Nuclear versus Side-Chain Bromination of Methyl-Substituted Anisoles by *N*-Bromosuccinimide

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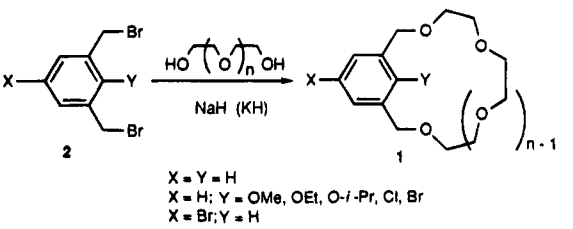
The reactions of methyl-substituted anisoles with *N*-bromosuccinimide in CCl_4 are reported. In the absence of a catalyst and under irradiation, some of these substrates undergo nuclear bromination in competition with the well-known side-chain bromination. With 2-methylanisole and with 2,6-dimethylanisole, nuclear bromination is not observed, whereas with 3,5-dimethylanisole, nuclear bromination at the 4-position is the dominating reaction. Investigation of the reactivity of several other methyl-substituted anisoles revealed the following general trend: methyl-substituted anisoles are attacked at the position para to the methoxy group rather than at the side chain when (at least) two methyl groups are present at positions 3 and 5. When positions 2 and 6 are both occupied, nuclear bromination is retarded; in 2,6-dimethylanisole and in 2,3,6-trimethylanisole, only side-chain bromination is observed. In contrast, in 2,3,5,6-tetramethylanisole, the 4-position is sufficiently reactive to be brominated, because the decrease in reactivity by the presence of two methyl groups at positions 2 and 6 is overruled by the two additional methyl groups at positions 3 and 5; as a result, both nuclear and side-chain bromination occur. The observed chemospecificity can be rationalized by a difference in mechanism: the side-chain bromination is a radical reaction, while the nuclear bromination is an electrophilic aromatic substitution reaction, which is so far contrary to expectation, as irradiation had been expected to favor radical processes.

The recent publication in this journal on the regioselective nuclear bromination of 2,3-dimethylanisole with NBS by Alper *et al.*[1] prompts us to present the results of our work in this field. We have not only observed similar nuclear brominations with other methyl-substituted anisoles as a highly competitive reaction to the normal and well-known side-chain bromination but have been able to identify some of the factors which determine whether and by which mechanism nuclear or side-chain bromination takes place in the reactions of these substrates with *N*-bromosuccinimide (NBS) in CCl_4.

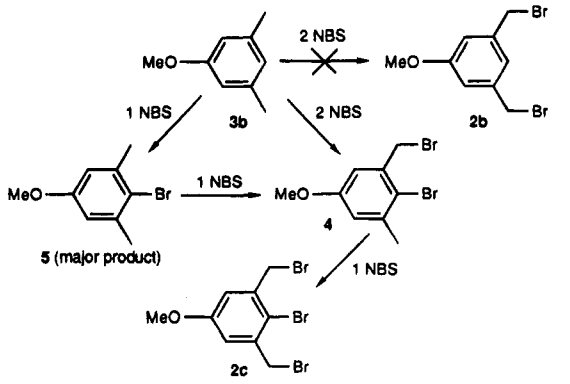
Our entry into this field was the following. For a number of years, we have been investigating many (substituted) 1,3-xylylene crown ethers **1** and especially their reactivity toward organomagnesium[2] and organozinc[3] compounds. Almost all of these xylylene crown ethers were prepared from (substituted) *m*-bis(bromomethyl)benzenes **2** and the appropriate oligoethyleneglycols (Scheme 1).

This route was also successful for the synthesis of 1,3-xylylene crown ethers carrying intraannular ether functions (Y = OR);[4] e.g. (2-methoxy-1,3-xylylene)-15-crown-4 (**1a**; X = H, Y = OMe, n = 2) was synthesized from 2,6-bis(bromomethyl)anisole (**2a**) which in turn was obtained by the light-induced radical bromination reaction of 2,6-dimethylanisole (**3a**) with 2 equiv of NBS. The synthesis of (5-methoxy-1,3-xylylene)-15-crown-4 (**1b**; X = OMe, Y = H, n = 2) was planned by the same route. However, bromination of 3,5-dimethylanisole (**3b**) with 2 equiv of NBS under irradiation did not yield the expected 3,5-bis(bromomethyl)anisole (**2b**) but resulted in the formation of 4-bromo-3-(bromomethyl)-5-methylanisole (**4**) instead (Scheme 2).

Scheme 1



Scheme 2



Reaction of **3b** with 1 equiv of NBS revealed that nuclear bromination was the favored initial reaction, leading to 4-bromo-3,5-dimethylanisole (**5**, 59%). Reaction with a second equivalent of NBS resulted in side-chain bromination to give **4**, and subsequent reaction with a third equivalent of NBS gave 4-bromo-3,5-bis-

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(bromomethyl)anisole (**2c**) resulting from bromination of the second methyl group. The surprising result of finding that nuclear bromination was the fastest reaction for **3b**, whereas this reaction mode was not occurring with **3a**, initiated further investigation of these reactions.

Electrophilic Substitution of an Aromatic Ring by NBS has been observed both in nonpolar and in polar solvents. In *nonpolar solvents* such as CCl_4, the reaction is well documented,[5] although the results are highly variable in terms both of products and yields. In the absence of a metal chloride catalyst, nuclear bromination of benzene and toluene by NBS does not occur. However, with polynuclear aromatic hydrocarbons, reaction was observed without a catalyst.[6]

Already in 1919, Wohl[7] observed reaction of N-bromoacetamide with anisole, and Buu-Hoï[8] has studied the action of NBS on a variety of benzene and naphthalene derivatives, notably ethers. No catalysts were used and the reactions with phenol ethers required several hours (reflux; no solvent) for completion, while ethers of α- and β-naphthol reacted within a few minutes.

In contrast, electrophilic aromatic substitution by NBS in *polar solvents* is less known. Ross *et al.*[9] have studied the reaction of toluene, fluorene, and acenaphthene in propylene carbonate, where predominantly nuclear bromination takes place. The general applicability of this reagent for a number of reactive aromatics was later investigated by Mitchell *et al.*[10] In the case of aromatic hydrocarbons, the nucleus must be sufficiently activated before significant reaction occurs. The reactivity of various monosubstituted benzenes (ArX; X = NMe_2, OH, OMe, OPh, alkyl, halogen, NO_2, or COPh) in electrophilic bromination reactions with NBS was investigated by Robertson *et al.*[11] In these compounds (except for X = NO_2, COPh), para bromination was prevailing.

Radical Bromination of Aromatic Side Chains by NBS (Wohl–Ziegler reaction) has been extensively used.[12] Mechanistic investigations have established that molecular bromine is the active halogenating agent under these conditions.[13] It is maintained at a low concentration throughout the course of the reaction by formation from NBS and hydrogen bromide. Another area which has received much mechanistic interest over the years is the influence of substituent effects on free radical reactions. The separation of truly radical-stabilizing effects from polar effects which are known to operate in many radical reactions remains a problem. Because of the magnitude of polar effects, many radical reactions correlate with Hammett σ or Brown σ+ values. The relative reactivity of substituted benzenes in free radical reactions[14,15] as well as the quantitative ability of various groups to stabilize (or destabilize) free radicals[16–22] has been investigated.

