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Methyl/Phenyl Attraction by CH/π Interaction in 1,2-Substitution Patterns

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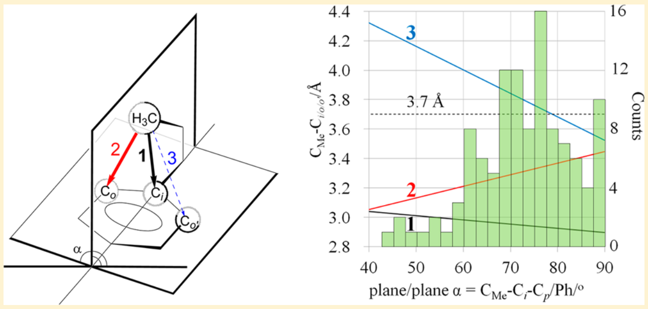
Supporting Information



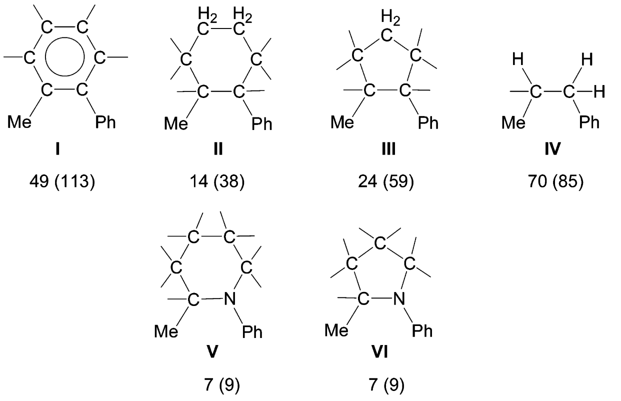
ABSTRACT: In 1,2-Me,Ph substitution patterns of organic compounds the methyl group attracts one of the phenyl sides to establish a CH/π bond with one of the *ortho* carbon atoms (the C_o side), leading to a characteristic tilting of the phenyl ring around its C_i−C_p axis. This phenyl rotation shortens the C_{Me}−C_o distances to bonding contacts between the methyl hydrogen atoms and the *ortho* carbon atom C_o well below the van der Waals distance of 3.70 Å. On the other hand, it elongates the C_{Me}−$C_{o'}$ distances outside of the reach of any CH/π interaction (>3.70 Å). Our study is based on a search in the Cambridge Structural Database for substructures Me−C═C−Ph, Me−C−C−Ph, and Me−C−N−Ph with 1,2-Me,Ph substitution patterns. In the 1,2-Me,Ph substitution motif the torsion angle C_{Me}−C−C−C_i determines the length of the C_{Me}−C_i and C_{Me}−C_o distances. For aromatic compounds these torsion angles are close to 0°, but in five- and six-membered ring compounds and in open-chain compounds the torsion angles vary considerably. Universally, for torsion angles up to 80° CH/π bonds were found, whereas the long C_{Me}−C_i and C_{Me}−C_o distances for torsion angles >80° do not allow a CH/π interaction. The results of the present CSD analysis are supported by calculations.

INTRODUCTION

The hydrogen bridge between electronegative elements has been recognized for a long time as an eminent and universal weak bond in chemistry and biochemistry, but it was only in 1998 that the breakthrough for another ubiquitous weak bond, the CH···C_{sp^2} interaction, was achieved with the advent of the book *The CH/π Interaction.*[1] Since then, a variety of reviews have dealt with the weak acceptor/donor bond of π systems with nearby C−H bonds.[2−11] However, even today the role of CH/π interactions in the stabilization of molecules is underestimated.

Recently, we carried out a conformational analysis of the metal−Prophos chelate ring in transition-metal complexes.[12] (*R*)-Prophos, Ph_2P−CHMe−CH_2−PPh_2, is a chiral standard ligand in enantioselective catalysis with transition-metal compounds.[4,13,14] In this study we came across a surprising motif, the methyl/phenyl attraction between the methyl group at the asymmetric center of the Prophos ligand and the adjacent phenyl rings of the PPh_2 group. In an active process the methyl group attracts one of the two sides of the phenyl rings to establish an effective CH/π interaction with one of the *ortho* carbon atoms. These results referred to the Me−C−PPh_2 system of M−Prophos chelate rings. In the present compilation analysis we extend these studies to prominent 1,2-Me,Ph substitution patterns in the substructures **I**−**VI** shown in Scheme 1. We confined our search to aromatic compounds, five- and six-membered carbocyclic systems, open-chain compounds of the type X−CH(Me)−CH_2Ph, and two N-heterocycles. The open ends of the bond lines indicate the positions left for variation. The number of compounds found is given in Scheme 1. As the motif of 1,2-Me,Ph substitution may be present in the same molecule several times and also in independent molecules, the number of cases to be analyzed increased appreciably (given in parentheses).

Scheme 1. Substructures Used in the Cambridge Structural Database Search and Number of Compounds (Number of Motifs) To Be Analyzed



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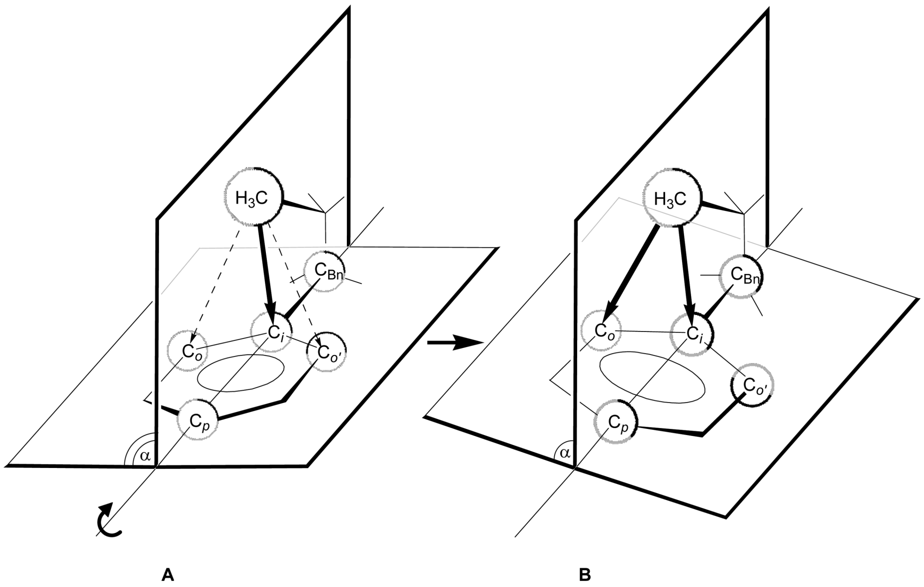
Scheme 2. Distances $C_{Me}-C_i$, $C_{Me}-C_o$, and $C_{Me}-C_{o'}$ in Structures A and B and Phenyl Rotation around the C_i-C_p Axis To Establish a Strong $H_{Me}-C_o$ Bond[a]



[a] C_{Bn} = benzylic carbon atom.

