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Substituent effects on the stability of extended benzylic carbocations: a computational study of conjugation†

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A set of design rules for the prediction of relative stabilities of methoxy substituted naphthyl methyl carbocations are presented based on a series of DFT calculations. The *peri*-effect, over-crowding, substitutions on the ring carrying the CH_2^+ group and substitution on the opposite ring are the principal factors that influence the stability of the carbocations. All of these factors have to be taken simultaneously into account. The most pronounced destabilization occurs when the methyl part of the methoxy substituent lies out of the plane of the aromatic core because this causes the resonance stabilization of the carbocation to become hindered. The performance of the DFT-calculations was assessed on the results of a G3(MP2)//B3LYP calculation—a method that is known to predict energies to within chemical accuracy. These values were found to compare well with those obtained at the B3LYP/6-31G(d) level. Thus, a computationally inexpensive method such as the B3LYP/6-31G(d) might prove to be a powerful tool in the design of future complex extended aromatic systems.

Introduction

Fundamental understanding of the factors that govern the stability of benzylic carbocations and extended benzylic carbocations is essential for the explanation of several phenomena observed in both biological systems and materials science.

An important research area where the prediction of the stabilization of extended benzylic carbocations has proved to be crucial is within the area of polycyclic aromatic hydrocarbons (PAHs) in cancer treatment. In the 1980s, a basic set of rules for the carcinogenic behaviour of PAHs was deduced.[1–3] These rules were based on the finding that PAHs are oxidized regiospecifically (by the enzyme monooxygenase) to epoxides. In aqueous solution these epoxides regiospecifically form extended benzyl-like carbocations.[4] These carbocations are responsible for the interactions with DNA and RNA and in turn the carcinogenic behaviour of the PAHs. A good example of this remarkable observation is the excessively carcinogenic benzo[*a*]pyrene shown in Fig. 1.[5]

The dominant carbocation species formed in the enzymatic process is remarkably similar to a 1-naphthyl methyl carbocation whereas the less abundant carbocation species more closely resembles a 2-naphthyl methyl carbocation (Fig. 1). The methyl naphthyl carbocation subunits are highlighted in Fig. 1. Stabilization of extended benzyl-like carbocations can be further achieved by the regiospecific introduction of electron donating substituents in specific positions on the aromatic core. To this end, a series of methyl substituted benzo[*a*]pyrenes has been studied and it has been shown that introduction of the slightly electron donating methyl substituent in specific positions gives a convincing correlation with carcinogenicity.[6]

A research area that also relies on the stability of carbocations is the development of handles (linkers) for solid-phase synthesis. The cleavage properties of a major series of acid-labile handles are determined by the stability of substituted benzylic carbocations in the sense that higher stability of the benzylic carbocation leads to a more acid-labile handle.

The goal of our present research is to develop new backbone amide linkers (BAL-type linkers, Fig. 2) with increased acid-lability as compared with the known linkers (handles).[7–9] One way of achieving this is to use systems that can stabilize the benzyl-like carbocation that are formed in the process of cleaving the substrates from the solid support.[10]

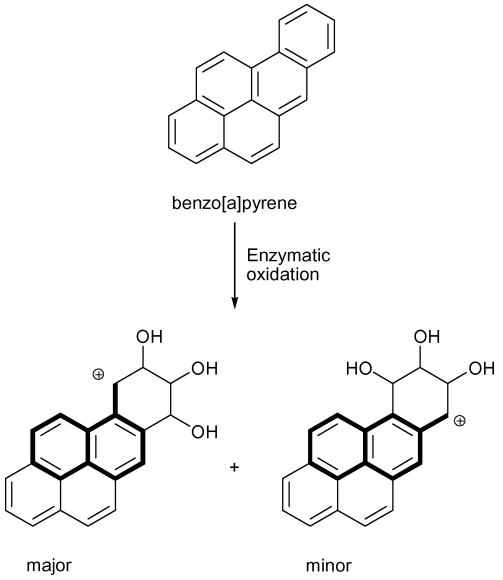

Fig. 1 Regiospecific formation of carbocations from benzo[*a*]pyrene after enzymatic oxidation to the corresponding epoxides. This PAH is a potent carcinogen. Naphthalene sections of the two carbocation isomers are highlighted to illustrate extended 1- and 2-naphthyl alkyl carbocations.

The search for more acid-labile handles can therefore be condensed to a search for more stabile benzyl-like carbocations. Stabilization of benzyl-like carbocations can be achieved in several ways.[3,11–15] One route is to increase the number of electron donating substituents on the aromatic core.[8] Alternative procedures include the use of electron-rich heteroaromatic compounds[16] and expansion of the aromatic system.[17–19]

An advantage of larger aromatic cores is the larger periphery available for substitution and the greater ability to form crystalline compounds during the synthesis of the handle. Our approach is to use naphthalene based aromatics to stabilize the benzyl-like carbocations.

In previous studies, a series of methoxy substituted benzene and naphthalene derived systems and their properties as handles for solid-phase synthesis were investigated.[20–22] It was found that other factors than simply the size of the aromatic system

† Electronic supplementary information (ESI) available: tables S1 and S2. See http://www.rsc.org/suppdata/ob/b5/b504967a/

