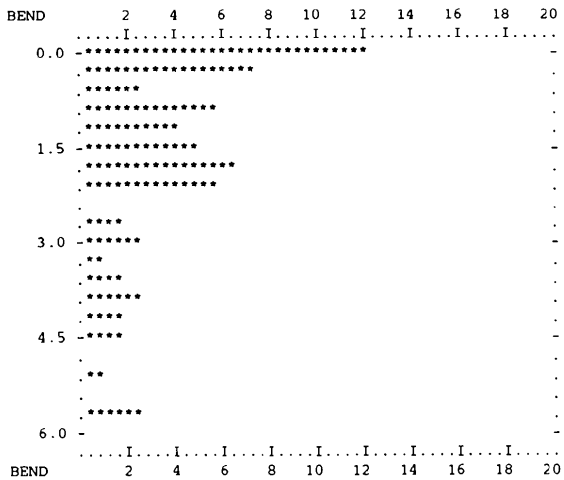


Table 4. NO-2 (*angles in* °)

Substituent 1	Substituent 2	No. of fragments	ANGLE Mean	ANGLE Range
OH	OH	1	66.6	—
OH	Cl	4	73 (8)	52–87
F	F	2	57.6 (2)	57.4–57.8
Cl	Cl	7	80 (3)	67–90
NO_2	NO_2	3	63 (2)	59–66
NO_2	N_{ar}	1	68.5	—
NH_2	NH_2	9	9 (2)	0.7–17
NEt_2	NEt_2	3	50.1 (5)	49.3–51.2
NH_2	OH	2	32 (23)	9–55
NH_2	F	2	20 (3)	17–23
NH_2	$COOH/CONH_2$	4	28 (4)	20–39
NH_2	NO_2	1	44.5	—
C	Halogen	2	68 (12)	56–80
C	NO_2	3	63 (5)	58–74
C	NCOOEt	1	78.0	—
C	OMe	1	82.7	—
C	NH_2/NR_2	6	47 (12)	7–75
C	C	30	80 (2)	45–90



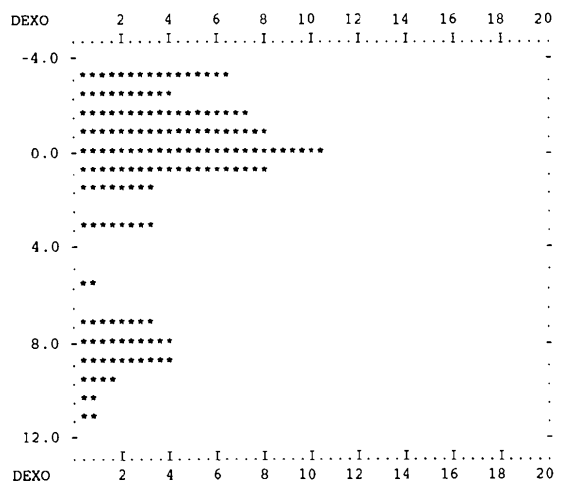


Fig. 7. Distributions of ANGLE, BEND and DEXO of the NO-2 compounds. In the histogram of BEND three values are not shown (see text).

absence of other substituents on the ring in the study of Dashevskii, Struchkov & Akopyan (1966).

NO-2

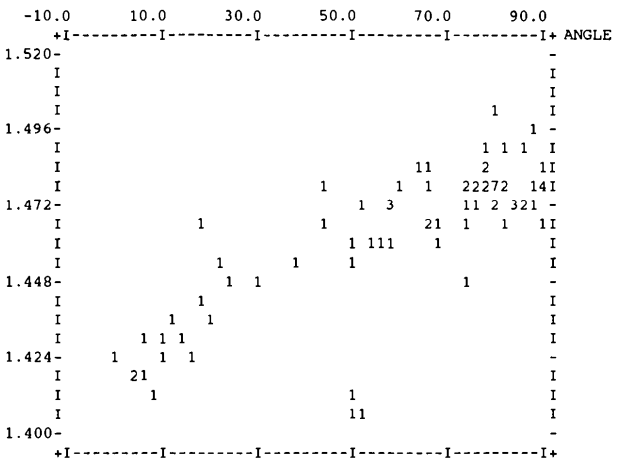
In total 82 fragments with a nitro group and two adjacent non-H substituents were matched in *GSTAT*. The distributions for ANGLE, BEND and DEXO are shown in Fig. 7. The fragments have been ranked by type in Table 4.

The distribution for ANGLE is a composite one reflecting the size and behaviour (hydrogen-bond formation) of the various substituents listed in Table 4.