Nishio et al. reported extensive conformational analyses of molecules containing 1,2-Me,Ph substituents by high-level ab initio MO calculations and a crystallographic database survey.[15−17] However, these extensive studies did not address the specific problem of methyl/phenyl interactions to establish bonding between the methyl group and the *ortho* carbon atom of the phenyl by the characteristic tilting of the phenyl ring.

RESULTS AND DISSCUSSION

CH/π Bonding in 1,2-Me,Ph Substructures. We retrieved the compounds with the substructures of Scheme 1 from the Cambridge Structural Database (updated Aug 14, 2014).[18] We determined the torsion angle C_{Me}−C−C/N−C_i(Ph), an important parameter for the distances $C_{Me}-C_i$, $C_{Me}-C_o$, and $C_{Me}-C_{o'}$ (C_i, C_o and $C_{o'}$, and C_p = *ipso*, *ortho*, and *para* carbon atoms of Ph), and the plane/plane angle $C_{Me}-C_i-C_p$/Ph, abbreviated α (Scheme 2). In this order the five parameters torsion angle, distances, and plane/plane angle are given in the tables to follow.

CH−C_{sp^2} distances of up to 2.9−3.1 Å are assessed to be attractive, using the van der Waals radii 1.2−1.4 Å for H and 1.7 Å for C_{sp^2}, provided the overlap angles are large enough (see below).[1] For the C−H bonds of a methyl group a different approach is necessary. In X-ray analysis the hydrogen atoms are usually not determined from the electron density but are calculated at geometrically idealized positions. If not properly constrained or due to poor data quality, the hydrogen atoms of methyl groups can be incorrectly oriented along the X−CH_3 axis of the structure model. Therefore, we do not use the distances between the hydrogen atoms of the methyl group and the C_{sp^2} atoms at the *ipso* and *ortho* positions of the phenyl ring. Instead, we use the distance of the carbon atom of the methyl group (C_{Me}) to the *ipso* and *ortho* carbon atoms. There is precedence for such an approach.[1,12,19,20] Attractive interactions are indicated for distances smaller than the van der Waals radii, which are 2.0 Å for Me and 1.7 Å for C_{sp^2} (sum 3.7 Å).[1] It is important to note that, although the analysis is based on the distances $C_{Me}-C_{sp^2}$, the attractive forces are CH···C_{sp^2} interactions. Distances below 3.20 Å are considered strongly bonding. The distances 3.20−3.50 and 3.50−3.70 Å allow middle and weak CH/π interactions, respectively.

Effective CH/π interactions require not only short CH···C_{sp^2} contacts but also good overlap of the orbitals of the methyl group and the C_{sp^2} atoms. In structure **A** of Scheme 2 the plane $C_{Me}-C_i-C_p$ and the phenyl plane are perpendicular to each other (α = 90°). Consequently, the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ are identical and the overlap of the orbitals of the methyl group and the *ipso* carbon atom is optimal. However, the long distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ only allow weak $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ bonding. Rotation of the phenyl plane around the C_i-C_p axis leads to structure **B** with $\alpha < 90°$. This rotation does not change the $C_{Me}-C_i$ distance, but it dramatically changes the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$. In structure **B** the distance $C_{Me}-C_o$ is much shorter than $C_{Me}-C_{o'}$. This brings the *ortho* carbon atom C_o close to the methyl group, allowing for a strong CH/π interaction. In the following discussion the shorter of the two distances from the methyl carbon atom to the *ortho* carbon atoms is called $C_{Me}-C_o$. The bold arrows in **A** and **B** indicate the bonding interaction of the methyl hydrogen atoms with the delocalized system at the atoms C_i and C_o.

The plane/plane angle α = $C_{Me}-C_i-C_p$/Ph and the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ go hand in hand: the smaller the plane/plane angle α, the smaller the $C_{Me}-C_o$ distance and the larger the $C_{Me}-C_{o'}$ distance. On the other hand, the rotation definitely decreases the overlap of the orbitals of the methyl group and the C_i atom in comparison to structure **A**. To be effective, this decrease must be counterbalanced by the increasing C_{Me}/C_o interaction. Thus, the system will rotate so as to find the best compromise. The typical phenyl tilting, shown in **B**, is superior to the face-exposed arrangement in **A**, as confirmed by the compilation analysis and the calculations given below. For small plane/plane angles α the CH/π stabilization diminishes.

The torsion angles $C_{Me}-C-C_{Bn}-C_i$ in structures **A** and **B** are close to 0°. This is typical for 1,2-Me,Ph-substituted arenes. In saturated five- and six-membered rings and in open-chain

Table 1. 1,2-Me,Ph Substitution at Carbocyclic Aromatic Six-Membered Rings[a]

entry	CSD symbol[b]	torsion angle C_{Me}—C═C—C_i, deg	C_{Me}—C_i, Å	C_{Me}—C_o, Å	C_{Me}—$C_{o'}$, Å	plane/plane angle α (C_{Me}—C_i—C_p/Ph), deg
1	IBIFII(1)	0.2	2.98	3.20	(4.00)	61.1
5	PUNVAW[2](1)	0.4	2.89	3.47	3.50	89.0
11	NOQNEM[1](1)	0.9	2.97	3.34	(3.81)	74.2
18	SANPII	1.5	2.92	3.19	(3.82)	69.0
34	WEVYAY(1)	2.1	3.02	3.25	(4.05)	61.5
51	NOQPAK[2](3)	2.7	2.82	3.19	3.63	74.9
61	GAQQOG	3.5	2.97	3.15	(4.00)	60.0
72	VINWEU(2)	4.2	2.95	3.26	(3.87)	68.7
82	PARKUO[1]	5.3	3.06	3.09	(4.27)	43.4
95	PENBAN	5.9	3.00	3.55	(3.72)	84.2
111	MUJKIM[3]	8.7	3.01	3.13	(4.12)	53.7