Whereas side-chain bromination has not been reported as a side reaction of electrophilic aromatic substitution, nuclear bromination may occur under apparent radical conditions. In a few cases, the rates of nuclear and of side-chain bromination have been compared within the same substrate. Braun and Looker found the nuclear bromination product benzyl 4-bromophenyl ether from the reaction of benzyl phenyl ether with NBS.[23] A second unusual nuclear bromination is the reaction of 2,6-dimethoxytoluene with NBS which gave 3-bromo-2,6-dimethoxytoluene in high yield.[24] Finally, 3-methylanisole was para brominated to yield 4-bromo-3-methylanisole when heated under reflux (without solvent) with *N*-bromoacetimide.[8] And, last but not least, the initially mentioned reaction of 2,3-dimethylanisole[1] belongs to this category.

Results

While electrophilic, nuclear aromatic bromination of anisole with NBS is a known reaction, nuclear bromination of anisoles with NBS in CCl_4 under irradiation ("side-chain bromination conditions") has to our knowledge not been reported before. We performed our reactions in CCl_4 as the solvent with 0.5 equiv of NBS relative to the amount of the anisole, to prevent as much as possible the formation of dibromides which complicate the ^1H NMR analysis of the monobrominated products. In the light-induced reactions, the light source was placed at such a distance from the reaction vessel that reflux was maintained. For reasons of comparison, we also performed some reactions without an extra light source, where reflux was achieved by heating with an oil bath; no effort was made to shield the reaction vessel from daylight in these experiments. The results of the bromination reactions are summarized in Table 1.

The light-induced reaction of anisole resulted in quantitative nuclear bromination within 30 min: *p*-bromoanisole (98%) and *o*-bromoanisole (2%) were identified by

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Table 1. Distribution of Products of Nuclear and Side-Chain Bromination of (Substituted) Anisoles[a]

			nuclear bromination		
no.	compound	method[b]	*o*	*p*	side-chain bromination
	anisole	L	2	98	
	1,3-dimethoxybenzene	L		100[c]	
	2-methylanisole	L			100
	3-methylanisole	L		8	92
		H		25	75
	4-methylanisole	L			100
3a	2,6-dimethylanisole	L			100
3b	3,5-dimethylanisole	L		75 (**5**)	24 (**34**)
3c	2,3-dimethylanisole	L		3 (**7**)	97 (87 (**6**) + 10 (**10**))[d]
3d	2,4-dimethylanisole	L			100 (34 (**12**) + 66 (**13**))[d]
14	2,3,6-trimethylanisole	L			100 (40 (**22**) + 29 (**23**) + 31 (**24**))[d]
		H			100 (40 (**22**) + 27 (**23**) + 33 (**24**))[d]
15	2,3,5-trimethylanisole	L		100 (**31**)	
16	2,3,5,6-tetramethylanisole	L		28 (**27**)	72 (50 (**25**) + 22 (**26**))[d]
17	1,2,3,4-tetramethylbenzene	L			100 (40 (**18**) + 60 (**19**))[d]
20	1,2,4,5-tetramethylbenzene	L			100 (**21**)

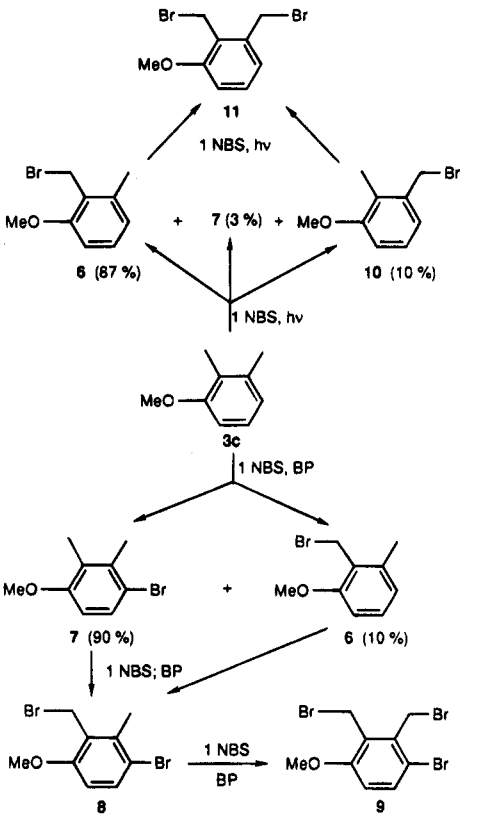
[a] Relative percentages of bromination products; bold numbers given in parentheses are compound numbers. [b] L: reflux by light source. H: reflux for 8 h by heating with oil bath (in daylight). [c] In this case the product is 2,4-dimethoxybromobenzene. [d] Numbers given in parentheses are relative percentages for regioisomers. followed by the number of the compound.

^{1}H NMR spectroscopy. In contrast, 2-, 3-, and 4-methylanisole were almost exclusively brominated at the methyl group. Only in the reaction of 3-methylanisole was some nuclear bromination (8%, para to the methoxy group) observed. In the reaction of 4-methylanisole, ortho bromination did not occur. In an extension of this investigation, we studied most di-, tri-, and tetramethyl-substituted anisoles, generally with the exception of those carrying a methyl group at the 4-position, because in the latter case nuclear bromination cannot compete with side-chain bromination, as is illustrated by 4-methylanisole.

With two methyl substituents, depending on the substitution pattern, either nuclear bromination takes place predominantly (cf. 3,5-dimethylanisole (**3b**)) or side-chain bromination occurs (cf. 2,6-dimethylanisole (**3a**), 2,3-dimethylanisole (**3c**), and 2,4-dimethylanisole (**3d**)); with **3a** and **3d**, nuclear bromination was not observed. The lack of ortho bromination in the case of **3d** can be ascribed to the corresponding ortho-quinoidal transition state being less stable than the corresponding para transition state (such as in **3b**; cf. also the low ortho:para ratio for anisole!).

In the recent publication by Alper *et al.*,[1] the reaction of 2,3-dimethylanisole (**3c**) with NBS in CCl_4 under reflux, with or without the presence of benzoyl peroxide (BP), was described. The authors state that free radical bromination of **3c** with BP as a radical initiator initially leads to the ring brominated 4-bromo-2,3-dimethylanisole (**7**; 90%), together with the side-chain-brominated product 2-(bromomethyl)-3-methylanisole (**6**, 10%; Scheme 3). In the subsequent reaction with a second equivalent of NBS, both **6** and **7** were transformed into the dibromide 4-bromo-2-(bromomethyl)-3-methylanisole (**8**). Finally, from **8**, 4-bromo-2,3-bis(bromomethyl)anisole (**9**) was formed after reaction with a third equivalent of NBS. However, when we performed the same reaction under irradiation conditions, our observations were completely opposite: with 0.5 equiv of NBS, side-chain bromination was found to be the predominant reaction. In addition to less than 3% nuclear bromination leading to **7**, both possible side-chain brominated products **6** (87%) and 3-(bromomethyl)-2-methylanisole (**10**, 10%) were formed. When, in another experiment, **3c** was reacted with 1.5 equiv of NBS, 2,3-bis(bromomethyl)anisole (**11**) was the only dibromide observed in the GCMS and ^{1}H NMR spectra.