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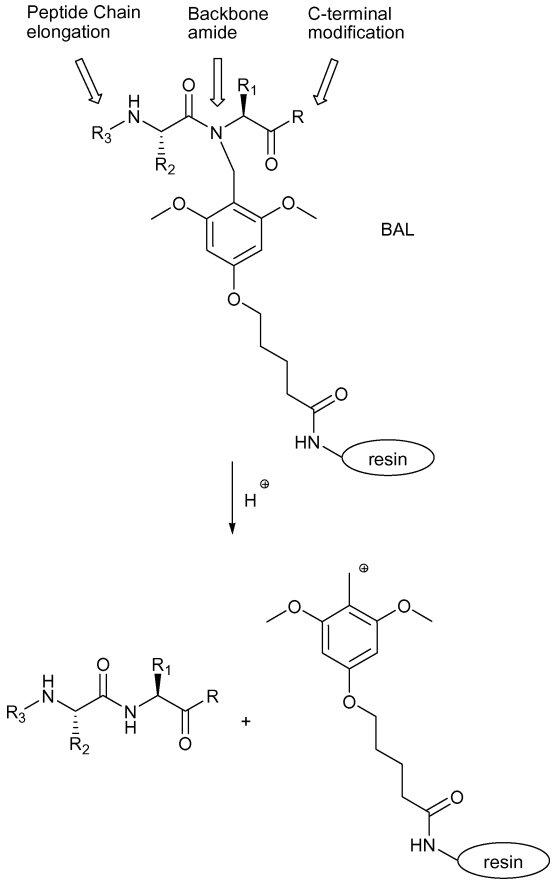


Fig. 2 General backbone amide linkage (BAL) strategy for solid-phase synthesis illustrated with the original 2,4,6-trialkoxybenzene derived BAL handle.[7]

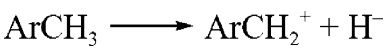
and the number of methoxy substituents are important for the cleavage properties of the handles and therefore also for the stability of the benzyl-like carbocation. These findings prompted this computational study where the substitution pattern is varied systematically on methylnaphthalene to map how the substituents influence the structure and stability of the involved carbocations.

Computational details

All molecular geometries were calculated at the B3LYP/6-31G(d) level of theory using the GAUSSIAN 98 suite of programs.[23] The vibrational frequencies were also calculated to verify the complete optimization of the geometries (zero imaginary frequencies). The energy of a molecule was then calculated as the sum of the electronic energy and the zeropoint vibrational energy (zpve). To assess the performance of the B3LYP/6-31G(d) model chemistry, the energetics for two test reactions were also calculated at the G3(MP2)//B3LYP level, this method has been shown to agree with experiments within 1.25 kcal mol^{-1}.[24] Intrinsic to the G3(MP2)//B3LYP method is a QCISD(T)/6-31G(d) single point calculation and the energetics for the test reactions were also included at this high level. For one of the larger molecules where the G3(MP2)//B3LYP method was too computationally demanding, a QCISD(T)/6-31G(d) single point calculation of the energy was employed and compared to the reactions for which QCISD(T)/6-31G(d) as well as G3(MP2)//B3LYP values are available. This provides a firm basis for assessment of the B3LYP/6-31G(d) values.

Results and discussion

A measure of the stability of the aromatic ions was expressed by the energy differences between $ArCH_3$ and $ArCH_2^+$ in Scheme 1 where Ar represent various methoxy substituted



Scheme 1 General reaction scheme that expresses the energetic requirements for the formation of the carbocation.

aromatic species. It is important to note that the hybridization of the carbon atom changes from sp^3 in the methyl group to sp^2 in the carbocation (*i.e.*, from tetrahedral to planar). This also changes the steric requirements.[6]

The numbering of the two different methyl substituted naphthalene cores is shown in Fig. 3.

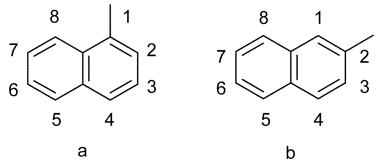
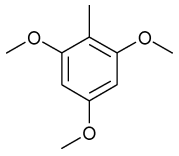
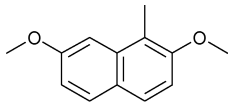
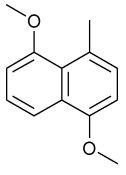
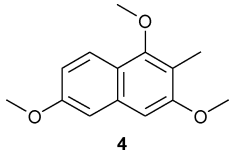


Fig. 3 Definition of the numbering used in this work for (a) 1-methylnaphthalene and (b) 2-methylnaphthalene.

It was established that the B3LYP/6-31G(d) level of calculation is of a sufficient quality by performing test calculations on higher levels (G3(MP2)//B3LYP and QCISD(T)/6-31G(d)). These resulted in approximately the same relative numbers (**1**, **3** and **4** in Table 1). In general, a B3LYP/6-31G(d) geometry and frequency calculation on one of the naphthalene systems required approximately 16–48 hours which has to be compared to a calculation time of up to several weeks (8 weeks in the case of **4**) for a calculation performed at the QCISD(T)/6-31G(d)//B3LYP/6-31G(d) level. All the results from the calculations are shown in Tables 1–7.

Table 1 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})
 **1**	525[a]/525[b]/536[c]
 **2**	528[a]
 **3**	529[a]/531[b]/541[c]
 **4**	530[a]/533[b]

[a] B3LYP/6-31G(d) + zpve. [b] QCISD(T)/6-31(d)//B3LYP/6-31(d) + zpve. [c] G3(MP2)//B3LYP; G3(MP2)//B3LYP without the higher level corrections yields 530 (**1**) and 535 (**3**), respectively.

Our goal was to obtain a general set of rules for the design of the most stabile naphthyl methyl carbocations. As the number of methoxy substituted methyl naphthalene isomers is considerable, especially upon addition of additional methoxy substituents (number of isomers = $n!/p!(n-p)!$; n = number of available positions (7), p = number of the substituent in question; 14 monomethoxy monomethyl derivatives, 42 dimethoxy monomethyl derivatives, 70 trimethoxy monomethyl derivatives, 70 tetramethoxy monomethyl derivatives, 42 pentamethoxy monomethyl derivatives, 14 hexamethoxy monomethyl derivatives and 2 heptamethoxy monomethyl derivatives), we have chosen to look at a selected number of isomers that give the global stabilization trends.