[a] All other valences were left open in the search. Eleven examples with representative torsion angles C_{Me}—C═C—C_i were selected from Table S1 (Supporting Information). [b] In this column the brackets indicate independent molecules and parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

compounds the 1,2-Me,Ph substituents can adopt torsion angles from 0 to 180°. Large torsion angles increase the C_{Me}—Ph distances. The borderline for bonding is 3.70 Å for distances C_{Me}—C_i and C_{Me}—C_o.[1,12]

The Motif 1,2-Me,Ph Attraction. In a 1,2-Me,Ph substitution pattern a given torsion angle C_{Me}—C—C/N—C_i sets up a certain C_{Me}—C_i distance, as shown by the bold arrow for C_{Me}—C_i in structure **A** of Scheme 2. Conformer **A** has identical C_{Me}—C_o and C_{Me}—$C_{o'}$ distances (dashed arrows). In conformer **B**, however, C_o is much closer to C_{Me} (bold line) than to $C_{o'}$, indicating an attraction of the C_o side by the methyl group. This Me/Ph attraction is a universal structural feature in 1,2-Me,Ph-substituted compounds, as will be demonstrated by Tables 1−6, provided the torsion angles C_{Me}—C—C/N—C_i are not too large.

Ordering in Tables 1−6 is done according to the torsion angles C_{Me}—C—C/N—C_i, which determine the distance between the methyl group and the *ipso* carbon atom of the phenyl ring. It is important to note that the torsion angles C_{Me}—C—C/N—C_i and plane/plane angles α are independent of each other, whereas distances C_{Me}—C_o and C_{Me}—$C_{o'}$ are correlated with the plane/plane angle α. The analysis of aromatic six-membered rings contains 113 cases (Table 1 and Table S1 (Supporting Information)). In the text a truncated Table 1 with only 11 typical entries is presented and the complete Table S1 is given in the Supporting Information. A histogram in the text illustrates relevant distances of all the compounds in Table S1. The same procedure is used for all the other tables.

1,2-Me,Ph Substitution in Compounds with an Aromatic Six-Membered Ring and Four Open Valences (Substructure I). For the aromatic derivatives, discussed here, the carbon atom C_{Bn} in Scheme 2 is not a benzylic carbon atom but an sp^2-hybridized arene carbon atom. Due to C_{sp^2} hybridization in the benzene ring the torsion angles C_{Me}—C═C—C_i should be close to 0°. They actually extend from 0.2 to 11.4° (Table 1 and Table S1 (Supporting Information)).

The distances C_{Me}—C_i of all 113 entries in Table S1 (Supporting Information) are between 2.82 and 3.10 Å, allowing strong CH/π bonding. More important, however, for the aspect of phenyl tilting are the C_{Me}—C_o distances to establish a strong interaction of the methyl group with one of the *ortho* carbon atoms. These C_{Me}—C_o distances start at 3.02 Å, and all are below the borderline of 3.70 Å. Most of them are concentrated between 3.20 and 3.40 Å in an area of relatively strong bonding. Only 10 of the C_{Me}—C_o distances fall into the weakly bonding range of 3.50−3.60 Å, and 1 at 3.68 Å is close to the borderline. This attraction of the C_o side of the phenyl ring by the methyl group goes at the cost of the $C_{o'}$ side. Only 36 of the 113 cases make it into the bonding range below 3.70 Å, but none of them are below 3.49 Å. Six C_{Me}—$C_{o'}$ distances profit from the large plane/plane angles α, which result in small differences between C_{Me}—C_o and C_{Me}—$C_{o'}$ of 0−0.3 Å. Distances above 3.70 Å, too long for CH—C_{sp^2} interactions, are given in parentheses. The plane/plane angles α do not drop below 43°. They are all in a range to establish strong CH/π bonding of the methyl group with the attracted C_o side of the phenyl ring. The histogram in Figure 1 gives a survey for all the compounds in Table S1. Different from the organization in Table 1 and Table S1, the distances C_{Me}—$C_{i/o/o'}$ are plotted as a function of the plane/plane angle α. The average plane/plane angle α is 72.6°, and the average C_{Me}—C_o distance is 3.31 Å.

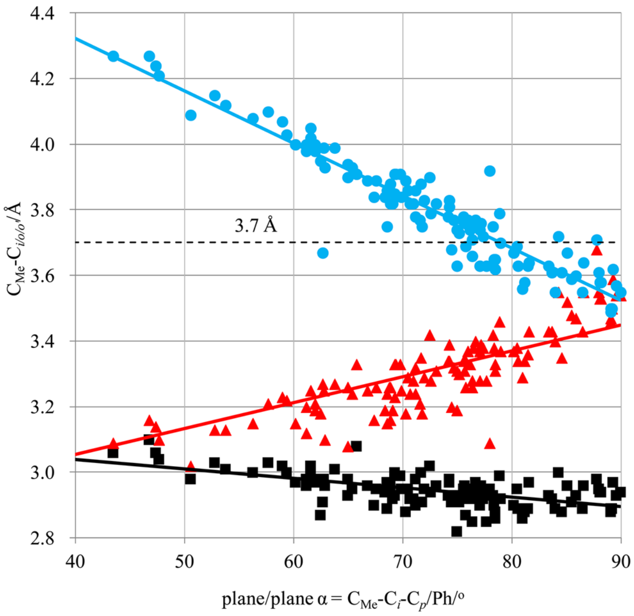


Figure 1. Distances C_{Me}—C_i (black ■), C_{Me}—C_o (red ▲), and C_{Me}—$C_{o'}$ (blue ●) as a function of the plane/plane angle α (C_{Me}—C_i—C_p)/Ph for the aromatic six-membered ring compounds of Table S1 (Supporting Information).