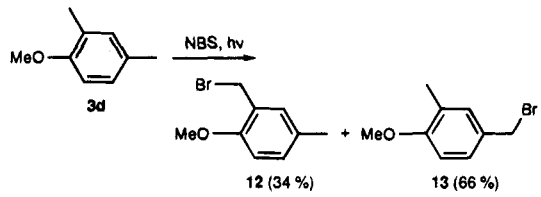
Scheme 3



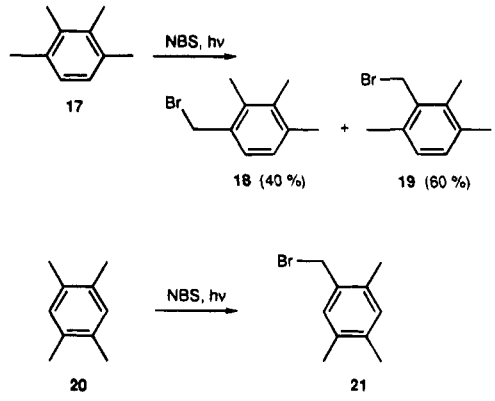
The only dimethylanisole with a para methyl substituent which we included in our studies (*vide supra*) was 2,4-dimethylanisole (**3d**); it was used to determine the relative reactivity of an ortho and a para methyl group in the light-induced radical process. In this case, again both possible monobrominated products 2-(bromomethyl)-4-methylanisole (**12**; 34%) and 4-(bromomethyl)-2-methylanisole (**13**; 66%) were formed (Scheme 4). Two isomers, 2,5- and 3,4-dimethylanisole, were not investigated, but extrapolating from the other results, only side-chain bromination is to be expected.

Turning from di- to trimethyl-substituted anisoles, it is obvious that the addition of an extra methyl group to

Scheme 4



Scheme 5



2,6-dimethylanisole (**3a**) as in 2,3,6-trimethylanisole (**14**) does not influence the specificity: only side-chain bromination was observed. However, an extra methyl group added to 3,5-dimethylanisole (**3b**), as in 2,3,5-trimethylanisole (**15**), completely changes the behavior and leads to quantitative nuclear bromination. Going from tri- to tetramethyl-substituted anisole, only one substrate with an unsubstituted 4-position is feasible: 2,3,5,6-tetramethylanisole (**16**). With this substrate, the bromination was not regioselective: 28% nuclear and 72% side-chain bromination occurred. To demonstrate that the presence of the methoxy group is a prerequisite for nuclear bromination, 1,2,3,4-tetramethylbenzene (prehnitene, **17**) and 1,2,4,5-tetramethylbenzene (durene, **20**) were reacted with NBS under analogous conditions. In the reaction of **17**, the two possible methyl monobrominated products, 1-(bromomethyl)-2,3,4-trimethylbenzene (**18**) and 2-(bromomethyl)-1,3,4-trimethylbenzene (**19**), were obtained in a 2:3 ratio (Scheme 5). Likewise, the reaction of **20** gave the methyl bromination product 1-(bromomethyl)-2,4,5-trimethylbenzene (**21**) only (Scheme 5). In both cases, not even traces of nuclear brominated products were found.

For two substrates, 3-methylanisole and 2,3,6-trimethylanisole (**14**), additional reactions were performed as controls without the extra light source (but in daylight). Reflux was maintained by heating with an oil bath. With the first substrate, more nuclear bromination was observed, but the side-chain bromination was still occurring. With **14**, the result was the same as obtained in the light-induced reactions: 100% side-chain bromination (Table 1).

Discussion

Mechanism. First let us consider the seeming contradiction between the results of Alper *et al.*[1] and our own results. Alper assumed that *free-radical* bromination of 2,3-dimethylanisole (**3c**) leads to the nuclear brominated product 4-bromo-2,3-dimethylanisole (90%) in the first step. Kinetic plots of the reaction of **3c** with 3 equiv of NBS and 0.01 equiv of benzoyl peroxide (BP) indicated that the reaction proceeded in a consecutive fashion (Scheme 3). First, the ring-brominated 4-bromo-2,3-dimethylanisole (**7**) was formed (90%), together with 2-(bromomethyl)-3-methylanisole (**6**; 10%). The second bromination resulted in the formation of 4-bromo-2-(bromomethyl)-3-methylanisole (**8**). Finally, bromination of the second methyl group afforded the tribromide 4-bromo-2,3-bis(bromomethyl)anisole (**9**) in nearly quantitative yield. Addition of 0.01 equiv of BP suggests that the authors consider the reaction to be a radical chain reaction. However, their kinetic plots indicate that the reaction is far from being a radical chain reaction. The formation of the monobromide **7** takes 7 h in refluxing CCl_4, and the slope of the plot of the reaction time versus % product formation is approximately linear. The corresponding plots of our radical bromination reactions with 0.5 equiv of NBS under irradiation had a completely different shape: it took some time (15–30 min) for the reaction to start (initiation), after which the reaction propagated within a few minutes as indicated by evolution of heat and color change to brown-red (Br_2!). After a few minutes (!), this red color disappeared again and the reaction was complete and solid NBS was no longer present. Against the background of these observations, it is unlikely that in the case of the BP "initiatiation", the radical chain process continues for more than 34 h. It has, incidentally, been pointed out previously that the chance of success to start a radical chain reaction by the direct addition of an initiator as a single portion is low; the "ensuing flood of radicals can combine and disproportionate in a counterproductive way",[25] and thus the initiator is not likely to influence the course of the reaction significantly. Indeed, when the authors[1] carried out the reaction of **3c** with 1 equiv of NBS in the absence of the radical initiator, the ratios of **7** and **6** were the same as with BP (*vide supra*); without BP, the reaction rate was lower, but this is probably due to the lower concentration of NBS (1 equiv without versus 3 equiv with BP).

We have performed the reaction of **3c** under conditions identical to those of Alper, except that the initiation was induced not by BP but by light, and therefore reliably of the radical chain type. With 0.5 equiv of NBS, we found almost exclusively (97%) side-chain bromination (**6** + **10**; Scheme 3); only 3% nuclear bromination (**7**) was observed. Note that besides **6** (87%), the regioisomeric side-chain bromination product 3-(bromomethyl)-2-methylanisole (**10**; 10%) was formed under our conditions; **10** has not been observed with BP.[1] When the same reaction was performed with 1.5 equiv of NBS, we found that in addition to **6**, **7**, and **10**, the only dibromide product formed was 2,3-bis(bromomethyl)anisole (**11**). This means that even the apparently less reactive meta methyl group reacts in a radical process before the aromatic ring does.

