New Crystalline Hosts Based on Tartaric Acid. Synthesis, Inclusion Properties, and X-ray Structural Characterization of Interaction Modes with Alcohol Guests

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A series of host molecules derived from tartaric acid have been synthesized in optically resolved and racemic forms. Apart from two endo hydroxyl functions and four bulky aromatic groups (TADDOL-type = α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanols), they have specific polar and apolar substituents of different size, in different number, and in different positions laterally attached to the molecular framework as the characteristic features. These hosts form crystalline inclusion compounds with uncharged organic molecules ranging from protic dipolar (alcohols, amines) to apolar compounds (in all 143 different inclusion species). Inclusion formation, host:guest stoichiometric ratios, and interaction modes depend on the structural features of the host, as supported by X-ray crystallographic studies in nine cases involving MeOH, EtOH, and 2-PrOH. The optically resolved host species with Me and F substituents form linear (spiral) host–guest H-bonded chains in compounds containing MeOH guests, circular motifs of H-bonds in crystals consisting of the racemic host species, while in the presence of larger guest alcohols (2-PrOH) a finite noncyclic H-bonded cluster occurs with the chiral constituents. The crystal packings in structures involving the tetrachloro-substituted hosts and MeOH as guest are dominated by specific Cl···Cl nonbonding interactions which create interhost voids sufficiently large to accommodate a cluster of three H-bonded MeOH moieties. The packing structure of inclusion compounds containing fluoro substituted hosts are stabilized by CH(phenyl)···F interactions.

Considerable interest in crystalline inclusion compounds (clathrates) has arisen in the past few years due to their practical uses in compound separation, stabilization and protection of labile species, topochemistry, or the development of new solid materials.[1-7] This has stimulated development of new strategies in crystalline inclusion formation and motivated the design of novel host types.[1,2] Most consistent results refer to inclusion compounds which are based on coordination-assisted clathrate formation between functionalized hosts and polar guest components.[8] The formation and stability of these crystalline inclusion complexes are affected by functional as well as by topological complementarity and consequently are sensitive to small structural variations.[9]

Among the many new types of polar host structures,[1,2,8-10] the tartaric acid derived compound 1 has proved particularly successful in this respect.[11] In its optically resolved form (1a), it was found to be very effective in the chiral resolution of racemic guest molecules[12] and quite useful for enantioselective topochemical reactions.[13] On the other hand, as shown by competition experiments, both the optically resolved (1a) and the racemic (1b) stereoisomers exhibit preferential enclathration of secondary and primary amines, respectively, the inclusion of the tertiary amines being considerably less effective.[14] The relation between these selectivity features to structure was carried out on the propylamine series of guest compounds.[15] Very recently, a series of optically active derivatives of compound 1, called TADDOL's (α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanols),[16] were described to be useful as versatile auxiliaries for enantioselective reactions.[17] However, systematic studies

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Table I. Crystalline Inclusion Compounds with Alcohol Guests (Host:Guest Stoichiometric Ratios)[a]

	host compound										
guest solvent	1a	1b	2a	2b	3a	3b	4a	4b	5a	6a	6b
MeOH	1:1	1:1	1:1	1:1	1:1	1:1	2:3	2:3	1:1	3:1	2:3
EtOH	1:1	1:1	1:1	1:1	2:1		1:2	2:3	1:1	2:1	2:3
2-PrOH		1:1	1:1	1:1	2:1	1:1	1:2	1:1	1:1	2:1	1:1
t-BuOH	1:2	1:1	*b*	1:1	3:2	1:1	1:2	1:1	1:1	3:2	1:3
c-HexOH	*b*	1:1	*b*	1:1	2:1	1:1	1:1	1:1	*b*	3:2	2:3

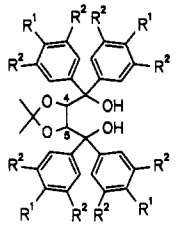
[a] See the Experimental Section for method of preparation, drying standard, and characterization. [b] Difficult to crystallize.