It requires less energy to form the original BAL carbocation (2,4,6-trimethoxy benzyl carbocation, **1**)[22,25] from the corresponding neutral than the three known naphthalene based (NAL) handles (**2–4**).[20–22] This is in agreement with the actual cleavage properties of the handles in solution.[20–22,25] The calculations also show that the two dialkoxy naphthyl methyl carbocations (**2–3**) are more stabile than the known trialkoxy naphthyl methyl carbocation (**4**). This somewhat odd result is also in agreement with the experimental results in solution.[20–22]

In the following sections the computational results are summarized starting with the parent naphthyl methyl systems; these are then augmented by the systematic addition of one methoxy group at a time to the aromatic core.

Zero methoxy substituents

The unsubstituted parent systems are the first systems of interest (Table 2). The results show a slight preference for substitution in the 1-position. This is in agreement with previous results from the groups of Olah,[17] Krygowski[18] and Flesher.[4] The formation of the two naphthyl methyl carbocations (**6**$^+$ and **7**$^+$) requires less energy that the formation of the benzyl carbocation from toluene (**5**), and this gives an initial rise to optimism for the idea of using naphthalene as the aromatic core instead of benzene for the stabilization of benzyl-like carbocations. The extra ring present in naphthalene lowers the energy requirements for carbocation formation by approximately 10–12 kcal mol^{-1} relative to the benzene based system (**5–7**).

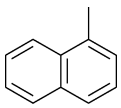
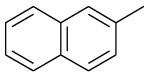
One methoxy substituent

Generally, the substitution of a hydrogen for an electron donating substituent such as a methoxy group gives an increase in carbocation stability due to the larger polarization of a methoxy group. This stabilizing effect can be enhanced further through delocalization of the positive charge. The resonance effect requires that the methoxy groups are in contact with the charged site. Thus, if the methyl group is placed in the 1-position on the naphthalene ring the methoxy group must be placed in the 2, 4, 5 or 7-position in order to gain stability by resonance (Table 3). Similarly, when the methyl group is placed in the 2-position on the naphthalene core the methoxy group must be placed in the 1, 3, 6 or 8-position on the ring (Table 4).

Resonance stabilization is evident in the systems with the methyl group in the 1-position. A comparison of the three 1-methylnaphthalene isomers that have the methoxy group and the methyl group on the same ring (**8**, **9** and **10**) shows that the isomers that allow direct resonance stabilization of the carbocation (**8**$^+$ and **10**$^+$) are ionized much easier than the isomer that does not (**9**$^+$).

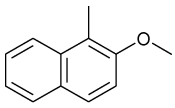
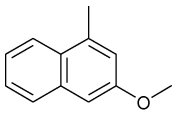
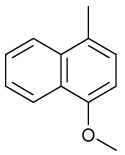
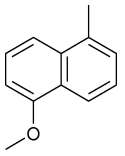
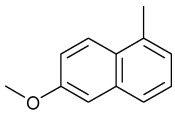
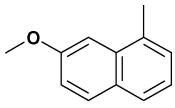
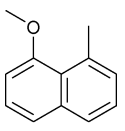
In Fig. 4 the calculated geometries of **8** and the corresponding carbocation (**8**$^+$) are shown. In the neutral species both the substituents lie in the plane of the aromatic core in the sense that one of the CH bonds of the CH_3 moieties are in the plane of the aromatic core. The carbocation also has both the

Table 2 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})[a]
 **5**	561
 **6**	549
 **7**	551

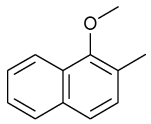
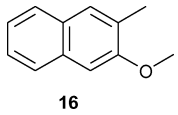
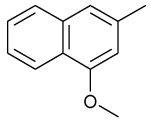
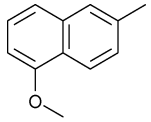
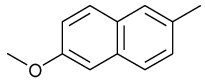
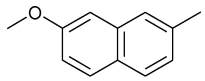
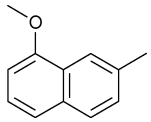
[a] B3LYP/6-31G(d) + zpve.

Table 3 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})[a]
 **8**	535
 **9**	547
 **10**	535
 **11**	542
 **12**	546
 **13**	540
 **14**	542

[a] B3LYP/6-31G(d) + zpve.

Table 4 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})[a]
 **15**	543
 **16**	545
 **17**	547
 **18**	548
 **19**	539
 **20**	548
 **21**	542

[a] B3LYP/6-31G(d) + zpve.

CH_2^+-substituent and the methoxy group situated in the aromatic plane. This allows for maximum carbocation stabilization. The result that all of the geometric parameters are close to those that would have been anticipated based on regular sp^2/sp^3 hybridization schemes shows that there is effectively no steric repulsion to distort the geometries.

The results of the calculations on **11**, **12**, **13** and **14** (the four isomers that have the methoxy group and the methyl group situated on opposite rings) give rise to a number of conclusions. The energy requirements for the formation of $\mathbf{11}^+$ and $\mathbf{13}^+$ are lowered significantly relative to the 1-methylnaphthalene (7 kcal mol^{-1} and 9 kcal mol^{-1} respectively); in these two cases the methoxy group is situated in a position that allows for extended resonance stabilization of the carbocation. In **12** the lowering of the energetic requirements is only 3 kcal mol^{-1}. This is in agreement with the methoxy arrangement which does not allow for resonance stabilization. In the case of **14** (Fig. 5) the lowering of the energetic requirements is comparable to what was the case for the two extended resonance stabilized isomers (7 kcal mol^{-1}), despite the fact that no resonance stabilization is possible. We ascribe this to an enhanced polarization effect (possibly ion–dipole) due to the proximity of the carbocation site in the 1-position and the electronegative oxygen atom in the 8-position (*peri*-distance).[26]