To investigate whether the nuclear substitution reaction follows an electrophilic or a radical mechanism, 3,5-dimethylanisole (**3b**; 24% side-chain versus 76% nuclear bromination under light-induced radical bromination conditions; Table 1) was reacted with 0.75 equiv of NBS in the presence of the 2,2,6,6,-tetramethylpiperidinyloxy radical (TEMPO). The addition of this radical scavenger resulted in complete suppression of the side-chain bromination reaction: as expected, not a trace of side-chain bromination product was detected, in line with the

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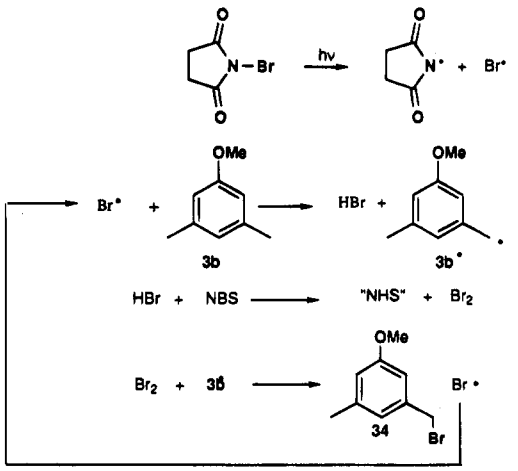
Scheme 6



generally accepted radical mechanism for this process. The nuclear bromination product 4-bromo-3,5-dimethylanisole (**5**; Scheme 2) was now formed in quantitative yield (relative to the amount of NBS). This clearly proves that the nuclear brominated product is not formed via a radical process!

In another experiment, 5 equiv of water was added to a mixture of 1 equiv of **3b** and 0.5 equiv of NBS. In this case, the side-chain bromination was found to be the favored reaction (7% nuclear versus 93% side-chain bromination). This shift from predominantly nuclear to predominantly side-chain bromination by adding water may result from either suppression of the nuclear bromination or acceleration of the radical side-chain bromination or both. The influence of water on the course and relative reaction rates of NBS brominations in refluxing CCl_4 is known: "a small amount of water very finely dispersed in the CCl_4 usually gave a strong catalytic effect (acceleration), while an equal quantity of water present as two or three droplets showed essentially no effect".[26] A conceivable explanation might be suppression of the nuclear bromination due to the diminished mesomeric electron donation from the methoxy oxygen to the aromatic ring under the influence of the formation of hydrogen bridges between water and the methoxy oxygen in the apolar solvent CCl_4.

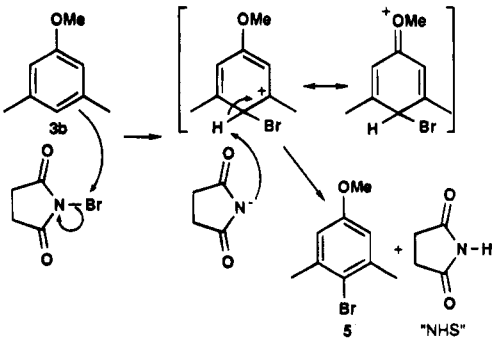
It is thus evident that two different reaction mechanisms are operative. The side-chain bromination follows a radical pathway (Scheme 6),[12] while nuclear bromination is probably an electrophilic substitution reaction (Scheme 7),[27] with NBS acting as a Br^+ donor, while the succinimide anion acts as the proton abstracting base.

Both reactions may take place simultaneously, and the competition depends on the relative reactivities of the various sites within a certain substrate as well as on the reaction conditions. Obviously, in the bromination reaction of **3c** with BP, bromination by nuclear substitution is favored over the radical side-chain bromination: 1 mol % of BP, when added at once at the beginning of the reaction, is apparently not sufficient to effectively initiate a radical chain reaction. Continuous irradiation proved to be more reliable as a radical-initiating procedure.

Substituent Effects. From the results of the large variety of reactions we have performed, we can conclude

(26) Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863.
(27) Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129.
(28) Baddeley, G.; Smith, N. H. P.; Vickars, M. A. *J. Chem. Soc.* **1956**, 2455.

Scheme 7



that several factors are influencing the regioselectivity of bromination in methyl-substituted anisoles. The relative position of the substituents influences the reactivity toward both nuclear and side-chain bromination; some of them are in line with general experience.

1. The methoxy group activates the aromatic nucleus for nuclear bromination at the para position.

2. Each additional methyl group increases this activation of the para position for nuclear bromination, but more so if the methyl group is located at the positions meta to the methoxy group than at the ortho positions; this is expected if the reaction involves electrophilic attack at the para position by (formal) Br^+.

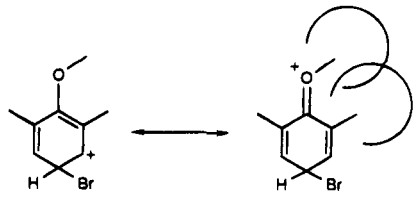
3. When both positions ortho to the methoxy group are occupied by methyl groups, the rate of the nuclear bromination is highly reduced.

4. The different reactivities with which the ortho and meta methyl groups undergo radical bromination probably is caused by the electronic influence of the methoxy group rather than by steric hindrance, as the sterically more hindered ortho methyl group in 2,3-dimethylanisole (**3c**) is about 10 times more reactive than the less hindered meta methyl group. This reactivity difference disappears when both positions ortho to the methoxy group are occupied as in 2,3,6-trimethylanisole (**14**). Furthermore, the reactivity difference of the two different methyl groups in 1,2,3,4-tetramethylbenzene (**17**) is marginal, the two more hindered methyl groups 2 and 3 being slightly more reactive.

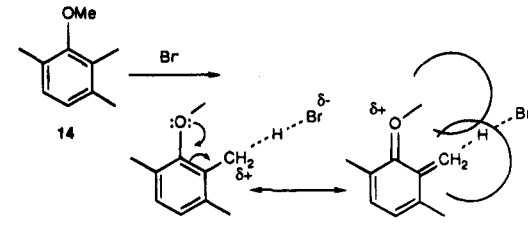
Which of the two reaction modes of bromination, electrophilic nuclear versus radical side-chain bromination, predominates depends in a subtle and complex way on the interplay of activation and deactivation and will be discussed in the following paragraph.

Relative Rates. Anisole is easily brominated; the methoxy group is activating and ortho and para directing, but in this case, the reaction predominantly takes place at the para position. For the monomethyl-substituted anisoles, we observe side-chain bromination mainly, which signals a radical chain process (Scheme 6). Obviously, under irradiation, activation of the para position by the methoxy group is insufficient to make nuclear bromination competitive with side-chain bromination. Only for 3-methylanisole, some nuclear bromination does occur (8%), presumably because the 4-position is additionally activated by the 3-methyl group which is ortho to it. The 4-position in 2-methylanisole is probably also more activated for electrophilic substitution than in anisole itself, as is the meta position in toluene relative to benzene. Nevertheless, side-chain bromination is much faster, one of the factors being that an ortho methyl group is additionally activated toward side-chain bromination by the methoxy group ortho to it (*vide infra*).