Table 2. 1,2-Me,Ph Substitution at Saturated Carbocyclic Six-Membered Rings with CH_2 Groups at the 4,5-Positions[a]

entry	CSD symbol[b]	*cis*/*trans* position	torsion angle C_{Me}–C–C_{Bn}–C_i, deg	C_{Me}–C_i, Å	C_{Me}–C_o, Å	C_{Me}–$C_{o'}$, Å	plane/plane angle α (C_{Me}–C_i–C_p/Ph), deg
1	QASQOR[1](1)	*cis*	0.8	2.81	3.32	3.41	86.7
6	QASQOR[2](3)	*cis*	5.4	2.80	3.33	3.33	89.9
7	DAJGIF(1)	*cis*	10.6	2.78	3.25	3.33	88.2
8	QIMGUO(2)	*cis*	33.6	2.94	3.32	3.68	78.5
11	LEQMAW[1]	*trans*	47.4	2.92	3.35	3.66	79.4
17	TEFYUZ	*trans*	53.1	2.97	3.58	3.61	88.3
19	ITAKOD(1)	*trans*	54.3	3.01	3.54	(3.80)	80.4
22	ITAKOD(2)	*cis*	62.3	3.15	3.30	(4.23)	55.8
25	DAJGIF(3)	*trans*	110.5	3.60	(3.82)	(4.75)	48.5
28	QASQOR[2](8)	*trans*	119.2	3.67	(3.96)	(4.83)	44.4
33	LEQMEA[1]	*trans*	152.9	(3.83)	(4.42)	(4.86)	59.5

[a] All other valences were left open in the search. Eleven examples with representative torsion angles C_{Me}–C–C_{Bn}–C_i were selected from Table S2 (Supporting Information). [b] In this column brackets indicate independent molecules and parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

1,2-Me,Ph Substitution in Compounds with Carbocyclic Six-Membered Rings and CH_2 Groups in 4,5-Position (Substructure II). Unlike the aromatic compounds in Table 1 and Table S1 (Supporting Information), the torsion angles C_{Me}–C–C_{Bn}–C_i in saturated compounds with carbocyclic six-membered rings can vary appreciably. Interestingly, Table 2 and Table S2 (Supporting Information) show that the torsion angles C_{Me}–C–C_{Bn}–C_i of the 38 cases cluster in the ranges 0–15, 35–65, 110–130, and 150–170°. For torsion angles up to 63.5° strong bonds C_{Me}–C_i and C_{Me}–C_o are established, irrespective of the *cis* or *trans* position of the Me/Ph substituents at the six-membered ring. The distances C_{Me}–C_i are between 2.77 and 3.29 Å, indicating a strong interaction of the methyl group with the *ipso* carbon atom of the phenyl ring, which at least in part is a consequence of geometrical constraints for small torsion angles (entries 1–24). Typically, with 3.11–3.35 Å the distances C_{Me}–C_o show that the characteristic phenyl rotation makes for strong bonds between the methyl group and the near *ortho* carbon atom C_o in all of entries 1–24 except 17. On the other hand, only a few C_{Me}–$C_{o'}$ distances show weak bonding to the distant *ortho* carbon atom $C_{o'}$ with distances of 3.33–3.68 Å. Characteristically, for torsion angles larger than 110° the distances C_{Me}–C_i and C_{Me}–C_o are close to or above 3.70 Å and there are no Me/Ph interactions.

For torsion angles from 0 to 63.5° there is no correlation to the distances C_{Me}–C_i and C_{Me}–C_o. All distances are in the strongly bonding regime. However, the correlation between the distances C_{Me}–C_o and C_{Me}–$C_{o'}$ and the plane/plane angle α is obvious. The larger the α value, the closer together are C_{Me}–C_o and C_{Me}–$C_{o'}$. QASQOR[2](3) and TEFYUZ (entries 6 and 17) are the only examples in Table 2, which match up with the symmetrical structure of type **A** (Scheme 2). They have short C_{Me}–C_i bonds but rather long C_{Me}–C_o contacts. In all other examples with torsion angles below 65° there is a clear differentiation between the C_{Me}–C_o and C_{Me}–$C_{o'}$ distances, demonstrating the characteristic phenyl rotation.

The histogram in Figure 1 for the compounds of Table S1 (Supporting Information) had been organized according to the plane/plane angle α, because the torsion angles C_{Me}–C=C–C_i for aromatic compounds are close to 0°. Differently, in the compounds of Table 2 and all the other tables the torsion angles C_{Me}–C–C_{Bn}–C_i are the conformation-determining parameters. Therefore, the histograms in Figures 2–4 and Figures S1 and S2 (Supporting Information) present the distances C_{Me}–$C_{i/o/o'}$ as a function of the torsion angles C_{Me}–C–C_{Bn}–C_i. The histogram in Figure 2 clearly shows the clustering into the four areas mentioned above.

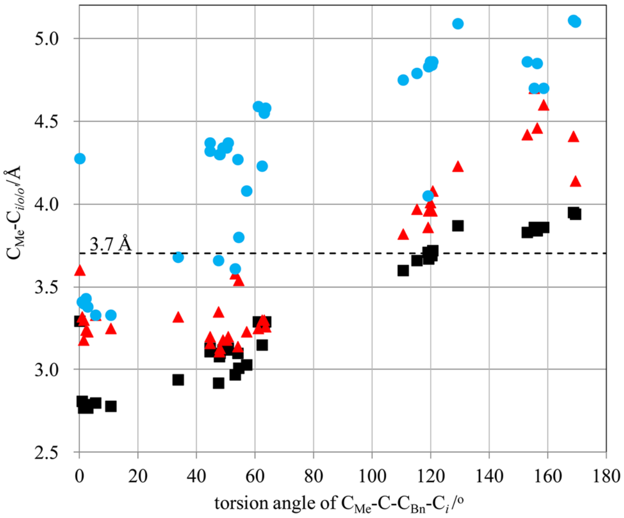


Figure 2. Distances C_{Me}–C_i (black ■), C_{Me}–C_o (red ▲), and C_{Me}–$C_{o'}$ (blue ●) as a function of the torsion angles C_{Me}–C–C_{Bn}–C_i for the carbocyclic six-membered ring compounds of Table S2.

1,2-Me,Ph Substitution in Compounds with Carbocyclic Five-Membered Rings and a CH_2 Group in 4-Position (Substructure III). The 11 entries in Table 3 (59 entries in Table S3 (Supporting Information)) show the same trends as Table 2 and Table S2 (Supporting Information). The distances C_{Me}–C_i start at 2.77 Å and stay in the strongly bonding regime for torsion angles up to 80° (entries 1–36). Due to the rotation of the phenyl ring ($\alpha < 90°$) the distances C_{Me}–C_o of entries 1–36 demonstrate relatively strong bonding with distances between 3.10 and 3.50 Å. On the other hand, the phenyl tilting, establishing bonding between the methyl group and the *ortho* carbon atom C_o, moves the other *ortho* carbon atom $C_{o'}$ outside bonding contact with the methyl group, except in 9 cases at the top of Table S3 with plane/plane angles between 89.9 and 83.3°. For torsion angles 110–120° (entries 38–44) C_{Me}–C_i distances of about 3.60–3.70 Å indicate weak Me–C_i bonding. Higher torsion angles prevent any intramolecular CH/π interactions (entries 45–59).