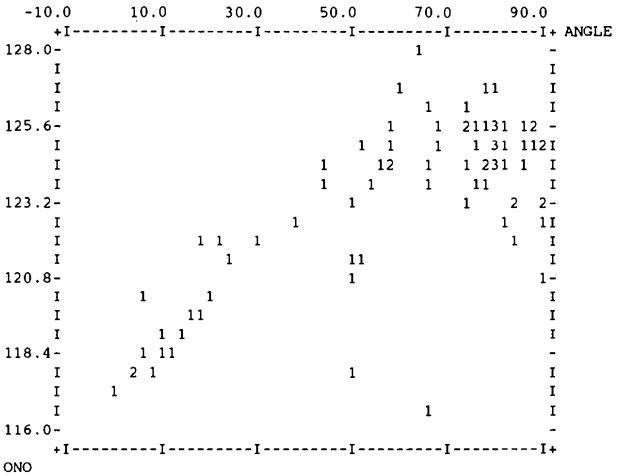
From Table 4 it can be seen that larger values of ANGLE occur when the nitro group is adjacent to two bulky or electronegative substituents or a combination of the two. The presence of a vicinal amino group results in lower angles caused by the intramolecular hydrogen bond. The larger rotation angles of two adjacent Cl atoms compared with two F atoms or two N-disubstituted amino groups compared with two amino groups can easily be explained in terms of a greater intramolecular steric hindrance. The spread in BEND and DEXO is larger than in the NO-0 and NO-1 groups due to increased possibility of steric hindrance. In general, lower values of BEND and DEXO (*i.e.* within the range 0–1.5° for BEND and −1.5–1.5° for DEXO) occur when the nitro group is positioned between two equal substituents. In the case of the N-disubstituted amino groups there is also a significant out-of-plane bending (BEND) observed (JARLOD, range 16–23°). The three data points corresponding to this compound are not shown in the histogram of BEND in Fig. 7.

The scatter diagrams of ANGLE *versus* CN, ANGLE *versus* ONO and CN *versus* ONO are given in Fig. 8.

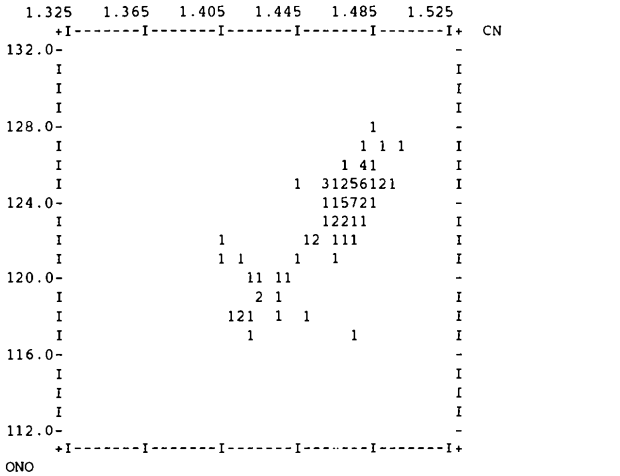
It can be seen that, in general, high values of ANGLE coincide with high values of ONO (correlation coefficient = 0.74) and CN (correlation coefficient = 0.80). The latter is explained by the fact that when



(*a*)



(*b*)



(*c*)

Fig. 8. Scatter diagrams of (*a*) ANGLE *versus* CN, (*b*) ANGLE *versus* ONO and (*c*) CN *versus* ONO (NO-2).

ANGLE is increased the CN distance increases because of diminishing conjugation between the aromatic ring and the nitro group. There is also correlation between CN and ONO (correlation coefficient = 0.78).

Discussion

It can be argued that, especially for NO-0, some very strict conditions were imposed on the database search to reduce the large amount of data. On one hand it is judicious to have only that data which has a high degree of reliability, but on the other hand for statistical purposes it is also desirable to have the largest data set possible. For most of the analyses presented in the preceding section there were sufficient data points; however, some of the subsets discussed in Tables 3 and 4 have relatively few fragments, so that it may be difficult to distinguish trends from random fluctuations.

A tight restriction was placed on the planarity at the N atom (DIFF < 1°) in order to avoid strong inter- and/or intramolecular interactions of the nitro group. In spite of this restriction, these interactions cannot be entirely avoided by this criterion alone since such interaction will not always cause pyramidalization of the N atom. Indeed, in a few cases asymmetric N—O bonds were observed and explained as being the result of these interactions. A relaxation of this condition would not have yielded additional structures in the poorly populated subsets. In fact, in only six cases DIFF > 1°. Five of them (range 1.4–5.9°) are in data set NO-0, but are already omitted by the constraint of the average e.s.d. for a C—C bond. Moreover, in two cases $R > 0.075$. The sixth case (7.5°) is found in the sufficiently populated subset of the picrates in NO-1. From this it follows that the data set was not unnecessarily reduced by the tough restriction on DIFF.