Scheme 8



Scheme 9



The presence of the 2-methyl group in **3c** increases the ratio of reaction at the 4-position versus reaction at the 3-methyl group from 8:92 (= 0.087) [for 3-methylanisole] to 3:10 for **3c**. The ratio of the reactivities of the 2- and 3-methyl groups in the radical process amounts is 87:10 = 8.7.

The well-known fact that a methyl group is ortho–para activating is evident when comparing the reactions of **3c** (3% nuclear bromination versus 10% 3-methyl bromination) and **3b** (76% nuclear bromination versus (24:2 =) 12% 3-methyl bromination); the 2-methyl bromination in **3c** is disregarded. The activation of the aromatic 4-position by a 3-methyl group can be determined from the results of the reactions of 3-methylanisole (8% nuclear versus 92% side-chain bromination) and **3b** (76% nuclear versus 12% side-chain bromination per methyl). The extra methyl group in **3b** shifts the ratio nuclear:side-chain bromination from 8:92 (0.087) to 76:12 (6.33). In 2,3,5-trimethylanisole (**15**; 100% nuclear bromination), an additional meta methyl relative to **3c** provides again an additional activation of the aromatic 4-position, so that side-chain bromination is completely overruled. The magnitude of this effect is surprising (at least some bromination was expected at the 2-methyl group) and is at present not fully understood. With 2,3,6-trimethylanisole (**14**) another remarkable feature becomes apparent: with this substrate only side-chain bromination is observed. The reason for the reduced nuclear bromination in **14** is that two methyl groups ortho to the methoxy group prevent the (more or less) coplanar orientation of this group and the aromatic ring, which is required for the resonance stabilization of the Wheland intermediate in the SE_2 process (Scheme 8); this effect is well documented.[29,30]

Such steric hindrance of resonance also explains the difference in behavior between 2,3,5-trimethylanisole (**15**; 100% nuclear bromination) and 2,3,5,6-tetramethylanisole (**16**; 28% nuclear bromination); although electronically, the additional 6-methyl group is expected to slightly activate the 4-position, this effect is overcompensated by resonance inhibition. On the other hand, the electronic effect of additional methyl groups is strong enough to maintain a respectable level of nuclear bromination in **16** (28%) compared to **3a** (0%) in spite of the strongly detrimental resonance inhibition in both.

Another interesting feature becomes apparent from an analysis of the product distribution of the side-chain brominated products formed in the reaction of 2,3,6-trimethylanisole (**14**): 2-(bromomethyl)-3,6-dimethylanisole (**22**), 3-(bromomethyl)-2,6-dimethylanisole (**23**), and 6-(bromomethyl)-2,3-dimethylanisole (**24**, 31%) were found in the ratio 1.4:1:1.1 (Table 1). This is remarkable, as in **3c** the 2-methyl group (ortho to methoxy) was found to be 9 times more reactive than the 3-methyl group (meta to methoxy). It suggests that the increased reactivity of the ortho methyl group in **3c** results from a stabilization of the transition state of radical bromination through the methoxy group becoming coplanar with the benzene ring; two ortho substituents (as in **14**) will prevent the O–Me bond from doing so (Scheme 9). The underlying reason is possibly the somewhat polar character of the transition state;[30] note that steric effects must be unimportant as positions 2 and (unhindered!) 6 are equally reactive.

It cannot be excluded that other factors have a subtle influence, too. Unlikely is an *a priori* conceivable direct neighboring group effect of an ether oxygen because it would be expected to influence the product formation unfavorably.[31] Indeed, the bromination of **3d** gave the ortho bromomethyl isomer **12** as the minor and the para isomer **13** as the major product (Scheme 4), but this result can also be rationalized by invoking the better stabilization of the polar transition in the para-quinoid situation. As for **14**, the reactivity of ortho and meta methyl groups was (nearly) equal in 2,3,5,6-tetramethylanisole (**16**): 2-(bromomethyl)-3,5,6-trimethylanisole (**25**) and 3-(bromomethyl)-2,5,6-trimethylanisole (**26**) were formed in a ratio of 2.3:1. In this case, however, nuclear bromination was not completely suppressed by the presence of two ortho (= 2,6) methyl groups. The two meta (= 3,5) methyl groups provide so much additional activation of the aromatic 4-position that the nuclear bromination reaction becomes competitive with side-chain bromination: 28% 4-bromo-2,3,5,6-tetramethylanisole (**27**) is formed.

Competition Experiments. In order to check the relative reactivities of the various methyl-substituted anisoles, we have performed some competition experiments. In these experiments, two anisoles (1 equiv of each) were reacted with 0.5 equiv of NBS. The results are presented in Table 2.

The reaction of the couple anisole (only nuclear bromination possible and no additional activation by methyl groups) and 4-methylanisole (only methyl bromination observed (Table 1)) resulted in side-chain bromination of 4-methylanisole to give 4-(bromomethyl)anisole as the only product. Thus, without the presence of additional methyl groups at the aromatic ring, the activation of the para position by the methoxy group alone is insufficient to make its substitution competitive with side-chain bromination; this is in line with the behavior of 2- and 3-methylanisole. The competition experiment between the couple 2,3-dimethylanisole (pure **3c** gives almost exclusively side-chain bromination) and 2,3,5-trimethylanisole (pure **15** gives only nuclear bromination) shows that the 4-position in **15** is the most reactive one: nuclear bromination of **15** occurred exclusively to give 4-bromo-2,3,5-trimethylanisole (**31**).

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(30) March, J. In *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure*, 4th ed.; J. Wiley: New York, 1992; p 679.
(31) Friedrich, S. S.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1970**, *35*, 944.

Table 2. Distribution of Nuclear and Side-Chain Bromination Products of (Substituted) Anisoles in Competition Experiments[a]

compound	nuclear bromination (para)	side-chain bromination
(1) anisole	0	0
(2) 4-methylanisole	0	100
(1) 2,3-dimethylanisole (**3c**)	0	0
(2) 2,3,5-trimethylanisole (**15**)	100 (**31**)	0
(1) 2,3-dimethylanisole (**3c**)	4 (**7**)	79 (71 (**6**) + 8 (**10**))[b]
(2) *m*-xylene	0	17 (**33**)
(1) 3,5-dimethylanisole (**3b**)	45 (**5**)	26 (**24**)
(2) *m*-xylene	0	29 (**33**)

[a] The ratio was (anisole 1):(anisole 2):NBS = 1:1:0.5; percentages are related to the amount of NBS. [b] Numbers given in parentheses are relative percentages for regioisomers, followed by the number of the compound (bold).

To investigate the influence of the methoxy group on the radical reactivity of the meta methyl group, *m*-xylene was compared with 3,5-dimethylanisole (**3b**) in a competition experiment. Besides nuclear bromination in **3b** (**5**; 45%), approximately the same amounts of side-chain-brominated products were found for both compounds: 3-methyl(bromomethyl)benzene (**33**; 29%) and 3-(bromomethyl)-5-methylanisole (**34**; 26%).[32] Apparently, the reactivity of a methyl group is hardly influenced by a meta methoxy group in a radical hydrogen abstraction reaction. It must be emphasized that the nuclear bromination of **3b** is the major reaction and that consequently the concentration of **3b** decreases faster than that of *m*-xylene, which will bias the result toward a seeming higher reactivity of the latter.