Table 3. 1,2-Me,Ph Substitution at Saturated Carbocyclic Five-Membered Rings with a CH_2 Group at the 4-Position[a]

entry	CSD symbol[a]	*cis*/*trans* position	torsion angle $C_{Me}-C-C_{Bn}-C_i$, deg	$C_{Me}-C_i$, Å	$C_{Me}-C_o$, Å	$C_{Me}-C_{o'}$, Å	plane/plane angle α ($C_{Me}-C_i-C_p$/Ph), deg
3	QASQOR[2](1)	*cis*	1.4	2.79	3.30	3.41	86.3
8	DAJGIF(1)	*cis*	10.6	2.78	3.25	3.33	87.4
9	PONJIL	*cis*	15.5	2.98	3.26	(3.88)	68.5
11	DUVVEW	*cis*	30.6	2.89	3.40	3.52	86.5
15	PAGLEO	*cis*	45.6	3.02	3.25	(4.03)	62.3
27	FAPKUC	*trans*	57.4	3.15	3.25	(4.25)	55.2
33	PAGLOY(2)	*cis*	65.6	3.24	3.47	(4.27)	53.0
36	PAGKUD(2)	*trans*	76.9	3.26	3.44	(4.40)	51.9
37	YAFGAN	*trans*	85.4	3.30	(3.73)	(4.24)	69.8
38	FEGLAF	*trans*	109.7	3.67	(4.34)	(4.53)	82.2
51	LIGCAG[2](2)	*trans*	155.8	(3.90)	(4.68)	(4.74)	87.3

[a] All other valences were left open in the search. Eleven examples with representative torsion angles $C_{Me}-C-C_{Bn}-C_i$ were selected from Table S3 (Supporting Information). [a] In this column brackets indicate independent molecules and parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

The histogram in Figure 3 contains the carbocyclic five-membered ring compounds of Table S3 (Supporting Information). It shows the same clustering into four areas as for the six-membered ring compounds in Figure 2.

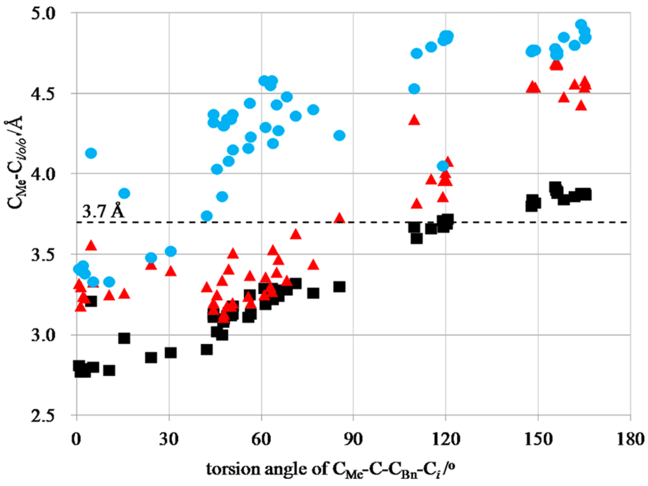


Figure 3. Distances $C_{Me}-C_i$ (black ■), $C_{Me}-C_o$ (red ▲), and $C_{Me}-C_{o'}$ (blue ●) as a function of the torsion angles $C_{Me}-C-C_{Bn}-C_i$ for the carbocyclic five-membered ring compounds of Table S3 (Supporting Information).

Open-Chain Methyl/Benzyl Compounds (Substructure IV). In a search of the substructure $-CH(Me)-CH_2Ph$ with one valence left open, 70 compounds were found. When independent molecules were included, 85 cases had to be analyzed (Table 4 and Table S4 (Supporting Information)). In addition to the 3 structures in which the parent molecule *n*-propylbenzene ($Me-CH_2-CH_2-Ph$) is present as a solvent (entries 70−72), the search embraced all the chiral compounds XCH(Me)(Bn) with a hydrogen atom, a methyl group, and a benzyl group at the asymmetric carbon atom. Different from the compounds in Tables 1−3, derivatives $XCH(Me)-CH_2Ph$ are open-chain compounds, in which the torsion angle $C_{Me}-C-C_{Bn}-C_i$ may adopt all of the values between 0 and ±180°. It is surprising that the torsion angles $C_{Me}-C-C_{Bn}-C_i$ crowd within the two narrow ranges 52.3−80.7 and 157.6−179.6° (except for entry 1). The large ranges between 0 and 52° (except for entry 1) and 81−157° are empty, an unexpected side effect. Another interesting aspect is that entries 10 and 62 are two independent molecules of OCUWAK, which belong to the two different cluster areas.

Twenty-five of the 85 cases have torsion angles of 157−180° (end of Table 4 and Table S4 (Supporting Information)), which result in an almost stretched $Me-C-C_{Bn}-Ph$ conformation. In all of these stretched molecules (entries

Table 4. 1,2-Me,Ph Substitution in Methyl/Benzyl Compounds[a]

entry	CSD symbol[b]	torsion angle $C_{Me}-C-C_{Bn}-C_i$, deg	$C_{Me}-C_i$, Å	$C_{Me}-C_o$, Å	$C_{Me}-C_{o'}$, Å	plane/plane angle α ($C_{Me}-C_i-C_p$/Ph), deg
1	PICJUG	22.3	2.96	3.58	3.59	88.6
2	AMPHMI	52.3	2.93	3.42	3.66	82.1
6	XIMVAQ	56.5	2.97	3.42	(3.74)	79.4
14	SUMYUU	60.2	2.97	3.62	3.69	85.1
33	AMPETP	65.3	3.13	3.55	(4.01)	72.3
40	FAKHOO	68.5	3.12	3.39	(4.14)	61.5
47	MPALCU[2]	72.1	3.19	3.64	(4.10)	72.2
58	MOYDUZ	76.0	3.17	3.65	(4.07)	73.5
60	QACCON	80.7	3.22	3.53	(4.21)	62.4
61	URUQAA	157.6	(3.85)	(4.39)	(4.92)	49.0
80	MEXVUI[2]	178.3	(3.89)	(4.62)	(4.83)	72.4

[a] One valence was left open at the CH(Me)Bn fragment in the search. Eleven examples with representative torsion angles $C_{Me}-C-C_{Bn}-C_i$ were selected from Table S4 (Supporting Information). [b] In this column brackets indicate independent molecules and parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

61−85) there is no CH/π interaction between the methyl group and the phenyl ring, including the structures with *n*-propylbenzene as solvent molecules. For *n*-propylbenzene and benzylmethyl ether detailed conformational analyses have been reported.[21] In Table 4 the beginning and the end of the range 157−180° are shown as the last two entries.