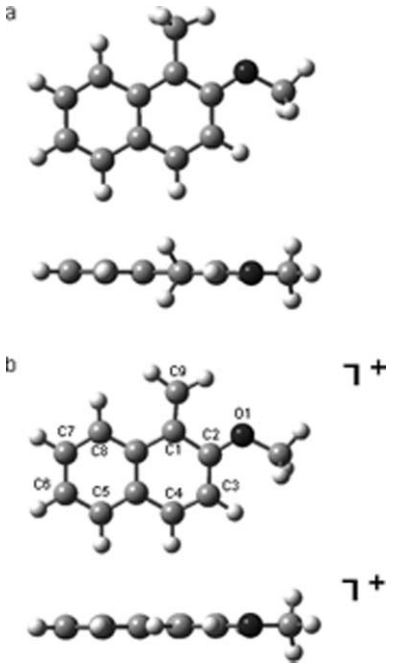


Fig. 4 (a) Calculated geometry (B3LYP/6-31G(d)) of **8** and (b) of the corresponding carbocation. The dihedral angles C9–C1–C2–O1: 0.007°, C2–C1–C9–H: 0.003°, C1–C2–O1–C(H_3): 0.003° and C9–C1–C–C8: 0.005° show that all heavy atoms lie in the same plane.

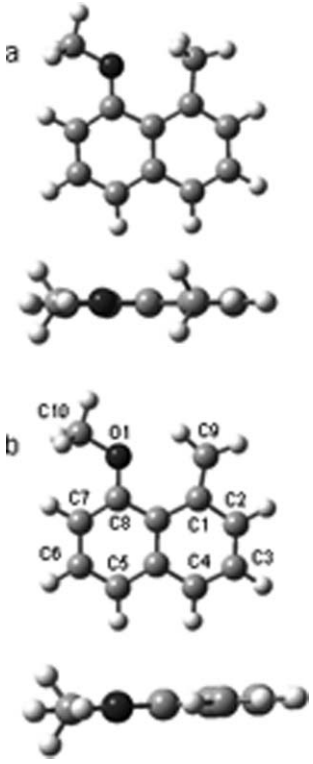


Fig. 5 (a) Calculated geometry (B3LYP/6-31G(d)) of **14** and (b) of the corresponding carbocation. The dihedral angles C9–C1–C–C8: 0.026°, C2–C1–C9–H: 0.003°, C7–C8–O1–C10: 0.147°and C8–O1–C8–C: 0.137° show that all heavy atoms lie in the same plane. Distance between O1–C9: 2.767 Å.

In general, the lowering of the energy requirements for carbocation formation by the addition of one methoxy group to one of the two rings in 1-methylnaphthalene is highest when the methoxy group is placed on the parent ring. Also, the lowering is more pronounced when the methoxy substituent is placed in a fashion that allows for direct resonance stabilization of the carbocation.

When the methyl substituent is placed in the 2-position, matters become more complicated. The isomer with the methyl group in the 2-position and the methoxy substituent in the 4-position (**17**) gives rise to a lowering of 4 kcal mol^{-1}. No direct resonance stabilization is possible for this isomer; a situation that compares to **9**. The placement of the methoxy groups in the *ortho* positions on the parent ring of **15** and **16** results in a relatively small lowering in energetic requirements for a carbocation that is stabilized by direct resonance. This lowering is comparable in size to the polarization effects observed in **9**, **12** and **17**.

From the calculated geometries of **15** and **15**$^+$ it is evident that the CH_3 part of the methoxy group and the CH_2^+ are locked in a position out of the aromatic plane (Fig. 6).

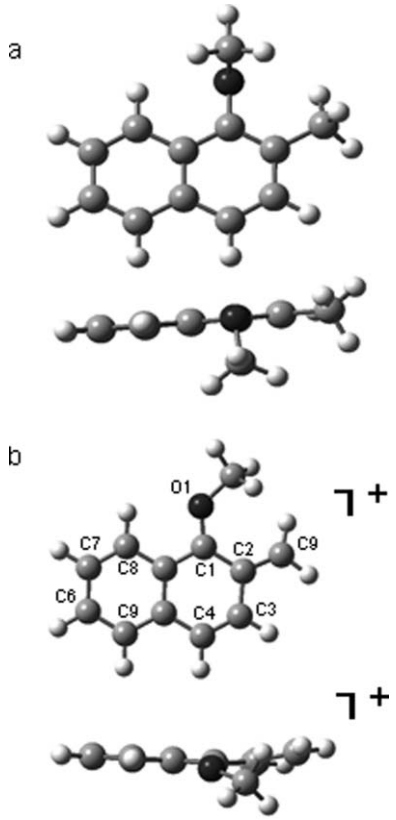


Fig. 6 (a) Calculated geometry (B3LYP/6-31G(d)) of **15** and (b) of the corresponding carbocation **15**$^+$. The dihedral angles O1–C1–C2–C9: 17.505°, O1–C1–C–C8: 5.154°, C3–C2–C9–H: 2.963°, C2–C1–O1–C(H_3): 15.130° and C4–C3–C2–C9: 14.329° show the distortion from planarity.

These structural features are due to steric congestion and are a result of the *peri*-effect. The combination of the carbocation site placed in the 2-position and the 1-methoxy group will impose an unfavorable steric demand on the system. The proton in the 8-position on the naphthalene core will force the 1-methoxy group out of plane and impose strain on the CH_2^+ substituent which will, in turn, also be forced out of the aromatic plane (Fig. 6b). This gives rise to a decrease of overlap between the π-electrons of the aromatic core and the empty 2p-orbital of the CH_2^+ substituent and thus the result is a significant destabilization of **15**$^+$ relative to **8**$^+$.