The competition reaction between 2,3-dimethylanisole (**3c**) and *m*-xylene again shows an intramolecular reactivity difference for **3c** in which the ortho methyl group is about 10 times more reactive than the meta methyl group (71% and 8%, respectively); this meta methyl group again has the same reactivity as a methyl group of *m*-xylene (17% reaction; 8.5% per methyl group). Apparently, steric hindrance by a neighboring methyl group does not significantly influence side-chain bromination. Furthermore, 4% nuclear bromination of **3c** was found to give **7**.

Conclusions

In the reactions of (methyl substituted) anisoles with *N*-bromosuccinimide (NBS) under the influence of light, nuclear, and/or side-chain bromination do occur. It has been established that the nuclear bromination follows an electrophilic aromatic substitution pathway, while the side-chain bromination is a free radical chain process. Both reactions can compete even under conditions which favor the radical process, such as irradiation.

From our experiments, it can be concluded that methyl-substituted anisoles are para brominated rather than side-chain brominated if at least two methyl groups are present at positions 3 and 5. With two methyl groups ortho to the methoxy group, nuclear bromination is adversely affected because of steric hindrance of the conjugation of the aromatic ring with the methoxy group: in 2,6-dimethylanisole (**3a**) and in 2,3,6-trimethylanisole (**14**), only side-chain bromination occurs. Methyl groups ortho to the methoxy group show a 10-fold increase in reactivity in radical bromination as compared to a methyl group meta to the methoxy group, but this activation disappears when two ortho methyl groups are present. This suggests that activation of methyl groups by an ortho methoxy group is due to a conjugative interaction, too. The reactivity of a meta methyl group in 3,5-dimethylanisole (**3b**) is hardly influenced by the methoxy group, as it has the same reactivity as a methyl group of *m*-xylene. Steric hindrance plays a minor role in the side-chain bromination reactions of anisoles.

While initially we (and others[1]) had intuitively expected to encounter predominantly radical products under conditions which favor radical processes—such as irradiation (or BP[1])—we have now demonstrated that the competition between radical and ionic reactions may strongly depend on the substitution pattern which has a pronounced influence especially on the ionic reaction pathway. In retrospect, this is quite understandable in view of the late transition state of the electrophilic aromatic bromination;[33] a high degree of positive charge has developed, and so the stabilizing effect of electron-donating substituents will be dramatic.

Experimental Section

NMR spectra (in $CDCl_3$) were measured on a Bruker AC 200 spectrometer (^1H NMR: 200 MHz; $\delta(CHCl_3) = 7.27$ ppm) and on a Bruker MSL 400 spectrometer (^1H NMR: 400.1 MHz; $\delta(CHCl_3) = 7.270$ ppm). GC/MS analysis were performed on a HP 5890 GC/ 5970 MS combination, operating at 70 eV and equipped with a Chrompack BP1 (QSGE) 50 m/0.25 mm column.

Materials. Anisole (Merck), 2,3-dimethylanisole (Aldrich), 2,4-dimethylanisole (Janssen), and 3,5-dimethylanisole (Janssen) were purchased as such. 2,6-Dimethylphenol (Janssen), 2,3,5-trimethylphenol (Coalite & Chem. Prod.), 2,3,6-trimethylphenol (Aldrich), and 2,3,5,6-tetramethylphenol were converted to the corresponding anisoles in high yields by a Williamson ether synthesis, using sodium and methyl iodide (Janssen) in THF. The THF needed for the anisole syntheses was dried by distillation from $LiAlH_4$ after predrying from NaOH before use.

General Procedure for the Bromination of (Substituted) Anisoles. In a 100-mL three-necked flask equipped with a reflux condenser and a magnetic stirring device were added the (substituted) anisole (10 mmol) and *N*-bromosuccinimide (NBS) (5 mmol) to dry CCl_4 (50 mL).

In the light-induced reactions, two Philips "IR 250 W" lamps were placed at such a distance from the reaction flask that reflux was maintained. In almost all cases, the color of the reaction mixture went from light yellow to dark yellow/red to colorless. In almost all cases, the reaction was complete within 30 min of reflux, which was visible by the formation of succinimide, which floats upon the surface of the CCl_4 when the stirring is interrupted. Note that NBS, due to its higher specific gravity, forms a precipitate in this system. The reactions were also monitored by gas chromatography. After the reaction mixture was cooled to room temperature, the succinimide was filtered off and the solvent was removed carefully by using a rotary evaporator. Recovered material was in all cases almost quantitative (by weight, taking into account the increase by introduction of bromine in 50% of the starting material).

In the thermal reactions, reflux was maintained by heating with an oil bath at 90 °C for approximately 8 h. It must be emphasized that these reactions were performed without an *extra* light source, but in the (neon) light of the laboratory. Most reactions were finished after this period, but the relative amounts of the products were calculated from the amount of

(32) Note that the ratio nuclear/side-chain bromination for **3b** (45/13 per methyl group) in the competition experiment is almost the same as was found in the reaction of only **3b** (60/20), as expected.

(33) References 30, pp 501–568.

starting material which had reacted. The results of these reactions are given in Table 1.

General Procedure for the Competition Experiments. In a 100-mL three-necked flask equipped with a reflux condenser and a magnetic stirring device were added 5 mmol of each of the (substituted) anisoles to be investigated in the experiment and 2.5 mmol of *N*-bromosuccinimide (NBS) to 50 mL of dry CCl_4. All further manipulations were as described above. The results of the competition experiments are given in Table 2.

Analysis of Starting Materials and Products. ^{1}H NMR spectra of most starting materials (di- and trimethylanisoles are reported here because the assignment of the different methyl signals in starting anisols and products has (for the first time) been performed by NOESY NMR spectroscopy. For convenience, all spectra are given in numerical order.

The monobrominated products were separated from starting material and dibrominated products (always formed in minor amounts) by preparative GC. No effort was made to separate the different monobrominated isomers formed in some of the reactions. Signals belonging to different isomers were assigned by integration and by NOESY NMR experiments. The product ratio was, if possible, determined by integrating the CH_2Br and OMe signals in the ^{1}H NMR spectrum of the crude reaction mixtures. The ratio thus obtained was checked by comparison with GC/MS and GC integration results. The experimental error of this analysis is <5%. The reproducibility of the experiments was tested by repeating several experiments up to 5 times. The results are presented in Table 1, and spectral data are given below.

4-Bromo-3,5-bis(bromomethyl)anisole (2c): ^{1}H NMR (200 MHz) δ 6.98 (s, 2H, aryl-(H2 and H6), 4.60 (s, 2H, CH_2-Br), 3.83 (s, 3H, OMe); GC/MS *m/z* (rel intensity) 370 ($M^{\bullet+}$, $C_9H_9Br_3O$, 5.2), 291 (100), 212 (16), 133 (15), 90 (11).