The majority of the 59 cases falls into the narrow range 52−81° for the torsion angle $C_{Me}-C-C_{Bn}-C_i$. With 2.93−3.23 Å all of the $C_{Me}-C_i$ distances confirm strong bonding and all of the $C_{Me}-C_o$ distances make it into bonding contact, except for six cases with plane/plane angles $\alpha > 80°$ (Table S4 (Supporting Information)). Such large plane/plane angles tend to adjust the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$, indicating little phenyl tilting. This brings 5 of the distances $C_{Me}-C_{o'}$ into bonding contact, whereas the other 54 distances $C_{Me}-C_{o'}$ are above 3.70 Å as a consequence of the attraction of the C_o side of the phenyl ring by the methyl group.

The drugs amphetamine and *N*-methylamphetamine are members of the class of open-chain compounds with the substructure $Ph-CH_2-CH-Me$. Table S4 (Supporting Information) contains 1 structure of amphetamine in a calixarene, 4 examples of protonated amphetamine, and 10 examples of protonated *N*-methylamphetamine with different anions. Due to the occurrence of independent molecules these 15 compounds result in a total of 26 entries in Table S4. In the neutral and protonated forms of amphetamine and *N*-methylamphetamine there is a competition of the $NH_2/NHMe$ and NH_3^+/NH_2Me^+ groups on the one side and the Me group on the other side for interaction with the phenyl ring. According to calculations (gas phase) and spectroscopic studies (solution) the $NH_2/NHMe$ and NH_3^+/NH_2Me^+ groups establish interaction with the phenyl ring.[22−24] In the solid state, however, this is different. The NH_3^+/NH_2Me^+ groups interact with the anions in a stretched conformation with respect to the $Ph-C-C-N$ unit. This brings the methyl group close to the phenyl ring with torsion angles between 55.9 and 74.8°. Three cases are exceptions, which have stretched conformations of the $Ph-C-C-Me$ unit. The other 23 cases show the characteristic phenyl tilting with formation of the typical $CH-C_{sp^2}$ bond between the methyl group and C_o of the phenyl ring (Table S4). Five examples of amphetamine and *N*-methylamphetamine are included in Table 4 (entries 2, 33, 40, 47, and 80).

The histogram in Figure 4 presents the open-chain compounds of Table S4 (Supporting Information). Interestingly, clustering of the open-chain compounds, for which in principle all torsion angles $C_{Me}-C-C_{Bn}-C_i$ from 0 to 180° are available, only occurs in the two areas discussed above.

1,2-Me,Ph Substitution in Compounds with Saturated C_5N Rings and All Other Valences Left Open (Substructure V). The motif $Me-C-N-Ph$ was found in 7 compounds with saturated C_5N rings; 9 cases had to be analyzed. It is only in the first entry of Table 5 that the disfavored $C_{Me}-C_{o'}$ distance with 3.62 Å makes it into bonding contact. This is due to the large plane/plane angle α of 85.2°, which equalizes the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$. In all other cases the distances $C_{Me}-C_{o'}$ are out of reach for bonding. On the other hand, the $C_{Me}-C_i$ and $C_{Me}-C_o$ distances of entries 1−8 with torsion angles $C_{Me}-C-N-C_i$ between 22 and 76° are well within strong bonding contact. Even for entry 9 with a torsion angle of 92.9° the distances $C_{Me}-C_i$ and $C_{Me}-C_o$ are very short. In this case, however, CH/π interactions are negligible, as the plane/plane angle α is only 22.1°, preventing good overlap of the orbitals of the methyl group and C_i/C_o of the phenyl ring.

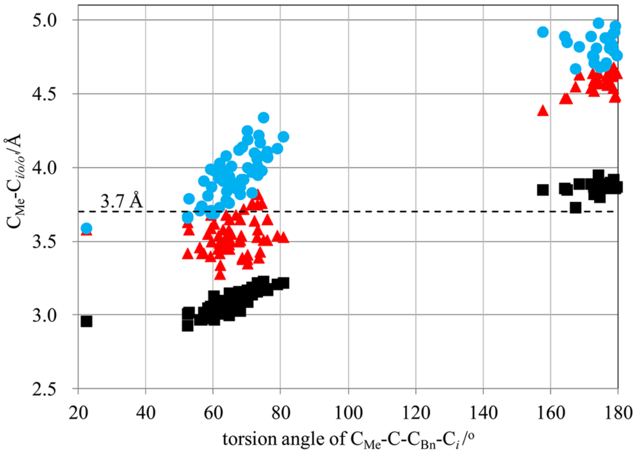


Figure 4. Distances $C_{Me}-C_i$ (black ■), $C_{Me}-C_o$ (red ▲), and $C_{Me}-C_{o'}$ (blue ●) as a function of the torsion angles $C_{Me}-C-C_{Bn}-C_i$ for the open-chain compounds of Table S4 (Supporting Information).

1,2-Me,Ph Substitution in Compounds with Saturated C_4N Rings and All the Other Valences Left Open (Substructure VI). For the 7 compounds (9 cases) in Table 6 exactly the same arguments apply as for the entries in Table 5.

Intermolecular Interactions. In the 49 aromatic compounds of Table S1 (Supporting Information) we looked for intermolecular contacts $C_{Me}\cdots C_{sp^2}$ below 3.7 Å and $CH\cdots C_{sp^2}$ below 2.9 Å, using the program OLEX2,[38] as we had done in the study of the CH/π interactions in M−Prophos chelate rings.[12] Table S5 in the Supporting Information gives the results. For 4 compounds we found intermolecular contacts $C_{Me}\cdots C_{i/o/m/p}$ below 3.7 Å and for 11 compounds contacts $C_{o/m/p}H\cdots C_{i/o/m/p}$ below 2.9 Å. No concise picture is emerging, as expected for compounds as different as the 49 arenes in Table S1. Therefore, we did not take into account other intermolecular contacts and packing effects, because they also should lead to situations which are different for each specific case.