The small energy lowering in the case of **16** can be rationalized by viewing the two condensed benzene rings in the naphthalene core as described by Clar.[27] This way of viewing extended aromatics uses the aromatic sextet to assess stability of extended aromatics; the more fully conjugated rings that contain 6 electrons, the more stable. When the carbocation of **16** is formed, the positive charge is partially transferred to the methoxy group and this formally breaks the aromaticity of both benzene rings and an unstable *o*-quinomethane cationic structure results (Fig. 7). Thus, the resonance form of **16** that should give rise to an energy

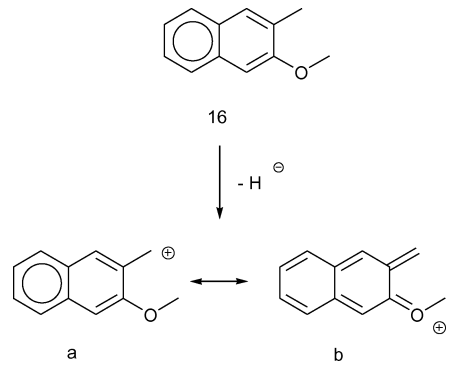


Fig. 7 (a) Parent carbocation from **16**. (b) Unstable *o*-quinomethane resonance structure of **16**.

lowering effect actually destabilizes the system (as compared to the other *ortho*- and *para*-substituted systems, **8** and **10**). This is the only one of the three monomethoxy substituted systems with the methoxy group in the *ortho*-position that has this destabilizing feature (the two other *ortho*-isomers are **8** and **15**).

The compounds **18**, **19**, **20** and **21** represent the four isomers that have the methyl group in the 2-position and the methoxy group on the opposite ring. The two isomers that do not allow for extended resonance stabilization (**18**$^+$ and **20**$^+$) only give rise to an energy lowering of *ca.* 3 kcal mol^{-1}, a finding that agrees with the observations from the isomer **12** in the sense that also in this case, the methoxy substituent is situated on the opposite ring and not in a position that allows for resonance stabilization of the carbocation. The two isomers that allow for extended resonance stabilization are **19**$^+$ and **21**$^+$. The lowering of the energy requirements of **21**$^+$ is in line with results for the analogue 1-methylnaphthalene isomers **11**$^+$ and **13**$^+$. Isomer **19**$^+$ is particularly energetically favourable to form compared to the other extended stabilized isomers and we ascribe this to the fact that the resonance structure with the positive charge on the methoxy oxygen is symmetrically stabilized throughout the system without cross conjugation as seen in Fig. 8.

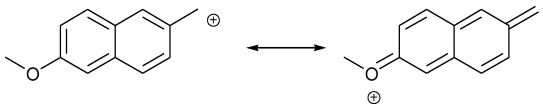


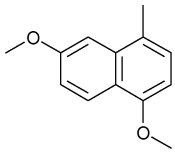
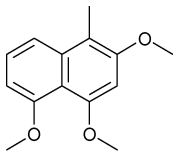
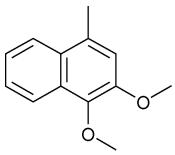
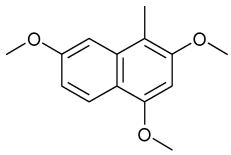
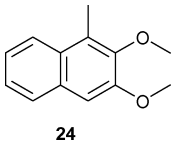
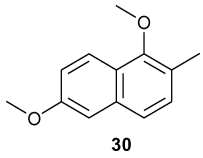
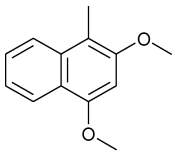
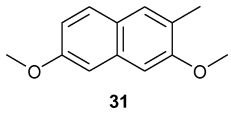
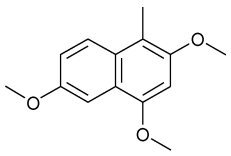
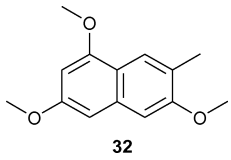
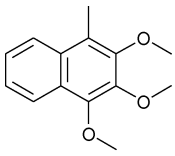
Fig. 8 Favorable resonance structure of **19**$^+$.

Two and three methoxy substituents

Generally, the introduction of more than one methoxy group gives rise to a lowering in the energy requirements for the formation of the naphthyl methyl carbocation due to increased stabilization by polarization. Resonance effects can further enhance the stability of the carbocations; it requires that the methoxy groups are introduced in an *ortho*, a *para* or an extended resonance stabilizing position. In this respect, the naphthalene core gives more possibilities for variety in the substitution pattern than the benzene core does.

If one considers some selected di- and tri-methoxy substituted systems with the methyl group placed in the 1-position (**2** and **3**, Table 1 and **22–29**, Table 5), the conclusions drawn in the previous section are to a large extent confirmed. When a methoxy group is placed onto the parent ring in a direct resonance position, the energy lowering of the neutral to carbocation reaction is largest, and the values lie between 10–16 kcal mol^{-1} as seen for **22** *vs.* **13**, **2** *vs.* **29**, **29** *vs.* **22**, **9** *vs.* **24**, **9** *vs.* **23**, **3** *vs.* **14** and **2** *vs.* **13**. When a methoxy group is placed on the opposite ring, and in a direct resonance position, the energy lowering range is from 5 to 7 kcal mol^{-1} (**10** *vs.* **22**, **28** *vs.* **25** and **25** *vs.* **29**). Placing a methoxy group on the parent ring in a position that does not

Table 5 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})	Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})
 **22**	528	 **28**	517
 **23**	531	 **29**	518
 **24**	536	 **30**	534
 **25**	523	 **31**	534
 **26**	521	 **32**	528
 **27**	527		

[a] B3LYP/6-31G(d) + zpve.

give direct resonance stabilization gives roughly a value of 4 kcal mol^{-1} (**10** *vs.* **23**). When extreme steric congestion is introduced, the energy of the system is no longer lowered but instead increased by *ca.* 1–4 kcal mol^{-1} (**25** *vs.* **27** and **8** *vs.* **24**). The lowest gain in energy requirements comes from methoxy groups placed on the opposite ring in positions that do not allow for direct resonance stabilization (approximately 2 kcal mol^{-1}, **25** *vs.* **26**). An exception to this observation is **3** where the methoxy group in the 8-position gives a surprisingly large stabilization of the carbocation. This substitution pattern with the methoxy substituent placed in the 8-position and the positively charged methylene group placed in the 1-position gives rise to a lowering that is comparable to the systems with extended resonance stabilization. We ascribe this to the close proximity of the substituents in the 1- and 8-positions (O–C$^+$: 2.755 Å; O–H (CH_2^+): 2.091 Å); this allows the electronegative oxygen atom to interact with the carbocation (these values compare well with the values in **14**, O–C$^+$: 2.768 Å; O–H (CH_2^+): 2.096 Å). This, combined with a sterically non-congested environment of both the CH_2^+ moiety and the methoxy moiety gives this large non-resonance stabilizing effect.