2,3-Dimethylanisole (3c): ^{1}H NMR (400 MHz) δ 7.148 (t, J = 7.9 Hz, 1H, aryl-(H5)), 6.868 (d, J = 7.6 Hz, 1H, aryl-(H4)), 6.799 (d, J = 8.2 Hz, 1H, aryl-(H6)), 3.892 (s, 3H, OMe), 2.362 (s, 3H, aryl-CH_3(3)), 2.244 (s, 3H, aryl-CH_3(2)); NOESY interactions: Me(3)-aryl(H4); OMe-aryl(H6).

2,4-Dimethylanisole (3d): ^{1}H NMR (400 MHz) δ 7.032 (bs, aryl-(H3) and -(H5)), 6.798 (d, J = 8.8 Hz, 1H, aryl-(H6)), 3.874 (s, 3H, OMe), 2.347 (s, 3H, aryl-CH_3(2)), 2.285 (s, 3H, aryl-CH_3(4)); NOESY interactions: Me(2)-aryl(H3); Me(4)-aryl(H3) and -(H5); OMe-aryl(H6).

4-Bromo-3-(bromomethyl)-5-methylanisole (4): ^{1}H NMR (200 MHz) δ 6.81 (d, J = 3.0 Hz, 1H, aryl-(H2)), 6.77 (d, J = 3.0 Hz, 1H, aryl-(H6)), 4.60 (s, 2H, CH_2Br), 3.80 (s, 3H, OMe), 2.41 (s, 3H, aryl-CH_3(5)); GC/MS *m/z* (rel intensity) 294 ($M^{\bullet+}$, $C_9H_{10}Br_2O$, 18), 213 (100), 134 (16), 91 (16).

4-Bromo-3,5-dimethylanisole (5): ^{1}H NMR (200 MHz) δ 6.66 (s, 2H, aryl-(H2 and H6)), 3.78 (s, 3H, OMe), 2.40 (s, 6H, aryl-CH_3(3 and 5)); GC/MS *m/z* (rel intensity) 214 ($M^{\bullet+}$, C_9H_{11}-BrO, 100), 199 (11), 171 (19), 135 (12), 105 (8), 91 (14).

2-(Bromomethyl)-3-methylanisole (6): ^{1}H NMR (400 MHz) δ 7.188 (t, J = 7.95 Hz, 1H, aryl-(H5)), 6.803 (d, J = 7.6 Hz, 1H), aryl-(H4)), 6.751 (d, J = 8.3 Hz, 1H, aryl-(H6)), 4.667 (s, 2H, CH_2Br), 3.890 (s, 3H, OMe), 2.409 (s, 3H, aryl-CH_3); GC/MS *m/z* (rel intensity) 214 ($M^{\bullet+}$, $C_9H_{11}BrO$, 11), 135 (100), 105 (59), 91 (24), 79 (6). NOESY interactions: CH_3-CH_2Br; CH_3-aryl(H4); OMe-CH_2Br; OMe-aryl(H6).

4-Bromo-2,3-dimethylanisole (7). Spectroscopic data are in accordance with those reported before. No NOESY interactions investigated due to low yield of **7** (3%).

3-(Bromomethyl)-2-methylanisole (10): ^{1}H NMR (400 MHz), aromatic signals unresolved because they were overlapped by the aromatic signals from **6** (ratio **6**:**10** = 9:1!), δ 4.532 (s, 2H, CH_2Br), 3.839 (s, 3H, OMe), 2.275 (s, 3H, aryl-CH_3); GC/MS *m/z* (rel intensity) 214 ($M^{\bullet+}$, $C_9H_{11}BrO$, 41), 199 (5), 135 (100), 105 (55), 91 (32), 79 (17).

2,3-Bis(bromomethyl)anisole (11): ^{1}H NMR (400 MHz) δ 7.28 (t, J = 7.6 Hz, 1H, aryl-(H5)), 6.98 (d, J = 7.6 Hz, 1H, aryl-(H4)), 6.89 (d, J = 7.6 Hz, 1H, aryl-(H6)), 4.80 (s, 2H, CH_2-Br(2)), 4.63 (s, 2H, CH_2Br(3)), 3.92 (s, 3H, OMe); GC/MS *m/z* (rel intensity) 292 ($M^{\bullet+}$, $C_9H_{10}Br_2O$, 4), 213 (100), 183 (13), 134 (62), 104 (52), 91 (34). NOESY interactions: CH_2Br(2)-CH_2-Br(3); CH_2Br(3)-aryl(H4); OMe-CH_2Br(2); OMe-aryl(H6).

2-(Bromomethyl)-4-methylanisole (12): ^{1}H NMR (400 MHz) δ 7.151 (s, 1H, aryl-(H3)), 7.097 (d, J = 8.3 Hz, 1H, H5), 6.790 (d, J = 8.3 Hz, 1H, aryl-(H6)), 4.573 (s, 2H, CH_2Br(2)), 3.892 (s, 3H, OMe), 2.300 (s, 3H, aryl-CH_3(4)); GC/MS *m/z* (rel intensity) 214 ($M^{\bullet+}$, $C_9H_{11}BrO$, 4.6), 135 (100), 120 (5), 91 (15). NOESY interactions: CH_2Br(2)-aryl-(H3); aryl-Me(4)-aryl(H3) and -(H5); OMe-aryl(H6).

4-(Bromomethyl)-2-methylanisole (13): ^{1}H NMR (400 MHz) δ 7.208 (d, J = 8.1 Hz, 1H, H5), 7.196 (s, 1H, aryl-(H3)), 6.783 (d, J = 8.1 Hz, 1H, aryl-(H6)), 4.507 (s, 2H, CH_2Br(4)), 3.857 (s, 3H, OMe), 2.225 (s, 3H, aryl-CH_3(2)); GC/MS *m/z* (rel intensity) 214 ($M^{\bullet+}$, $C_9H_{11}BrO$, 11), 135 (100), 105 (49), 91 (19), 79 (14). NOESY interactions: aryl-Me(2)-aryl-(H3); CH_2-Br(4)-aryl-(H3) and (H5); OMe-aryl(H6).

2,3,6-Trimethylanisole (14): ^{1}H NMR (400 MHz) δ 6.976 (d, AB, J = 7.6 Hz, 1H, aryl-(H5)), 6.891 (d, AB, J = 7.6 Hz, 1H, aryl-(H4)), 3.756 (s, 3H, OMe), 2.327 (s, 3 H, aryl-CH_3-(6)), 2.296 (s, 3H, aryl-CH_3(3)), 2.262 (s, 3H, aryl-CH_3(2)); GC/MS *m/z* (rel intensity) 150 ($M^{\bullet+}$, $C_{10}H_{14}O$, 93), 135 (100), 119 (14), 105 (20), 91 (49). NOESY interactions: CH_3(3)-aryl(H4); CH_3(2)-OMe; CH_3(6)-OMe; CH_3(6)-aryl(H5).