It is seen that the out-of-plane rotation angle of a nitro group attached to an aromatic ring depends on three factors: the steric hindrance caused by one or two adjacent substituents, the electronegativity of the adjacent substituent(s) and the crystal packing. The highest angles are observed with bulky and/or negatively charged adjacent groups. The lower angles are found in structures where the nitro group is able to form an intramolecular hydrogen bond.

From the study of the NO-0 compounds it follows that intermolecular steric effects or packing forces can cause an out-of-plane rotation angle of a nitro group between 0 and 28°. The broad range for ANGLE, which is also observed in the group of the NO-1 and NO-2 compounds, makes it almost impossible to predict the rotation angle of a nitro group for one or two given adjacent substituents.

Nitromusks of the benzene family

Among the crystal structures of benzene musk compounds described in the work dealing with X-ray crystal

studies of musk compounds (De Ridder, 1992), four compounds exhibiting the characteristic musk odour and one of its odourless isomers were present (De Ridder, Goubitz & Schenk, 1990; De Ridder, 1992; De Ridder, Fraanje & Schenk, 1994), the conventional structural formulae of which and classification according to Beets (1957, 1977) are given in Fig. 9. For the sake of the discussion the substituents on the benzene ring are labelled clockwise starting from the *tert*-butyl group. In the following the labels are given in Arabic numbers and the compounds in Roman numerals in brackets. The pseudo-classification is assigned to a nitrobenzene musk by considering the position of the molecular profile groups (*i.e.* *tert*-butyl or NO_2 groups). For example, according to Beets (1957, 1977) the acetyl group (4) in Musk Ketone (III) has the osmophoric function. Beets assigned this compound to the pseudo *meta* classification since the two nitro groups (2 and 6), which act as molecular profile groups, are attached to the benzene ring in *meta* position with respect to each other. The out-of-plane rotation angles of the nitro groups in these compounds are shown in Table 5.

According to Beets' postulates (1957, 1977), the nitro group having only one adjacent group (5) in Musk Ambrette (I) and the nitro group having two adjacent methyl groups (4) in Musk Xylene (II) act as the osmophoric group. From Table 5 it is seen that the difference between the out-of-plane rotation angles in both musks is important (49 *versus* 84°). The structure–activity theory of musk compounds of Beets (1977) leans heavily on the assumed orientation of the active group(s). This can mean that the out-of-plane rotation angle of the nitro group is no determining factor for muskiness.

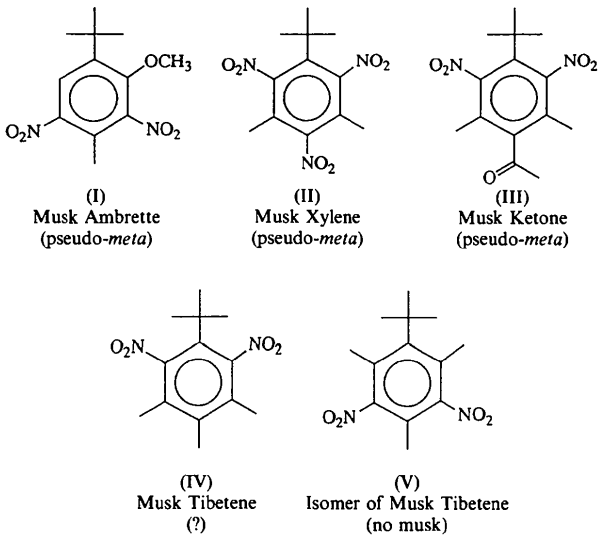


Fig. 9. Conventional formulae of the nitrobenzene compounds. The classification according to Beets (1957, 1977) is given in parentheses. The substituents are labelled clockwise starting from the *tert*-butyl group.

Table 5. *ANGLE for the nitrobenzene musks* (°)

Compound	Position	Substituent 1	Substituent 2	Angle
(I) Musk Ambrette*	3	OCH_3	CH_3	83
	5	CH_3	H	49
(II) Musk Xylene†	2,6	*t*-butyl	CH_3	79 (1)
	4	CH_3	CH_3	84
(III) Musk Ketone†‡	2,6	*t*-butyl	CH_3	82 (1)
(IV) Musk Tibetene†	2,6	*t*-butyl	CH_3	80 (1)
(V) Isomer of Musk Tibetene§ (non-musk)	3,5	CH_3	CH_3	79 (2)

* De Ridder, Goubitz & Schenk (1990).
† De Ridder (1992).
‡ The angles of the four molecules in the asymmetric unit have been averaged.
§ De Ridder, Fraanje & Schenk (1994).

The postulates do not make it clear whether Musk Tibetene (IV) is to be classified as a pseudo-*ortho* or a pseudo-*meta* musk. Obviously, both nitro groups (2 and 6) will have a potential osmophoric function. The average angle the nitro group makes with the plane of the aromatic ring is comparable to the corresponding angle in Musk Xylene (II) and Ketone (III). This is expected since in all these cases the nitro group has the same intramolecular steric environment. This would mean that nitro groups which have the same out-of-plane rotation angle can still have different functions.