■ THEORETICAL ASPECTS

For calculations we chose the parent compound 1,2-methylphenylbenzene (2-methylbiphenyl). We constructed the molecule on the basis of the following preconditions. The phenyl substituent was kept perpendicular to the benzene ring and one of the C−H bonds of the methyl group was placed in the plane of the benzene ring and oriented to C_i of the phenyl substituent. The perpendicular arrangement of the phenyl ring with respect to the benzene plane produced a structure of type **A** (Scheme 2) and guaranteed identical distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$, excluding any phenyl rotation around its C_i-C_p axis. Optimization resulted in structure $\mathbf{A_1}$ with C_s symmetry (Table 7). In structure $\mathbf{A_1}$ there is a short $C_{Me}-C_i$ contact of 3.00 Å (bold arrow). However, with 3.63 Å the distances $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ indicate only weak CH/π interactions, shown by dashed arrows in Scheme 3.

Canceling the maintenance of C_s symmetry leads to the local minimum structure $\mathbf{B_1}$ with C_1 symmetry. $\mathbf{B_1}$ is more stable than $\mathbf{A_1}$ by 4.80 kcal/mol on the B3LYP-D3/def2-TZVPP level. The $C_{Me}-C_i$ distance in $\mathbf{B_1}$ is similar to that in $\mathbf{A_1}$. However, phenyl rotation now makes the big difference. The short $C_{Me}-C_o$ contact of 3.18 Å allows a strong CH/π bond (bold arrow in Scheme 3), whereas with 4.09 Å the $C_{Me}-C_{o'}$ distance is out of reach for any CH/π interaction. This strong differentiation between C_o and $C_{o'}$ is caused by the plane/plane angle $\alpha = 56.9°$, indicating the characteristic phenyl rotation around its C_i-C_p axis. Including the torsion angle $C_{Me}-C{=}C-C_i$ of 1.2° structure

Table 5. 1,2-Me,Ph Substitution at the Saturated C_5N Ring (Ph at N)[a]

entry (ref)	CSD symbol[b]	torsion angle $C_{Me}-C-N-C_i$, deg	$C_{Me}-C_i$, Å	$C_{Me}-C_o$, Å	$C_{Me}-C_{o'}$, Å	plane/plane angle α ($C_{Me}-C_i-C_p$/Ph), deg
1 (25)	AHUDUC	21.7	2.94	3.48	3.62	85.2
2 (26)	GEFMEL(1)	49.2	2.88	3.15	(3.87)	64.6
3 (27)	CENCEF	50.1	2.89	3.13	(3.90)	63.0
4 (28)	GAGRAI	66.6	3.08	3.21	(4.26)	47.3
5 (29)	CINKEQ	67.8	3.12	3.34	(4.24)	53.8
6 (30)	COKZEI	69.8	3.20	3.27	(4.46)	37.8
7 (26)	GEFMEL(2)	71.7	3.02	3.20	(4.13)	54.2
8 (31)	FECQOU(1)	75.6	3.20	3.38	(4.38)	46.1
9 (31)	FECQOU(2)	92.9	3.35	3.48	(4.64)	22.1

[a] All other valences were left open in the search. [b] In this column parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

Table 6. 1,2-Me,Ph Substitution at the Saturated C_4N Ring (Ph at N)[a]

entry (ref)	CSD symbol[b]	torsion angle $C_{Me}-C-N-C_i$, deg	$C_{Me}-C_i$, Å	$C_{Me}-C_o$, Å	$C_{Me}-C_{o'}$, Å	plane/plane angle α ($C_{Me}-C_i-C_p$/Ph), deg
1 (32)	KEQBUD	33.9	3.05	3.47	(3.87)	75.4
2 (33)	DIXHOH	45.7	2.99	3.30	(3.94)	66.4
3 (34)	WEHZIT	48.3	3.01	3.61	3.68	87.5
4 (35)	DIVYUC(1)	50.1	3.03	3.21	(4.11)	55.9
5 (36)	ZUPGUM	51.6	3.10	3.08	(4.38)	32.9
6 (35)	DIVYUC(2)	53.1	3.00	3.32	(3.96)	66.2
7 (37)	LAZREJ(1)	66.3	3.12	3.22	(4.45)	38.4
8 (30)	COKZEI	69.8	3.20	3.27	(4.46)	37.8
9 (37)	LAZREJ(2)	77.0	3.21	3.33	(4.48)	33.8

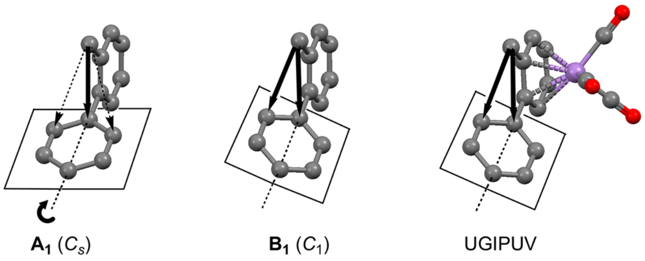
[a] All other valences were left open in the search. [b] In this column parentheses indicate repeating 1,2-Me,Ph motifs in the same molecule.

Table 7. Optimized Geometry of 1,2-Me,Ph−Benzene and 1,2-Me,Ph−Cyclohexane Derivatives at the B3LYP-D3/def2-TZVPP Level

entry	structure	torsion angle $C_{Me}-C-C-C_i$, deg	$C_{Me}-C_i$, Å	$C_{Me}-C_o$, Å	$C_{Me}-C_{o'}$, Å	plane/plane angle α ($C_{Me}-C_i-C_p$/Ph), deg
1[a]	**A_1** (1,2-Me,Ph)	0	3.00	3.63	3.63	90
2[a]	**B_1** (1,2-Me,Ph)	1.2	3.01	3.18	(4.09)	56.9
3[b]	(*cis*-1,2-Me_{ax},Ph_{equ})	59.2	3.07	3,46	(3.93)	74.1
4[b]	(*cis*-1,2-Me_{equ},Ph_{ax})	47.1	3.00	3.62	3.65	88.8
5[b]	(*trans*-1,2-Me_{equ},Ph_{equ})	56.6	3.02	3.65	3.67	89.2

[a] Benzene derivatives. [b] Cyclohexane derivatives.