2,3,5-Trimethylanisole (15): ^{1}H NMR (400 MHz) δ 6.672 (s 1H, aryl-(H4)), 6.600 (s, 1H, aryl-(H6)), 3.855 (s, 3H, OMe), 2.355 (s, 3H, aryl-CH_3(5)), 2.292 (s, 3H, aryl-CH_3(3)), 2.166 (s, 3H, aryl-CH_3(2)); GC/MS *m/z* (rel intensity) 150 ($M^{\bullet+}$, $C_{10}H_{14}O$, 100), 135 (92), 119 (18), 105 (29), 91 (34). NOESY interactions: CH_3(3)-aryl(H4); CH_3(2)-OMe; OMe-aryl(H6); CH_3(5)-aryl(H4) and (H6).

2,3,5,6-Tetramethylanisole (16): ^{1}H NMR (200 MHz) δ 6.78 (s 1H, aryl-(H4)), 3.66 (s, 3H, OMe), 2.20 (s, 6H, aryl-CH_3(2 and 6)), 2.18 (s, 6H, aryl-CH_3(3 and 5)); GC/MS *m/z* (rel intensity) 164 ($M^{\bullet+}$, $C_{11}H_{16}O$, 98), 149 (100), 133 (21), 119 (21), 105 (26), 91 (31), 77 (20).

1,2,3,4-Tetramethylbenzene (17): ^{1}H NMR (400 MHz) δ 6.995 (s 2H, aryl-H), 2.352 (s, 6H, aryl-CH_3(1 and 4)), 2.283 (s, 6H, aryl-CH_3(2 and 3)). NOESY interactions: CH_3(1 and 4)-aryl(H5and H6).

1-(Bromomethyl)-2,3,4-trimethylbenzene (18): ^{1}H NMR (400 MHz) δ 7.085 (d, J = 7.7 Hz, 1H, aryl-(H6)), 6.989 (d, J = 7.7 Hz, 1H, aryl-(H5)), 4.562 (s, 2H CH_2Br), 2.333, 2.298, and 2.216 (3 × s, 3 × 3H, aryl-CH_3(2, 3, and 4)); GC/MS *m/z* (rel intensity) 212 ($M^{\bullet+}$, $C_{10}H_{13}Br$, 14), 133 (100), 115 (23), 105 (20), 91 (24), 77 (10). NOESY interactions: CH_2Br-aryl(H6).

2-(Bromomethyl)-1,3,4-trimethylbenzene (19): ^{1}H NMR (400 MHz) δ 7.032 (d, J = 7.7 Hz, 1H, aryl-(H5)), 6.947 (d, J = 7.7 Hz, 1H, aryl-(H6)), 4.616 (s, 2H, CH_2Br), 2.400, 2.324, and 2.275 (3 × s, 3 × 3H, aryl-CH_3(1, 3, and 4)); GC/MS *m/z* (rel intensity) 212 ($M^{\bullet+}$, $C_{10}H_{13}Br$, 19), 133 (100), 115 (26), 105 (21), 91 (28), 77 (13). No NOESY interactions detected on the CH_2Br group with the aromatic hydrogens.

1-(Bromomethyl)-2,4,5-trimethylbenzene (21): ^{1}H NMR (200 MHz) δ 7.09 (s, 1H, aryl-(H6)), 6.97 (s, 1H, aryl-(H3)), 4.51 (s, 2H, CH_2Br), 2.36 (s, 3H, aryl-CH_3(5)), 2.23 (s, 6H, aryl-CH_3(2 and 4)); GC/MS *m/z* (rel intensity) 212 ($M^{\bullet+}$, $C_{10}H_{13}Br$, 9), 133 (100), 115 (9), 105 (6), 91 (9).

2-(Bromomethyl)-3,6-dimethylanisole (22): ^{1}H NMR (400 MHz) δ 7.086 (d, AB, J = 7.7 Hz, 1H, aryl-(H5)), 6.908 (d, AB J = 7.7 Hz, 1H, aryl-(H4)), 4.693 (s, 2H, CH_2Br), 3.914 (s, 3H, OMe), 2.418 (s, 3H, aryl-CH_3(3)), 2.310 (s, 3H, aryl-CH_3(6)). The GC/MS spectra of **22**, **23**, and **24** were almost identical: *m/z* (rel intensity) 228 ($M^{\bullet+}$, $C_{10}H_{13}BrO$, 17), 149 (100), 119 (72), 91 (37). NOESY interactions: CH_2Br-aryl-CH_3(3); CH_2Br-OMe.

3-(Bromomethyl)-2,6-dimethylanisole (23): ^{1}H NMR (400 MHz) δ 7.053 (d, AB, J = 7.8 Hz, 1H, aryl-(H5)), 7.027 (d, AB J = 7.8 Hz, 1H, aryl-(H4)), 4.547 (s, 2H, CH_2Br), 3.750 (s, 3H, OMe), 2.378 (s, 3H, aryl-CH_3(2)), 2.324 (s, 3H, aryl-CH_3(6)). GC/MS cf. **22**. NOESY interactions: CH_2Br-aryl-H(4); CH_2Br-aryl-CH_3(2); OMe-aryl-CH_3(2); OMe-aryl-CH_3(6).

6-(Bromomethyl)-2,3-dimethylanisole (24): ^{1}H NMR (400 MHz) δ 7.175 (d, AB, J = 7.7 Hz, 1H, aryl-(H5)), 6.961 (d, AB, J = 7.7 Hz, 1H, aryl-(H4)), 4.622 (s, 2H, CH_2Br), 3.888 (s, 3H, OMe), 2.298 (s, 3H, aryl-CH_3(3)), 2.243 (s, 3H, aryl-CH_3(2)). GC/MS cf. **22**. No NOESY interactions investigated.

2-(Bromomethyl)-3,5,6-trimethylanisole (25): ^{1}H NMR (200 MHz) δ 6.80 (s, 1H, aryl-(H4)), 4.67 (s, 2H, CH_2Br), 3.85

(s, 3H, OMe), 2.33 (s, 3H, aryl-CH_3(3)), 2.20 (s, 3H, aryl-CH_3-(5)), 2.15 (s, 3H, aryl-CH_3(6)); GC/MS *m/z* (rel intensity) 242 ($M^{\bullet+}$, $C_{11}H_{15}BrO$, 15), 163 (100), 133 (85), 105 (30), 91 (16).

3-(Bromomethyl)-2,5,6-trimethylanisole (26): ^{1}H NMR (200 MHz) δ 6.93 (s, 1H, aryl-(H4)), 4.50 (s, 2H, CH_2Br), 3.64 (s, 3H, OMe), 2.29 (s, 3H, aryl-CH_3(5)), 2.20 (s, 3H, aryl-CH_3-(2)), 2.17 (s, 3H, aryl-CH_3(6)); GC/MS *m/z* (rel intensity) 242 ($M^{\bullet+}$, $C_{11}H_{15}BrO$, 25), 163 (100).

4-Bromo-2,3,5,6-tetramethylanisole (27): ^{1}H NMR (200 MHz) δ 3.68 (s, 3H, OMe), 2.37 (s, 6H, aryl-CH_3(3 and 5)), 2.24 (s, 6H, aryl-CH_3(2 and 6)); GC/MS *m/z* (rel intensity) 242 ($M^{\bullet+}$, $C_{11}H_{15}BrO$, 53), 227 (25), 163 (100), 133 (23), 105 (30), 91 (19).

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