When considering the systems with two or three methoxy substituents and the methyl group in the 2-position (**4**, **30**, **31** and **32**), similar trends are observed. The lowering of the energy requirements for the neutral to carbocation reaction is 4–5 kcal mol^{-1} when introducing a methoxy substituent in the 1- or 3-positions (**4** *vs.* **31**, **19** *vs.* **31** and **4** *vs.* **30**). When the methoxy group is introduced in the 1- and 3- positions (keeping the 6-methoxy substituent constant), the lowering in energetic requirements is comparable (**4** *vs.* **30** and **31**). This illustrates that it is possible to partially 'switch-off' the stabilizing effect of a methoxy substituent by placing it in an unfavorable position on the naphthalene core. When the methoxy substituents are introduced on the opposite ring of the methyl group, the energy gain is 6–11 kcal mol^{-1} (**15** *vs.* **30**, **16** *vs.* **31** and **31** *vs.* **32**). Here the lowering is highest when the methoxy substituent is introduced in the 6-position (9–11 kcal mol^{-1}) on the naphthalene core,

and this is in accordance with the observations from the mono substituted systems (extended resonance stabilization).

The 1,3,6-trimethoxy-2-methyl case (4). In a previous study we have discussed the properties of $\mathbf{4}^+$ as the key intermediate in the cleavage process in solid-phase synthesis.[21] We observed that this trimethoxy methyl naphthalene isomer resulted in a less acid-labile handle than the two dimethoxy methyl naphthalene isomers (**2** and **3**).[20] We discussed this result on the basis of deviations from planarity in the crystal structure of 1,3,6-trimethoxynaphthalene-2-carbaldehyde. Compound **4** has the methyl group situated in the 2-position, two *ortho*-methoxy substituents on the parent ring and one methoxy substituent in an extended resonance position. The *ortho*-methoxy substituent in the 1-position is responsible for the non-planarity of the system (as in Fig. 9) and the *ortho*-methoxy substituent in the 3-position is involved in a resonance structure where the aromaticity of both rings is broken due to an *o*-quinomethane cationic structure (as in Fig. 7). The methoxy substituent in the 6-position is predicted to give the largest stabilization of the carbocation as compared to the two other methoxy substituents (compare **15**, **16** and **19**). The deviations from planarity in the carbocation of **4** are calculated to be pronounced and the geometries are shown in Fig. 9. These factors are responsible for the poor performance of **4** as an acid-labile handle in solid-phase synthesis; the reaction intermediate $\mathbf{4}^+$ is simply energetically unfavorable.

Four and five methoxy substituents

The computational results indicate that four methoxy substituents strategically placed around the naphthalene core and the methyl group in the 1-position is the optimal substitution pattern for stabilizing a naphthyl methyl carbocation. This system comprises two methoxy substituents on the parent ring in direct resonance and two methoxy substituents on the opposite ring (Table 6, **33**) that contribute to the stabilization of the carbocation by extended resonance stabilization.

This combination of stabilizing factors gives a pronounced 36 kcal mol^{-1} more favorable formation of the carbocation and is thereby the most favorable reaction in this study. The calculated geometries of the neutral species and the carbocation are shown in Fig. 10. This gives rise to maximum resonance stabilization by each of the four methoxy groups (the C–O bonds lie in the plane of the aromatic core) and therefore the energetically most favorable naphthyl methyl carbocation.

Both carbocation isomers of **33** and **34** have all four methoxy substituents placed in positions that allow for resonance stabilization (two on the parent ring and two on the opposite ring). The design trends observed in the previous sections are confirmed in the sense that the 1-methylnaphthalene isomer (**33**) is considerably more stabile than the 2-methylnaphthalene isomer.

The pentamethoxy isomer (**35**) has all the stabilizing features deduced from the previous sections; it can be viewed as the isomer **33** plus a methoxy group in the 8-position. In the monomethoxy and dimethoxy systems, a methoxy substituent placed in the 8-position with the CH_2^+ substituent placed in the 1-position introduced a lowering in the energetic requirements. In **35** this lowering is not observed, and this can be explained by steric congestion. The additional methoxy substituent in the 8-position actually enforces a steric strain that forces the entire aromatic core to be distorted from planarity.

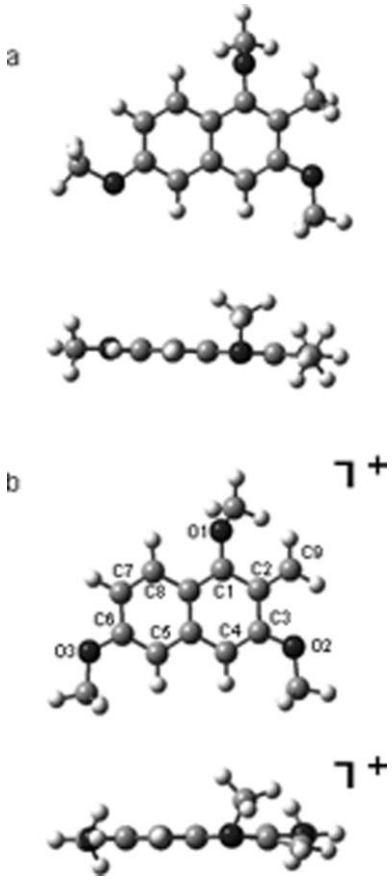
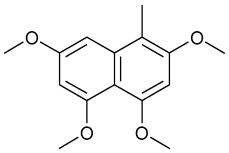
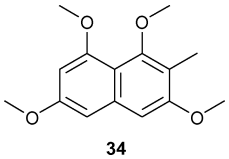
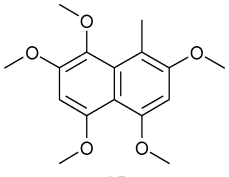