This is supported by the angles observed in Musk Tibetene (IV) and its isomer (V): although they are practically the same, the isomer of Musk Tibetene is odourless. The pseudo-*meta* classification can be assigned to Musk Ambrette (I) because of the presence of a *tert*-butyl group (1) and a nitro group (3). The same classification is given to Musk Xylene (II) and Ketone (III) considering the two nitro groups adjacent to the *tert*-butyl group (*i.e.* at 2 and 6). Taking one of the nitro groups (3 or 5) and the *tert*-butyl group (1), the isomer of Musk Tibetene (V) can easily be classified as a pseudo-*meta* musk. Observing that the out-of-plane rotation angle of the nitro group is comparable both to the molecular profile nitro group in Musk Xylene (II) and Ketone (III) (2 and 6: range 79–82°) and to the osmophoric nitro group in Musk Xylene (II) (4: 84°), the conclusion that the rotation angle of the nitro group is not a determining factor for muskiness is readily drawn.

Nitromusks of the indan and tetralin family

Although this paper is mainly dealing with the monocyclic musk compounds, a remark should be made on the bicyclic nitromusks for which the crystal structures have been determined (De Ridder, Fraanje, Goubitz & Schenk, 1994*a*,*b*), the conventional structural formulae of which are shown in Fig. 10. The out-of-plane rotation angle of the nitro groups are summarized in Table 6. The α-position denotes the aromatic C atom which is adjacent to the ring-fusion atom, the β-position to the aromatic C atom which is the next-nearest neighbouring aromatic C atom with respect to the ring-fusion atom. All

Table 6. *ANGLE for the nitromusks of the indan and tetralin family* (°)

Compound	α	β
Indans		
(VI)*	79.0	47.5
(VII)*	—	36.3
(VIII)*	85.5	40.3
Tetralins		
(IX)†	—	33
(X)†‡	86.1	44.3

* De Ridder, Fraanje, Goubitz & Schenk (1994*a*).
† De Ridder, Fraanje, Goubitz & Schenk (1994*b*).
‡ Average value of two molecules in the asymmetric unit.

compounds have two quaternary C atoms in the *ortho* position attached to the aromatic ring and are classified as *ortho* musks according to Theimer & Davies (1967). From Table 6 it is seen that the angle the β-nitro group makes, falls within the range (5–49°) given in Table 3, whereas the angle the α-nitro makes is well in agreement with the average value given in Table 4.

Concluding remarks

This study is in contradiction with Beets' postulates. Musk Tibetene cannot be classified according to these postulates and it is a strong musk. On the other hand, its structural isomer fulfils to the postulates but is odourless. It follows that the postulates seem to be unable to distinguish between the presence or the absence of the musk odour for a given compound. On the other hand, the presence of a *tert*-butyl group adjacent to a nitro group causes the latter to be almost perpendicular to the plane of the aromatic ring, which means that a nitro group can indeed fulfil a *molecular profile* function, according to Beets' postulates. It has to be remarked that a nitro group presumably will fulfil the latter function only in monocyclic musk compounds since the musk odour is observed in bicyclic compounds having only one nitro group but having two quaternary C-atom centres.

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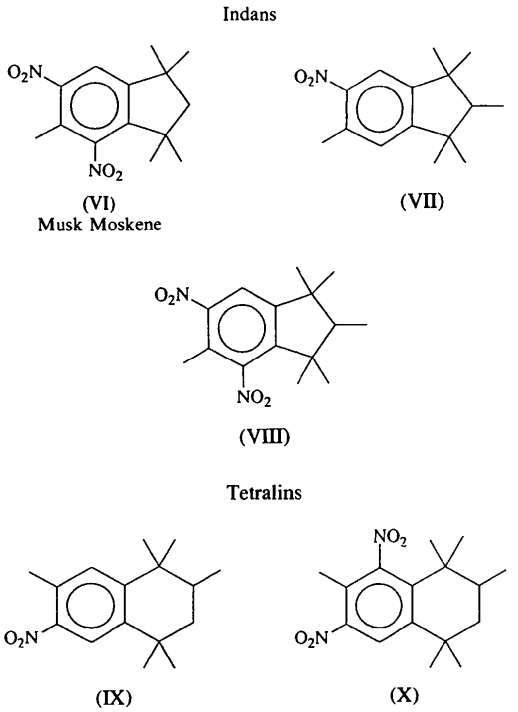

Fig. 10. Conventional formulae of the nitromusks of the indan and tetralin family. In the mononitro compounds [(VII) and (IX)] the nitro group is attached to a β-position. In the dinitro compounds [(VI), (VIII) and (X)] the nitro groups are attached to one α- and one β-position.

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