Scheme 3. Optimized Structures of 2-Methylbiphenyl, A_1 with C_s Symmetry and B_1 with C_1 Symmetry, and the Cation of $[(2\text{-Methylbiphenyl})Mn(CO)_3]BF_4$ (UGIPUV)



A_1 (C_s) B_1 (C_1) UGIPUV

B_1 would be a typical member of the aromatic compounds in Table 1 and Table S1 (Supporting Information).

In addition to the distances $C_{Me}-C_{i/o}$ in the calculated structures $\mathbf{A_1}$ and $\mathbf{B_1}$ the distances $H_{Me}-C_{i/o}$ can be discussed, which mediate the CH/π interaction. In the C_s structure **A1** one of the hydrogen atoms (H_{Me}) of the methyl group was placed in the plane of its benzene ring, perpendicular to the other benzene ring, and oriented to C_i of the phenyl substituent (Scheme 4, left side). Its distance $H_{Me}-C_i = 2.53$ Å is well within the bonding regime, whereas the distances $H_{Me}-C_o = H_{Me}-C_{o'} = 3.01$ Å are at the borderline. The van der Waals distances for $H-C_{sp^2}$ are 2.9−3.1 Å.[1] In the C_1 structure **B1** these distances are $H_{Me}-C_i = 2.72$ Å, $H_{Me}-C_o = 2.88$ Å, and $H_{Me}-C_{o'} = 3.55$ Å. Thus, phenyl tilting brings the *ortho* carbon atom C_o into bonding contact with H_{Me}. The hydrogen atom H_{Me} is somewhat displaced from its position in the plane of its benzene ring and perpendicular to the other benzene ring. The torsion angle $H_{Me}-C-C-C_i$ is 33.0° (Scheme 4).

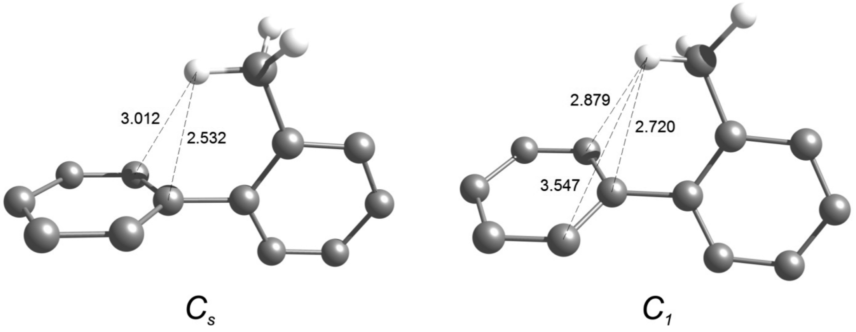
We carried out similar calculations with the following three isomers of 1,2-Me,Ph-cylohexane in the chair conformation: *cis*-1,2-Me_{equ},Ph_{ax}, *cis*-1,2-Me_{ax},Ph_{equ}, and *trans*-1,2-Me_{equ},Ph_{equ}. We did not include isomer *trans*-1,2-Me_{ax},Ph_{ax} because of its large torsion angle $C_{Me}-C-C_{Bn}-C_i$. The results concerning the local minima are given in Table 7. The isomer *cis*-1,2-Me_{ax},Ph_{equ} shows the typical phenyl tilting with a plane/plane angle $\alpha = 74.1°$ and a large difference in the $C_{Me}-C_o$ and $C_{Me}-C_{o'}$ distances (3.46 and 3.93 Å). For the two isomers *cis*-1,2-Me_{equ},Ph_{ax} and *trans*-1,2-Me_{equ},Ph_{equ} only small phenyl rotations were found in the calculations.

The oily 2-methylbiphenyl, the parent compound of the 1,2-Me,Ph-benzene derivatives in Table 1 and Table S1 (Supporting Information), refused to crystallize. However, the structure of its cationic $Mn(CO)_3$ complex is known and shown in Scheme 3 (UGIPUV, entry 35 in Table S1).[39] The plane/plane angle $\alpha = 52.7°$ is close to that of the calculation of 2-methylbiphenyl (56.9°). In addition, the existence of strong $H_{Me}-C_o/\pi$ bonds and the absence of any $H_{Me}-C_{o'}/\pi$ interactions are very similar in both cases.

■ CONCLUSION

In 1,2-Me,Ph substitution patterns of organic compounds the phenyl ring does not adopt a face-exposed arrangement with

Scheme 4. Calculated Distances $H_{Me}-C_i$ and $H_{Me}-C_o$ of 2-Methylbiphenyl in A_1 with C_s Symmetry and B_1 with C_1 Symmetry



respect to the methyl group. Instead, the methyl group attracts one of the phenyl sides to establish a CH/π bond with one of the *ortho* carbon atoms, leading to a characteristic tilting of the phenyl ring around its C_i-C_p axis.

For 1,2-Me,Ph-substituted arenes the average plane/plane angle α ($C_{Me}-C_i-C_p$/Ph) is 72.6°, indicating phenyl tilting. The average $C_{Me}-C_o$ distance (3.31 Å) is well below the van der Waals distance of 3.70 Å.

In the 1,2-Me,Ph substitution motif the torsion angle $C_{Me}-C-C-C_i$ determines the length of the $C_{Me}-C_i$ and $C_{Me}-C_o$ distances. For aromatic compounds the torsion angles $C_{Me}-C{=}C-C_i$ are close to 0°, but in five- and six-membered ring compounds and in open-chain compounds the torsion angles $C_{Me}-C-C-C_i$ vary appreciably. Universally, for torsion angles up to 80° CH/π bonds were found, whereas the long $C_{Me}-C_i$ and $C_{Me}-C_o$ distances for torsion angles >80° do not allow CH/π interaction.

The characteristic phenyl rotation in 1,2-Me,Ph substitution patterns to build up a strong CH/π bond from the methyl hydrogen atoms to one of the *ortho* carbon atoms is the message of this paper.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete Tables S1−S4 as well as references for all the compounds, Table S5 with the intermolecular CH/π interactions of the aromatic compounds in Table S1, Tables S6−S10 with the atom coordinates/energies of the calculations, and Figures S1 and S2 with the histograms of the compounds in Tables 5 and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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