Fig. 9 (a) Calculated geometry (B3LYP/6-31G(d)) of **4** and (b) of the corresponding carbocation. The dihedral angles O1–C1–C2–C9: 11.040°, O1–C1–C–C8: 0.736°, C1–C2–C9–H: 3.782°, C2–C1–O1–C(H_3): 70.681°, C2–C3–O2–C(H_3): 3.259°, C4–C3–C2–C9: 14.260°, O2–C3–C2–C9: 12.613°,C5–C6–O3–C(H_3): 0.224° and C–C5–C6–O3: 0.238° show the distortion from planarity.

Seven methoxy substituents

To complete the picture, the carbocation formations from the two heptamethoxy methyl naphthalene systems have been included. These two isomers are extremely sterically crowded, and this results in extreme distortion of both the aromatic cores and the substituents from planarity. This distortion from planarity destabilizes both carbocations ($\mathbf{36}^+$ and $\mathbf{37}^+$) and results in a higher energy demand for their formation than

Table 6 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})[a]
 **33**	513
 **34**	523
 **35**	521

[a] B3LYP/6-31G(d) + zpve.

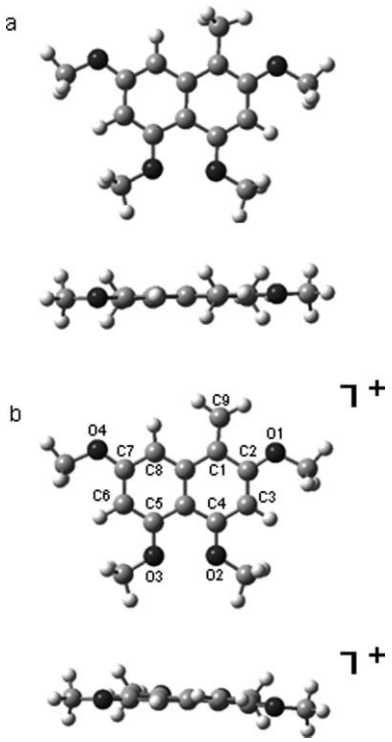


Fig. 10 (a) Calculated geometry (B3LYP/6-31G(d)) of **33** and (b) of the corresponding carbocation. The dihedral angles C9–C1–C2–O1: 5.940°, C9–C1–C–C8: 7.751°, C4–C3–C2–O1: 0.390° and C2–C3–C4–O2: 1.283° show some distortion from planarity.

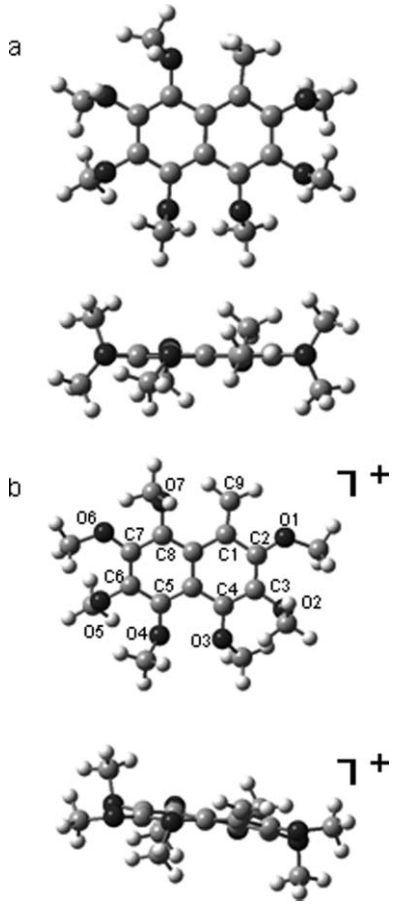


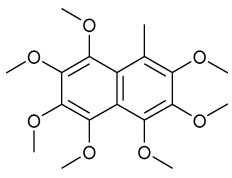
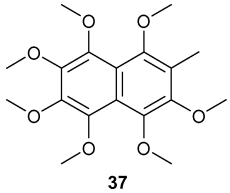
Fig. 11 (a) Calculated geometry (B3LYP/6-31G(d)) of **36** and (b) of the corresponding carbocation. The dihedral angles C9–C1–C2–O1: 13.750°, O1–C2–C3–O2: 3.640°, C8–C–C1–C9: 19.750°, C8–C–C1–C2: 14.544° and C8–C–C–C5: 8.702° show the distortion from planarity.

one might have anticipated based upon simple additivity of the various effects deduced in the previous sections (Table 7).

When comparing **36** and **37** with the two tetramethoxy substituted naphthalenes (**33** and **34**) the total energies are 4–6 kcal mol^{-1} higher when the three additional methoxy substituents are added. This shows that design is more important than brute-force addition of electron donating groups.

In Fig. 11 the calculated geometries related to isomer **36** are shown. They illustrate the enormous effect of steric congestion and make it clear why the stabilization of naphthyl methyl carbocations is not merely a matter of adding more methoxy substituents to the aromatic core.

Table 7 Energy difference between $ArCH_3$ and $ArCH_2^+$

Molecule ($ArCH_3$)	Δ Energy (kcal mol^{-1})[a]
 **36**	519
 **37**	527

[a] B3LYP/6-31G(d) + zpve.

Conclusions

It has been shown that a strategic placement of the methoxy groups is crucial for the maximum stabilization of naphthyl methyl carbocations. We have shown that the lowering of the energetic requirements for the formation of the carbocations upon addition of methoxy substituents onto the aromatic core is additive up until a certain point where the molecule becomes too crowded. An important structural feature that has to be obeyed in order to achieve maximum stability of naphthyl methyl carbocations is near-planarity of the carbocationic species. We observe that an angle of 8° out of the aromatic plane of the CH_2^+ substituent does not seem to disturb the stabilization of the carbocation. An out-of-plane rotation of the CH_3–O-group has a large effect. The disturbance of the oxygen lone-pair resonance seems to have the largest influence on the carbocation stability. This means, that if a methoxy substituent is forced out of the plane of the aromatic core (typically due to steric congestion) then the carbocation stabilization *via* (extended) conjugation is reduced and sometimes completely lost. These observations have given us a set of 'design rules' for the construction of the most stabile methoxy substituted naphthyl methyl carbocations. In short, the CH_2^+ substituent needs to be placed in the 1-position on the naphthalene core and this opens the possibility of placing two methoxy substituents in the favorable *ortho* and *para* positions without causing steric repulsion. On the opposite ring, it is possible to place two methoxy substituents that are in direct conjugation with the carbocation in the 1-position; those two positions are the 5- and 7-positions. This gives the tetramethoxy derivative, 2,4,5,7-tetramethoxy-1-methyl naphthalene (**33**), as the ideal candidate for the most stabile carbocation precursor. The two derivatives **28** and **29** are the most promising

candidates for the most stabile carbocations based on trimethoxy systems. They also follow the ideal design principles presented above.

References

1 J. P. Lowe and B. D. Silverman, *J. Am. Chem. Soc.*, 1981, **103**, 2852–2855.
2 J. P. Lowe and B. D. Silverman, *J. Am. Chem. Soc.*, 1984, **106**, 5955–5958.
3 J. P. Lowe and B. D. Silverman, *Acc. Chem. Res.*, 1984, **17**, 332–338.
4 (*a*) A. F. Lehner, J. Horn and J. W. Flesher, *THEOCHEM*, 1996, **366**, 203–217; (*b*) L. Doan, B. Lin, H. Yagi, D. M. Jerina and D. L. Whalen, *J. Am. Chem. Soc.*, 2001, **123**, 6785–6791; (*c*) L. Doan, H. Yagi, D. M. Jerina and D. L. Whalen, *J. Am. Chem. Soc.*, 2002, **124**, 14382–14387; (*d*) M. A. Graziewicz, J. M. Sayer, D. M. Jerina and W. C. Copeland, *Nucleic Acids Res.*, 2004, **32**, 397–405.
5 D. H. Phillips, *Nature*, 1983, **303**, 468–472.
6 J. March, in *Advanced Organic Chemistry*, Wiley, New York, 4th edn., 1992.
7 J. Alsina, K. J. Jensen, F. Albericio and G. Barany, *Chem.–Eur. J.*, 1999, **5**, 2787–2795.
8 I. W. James, *Tetrahedron*, 1999, **55**, 4855–4946.
9 J. Alsina and F. Albericio, *Biopolymers*, 2003, **71**, 454–477.
10 B. J. Backes and J. A. Ellman, *Curr. Opin. Chem. Biol.*, 1997, **1**, 86–93.
11 J. P. Richard, T. L. Amyes and M. M. Toteva, *Acc. Chem. Res.*, 2001, **34**, 981–988.
12 (*a*) A. Greenberg and B. D. Silverman, *J. Org. Chem.*, 1982, **47**, 3076–3081; (*b*) B. Reindl, T. Clark and P. v. R. Schelyer, *J. Phys. Chem. A*, 1998, **102**, 8953–8963.
13 G. A. Olah, R. D. Porter, C. L. Jeuell and A. M. White, *J. Am. Chem. Soc.*, 1972, **94**, 2044–2052.
14 D. Bethell and V. Gold, in *Carbenium Ions An Introduction*, Academic Press, London and New York, 1967, ch. 5, pp. 117–159.
15 C. D. Ritchie, *Acc. Chem. Res.*, 1972, **5**, 348–354.
16 D. A. Forsyth and G. A. Olah, *J. Am. Chem. Soc.*, 1979, **101**, 5309–5316.
17 D. A. Forsyth, R. J. Spear and G. A. Olah, *J. Am. Chem. Soc.*, 1976, **98**, 2512–2518.
18 T. M. Krygowski, M. K. Cyranski, K. Nakata, M. Fujio and Y. Tsuno, *Tetrahedron*, 1997, **53**, 11383–11398.
19 B. W. Laursen, F. C. Krebs, M. F. Nielsen, K. Bechgaard, J. B. Christensen and N. Harrit, *J. Am. Chem. Soc.*, 1998, **120**, 12255–12263.
20 U. Boas, J. B. Christensen and K. J. Jensen, *J. Comb. Chem.*, 2004, **6**, 497–503.
21 M. Pittelkow, U. Boas, M. Jessing, K. J. Jensen and J. B. Christensen, *Org. Biomol. Chem.*, 2005, **3**, 508–514.
22 U. Boas, J. Brask, J. B. Christensen and K. J. Jensen, *J. Comb. Chem.*, 2002, **4**, 223–228.
23 J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, S. J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, *GAUSSIAN 98 (rev. A.11.3)*, PA, Gaussian, Inc, 1998.
24 A. G. Baboul, L. A. Curtiss, P. C. Redfern and K. Raghavachari, *J. Chem. Phys.*, 1999, **110**, 7650–7657.
25 K. J. Jensen, J. Alsina, M. F. Songster, J. Vagner, F. Albericio and G. Barany, *J. Am. Chem. Soc.*, 1998, **120**, 5441–5452.
26 V. Balasubramaniyan, *Chem. Rev.*, 1966, **66**, 567–641.
27 E. Clar, in *The Aromatic Sextet*, Wiley, New York, 1972.