Table II. Crystalline Inclusion Compounds Involving Amine, Dipolar-Aprotic, and Apolar Guests (Host:Guest Stoichiometric Ratios)[a]

	host compound						
guest solvent	1a	1b	2a	3a	4a	5a	6a
1-$PrNH_2$	1:1	2:3	1:1	1:1	1:1	1:1	1:1
$(1\text{-Pr})_2NH$	1:1	1:1	1:1	1:1	1:1	1:1	1:1
$(1\text{-Pr})_3N$	1:1	1:1	*b*	2:1	*b*	1:1	1:1
c-$HexNH_2$	1:1	1:1	*b*	1:2	1:2	1:1	1:1
morpholine	1:1	1:1	*b*	2:3	*b*	3:2	*b*
piperidine	1:1	1:1	1:1	*b*	*b*	*b*	*b*
pyridine	1:1	1:1	1:1	2:1	2:1	1:1	1:1
acetone	1:1	*b*	2:1	2:1	2:1	2:1	2:1
cyclohexanone	1:1	*b*	1:1	1:1	2:3	1:1	*b*
acetonitrile	3:2		2:1	3:2	2:1	2:1	2:1
nitromethane	3:2		2:1	3:2	2:1	1:1	
DMF	1:1	1:1	1:1	1:1	1:1	2:1	*b*
DMSO	1:1	1:1	1:1	1:1	1:3	1:1	1:2
THF	4:1	*b*	4:3	2:1	*b*	2:1	1:1
dioxane	1:2	*b*	1:1	4:3	1:1	1:1	4:3
benzene	2:1	1:1	*b*		2:1	1:1	2:1
toluene		2:1	1:1		*b*		
xylene		2:1	*b*		*b*		
methylcyclohexane							2:1

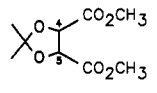
[a] See the Experimental Section for method of preparation, drying standard, and characterization. [b] Difficult to crystallize.

showing the range and structural characteristics of inclusion formation of this particular compound family, including the parent molecule **1**, have not yet been undertaken.



a (4*R*,5*R*)
b (4*RS*,5*RS*)

1 $R^1 = R^2 = H$
2 R^1 = Me, $R^2 = H$
3 $R^1 = F$, $R^2 = H$
4 R^1 = Cl, $R^2 = H$
5 $R^1 = CF_3$, $R^2 = H$
6 $R^1 = H$, $R^2 = F$



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a (4*R*,5*R*)
b (4*RS*,5*RS*)

8 2a · MeOH (1:1)
9 3a · MeOH (1:1)
10 3a · 2-PrOH (2:1)
11 4a · MeOH (2:3)
12 6a · EtOH (2:1)
13 2b · MeOH (1:2)
14 3b · MeOH (1:1)
15 4b · MeOH (2:3)
16 5a · 2-PrOH (1:1)

We report here the synthesis of several specified compounds of the TADDOL-type, **2–6**, that have particular polar and apolar substituents attached to the aryl groups. We describe in detail their crystal inclusion properties, inclusive of the parent host **1**, considering both the optically resolved and the racemic forms of the compounds. The crystal structures of nine different inclusion compounds (eight of them are fully refined) of the host stereoisomers with MeOH or other simple alcohols are presented, making possible a comprehensive evaluation of the structural patterns formed between the TADDOL's and alcohol guests. Correlation of the structural features with the chirality and substitution type of the host materials is also discussed.

Results and Discussion

Synthesis. All TADDOL's **1–6** (**a**, **b**) were synthesized via Grignard reaction from dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylates **7a** and **7b** with the corresponding aryl bromides.[16,18] The crystalline inclusion compounds were obtained by simple recrystallization of the host compound from the respective guest solvent.

Inclusion Properties. While the crystalline inclusion properties of the topical compound **1** (**a**, **b**) toward amine guests were communicated previously,[14,15] the potential clathrate formation with alcohols and other organic guests has remained unrevealed. Tables I and II show that **1a** and **1b** are effective, in fact, in the enclathration of alcohols as well as of various kinds of dipolar-aprotic and apolar organic molecules. The following points are remarkable.

The racemic species **1b** gives inclusion compounds with alcohols of different size and shape, and all these complexes have 1:1 stoichiometry. In some contrast, the optically resolved species **1a** yields 1:1 inclusion compounds only with MeOH and EtOH. Crystalline complex formation of **1a** with 2-PrOH failed. In turn, t-BuOH does form an inclusion compound with **1a**, but with a 1:2 (host:guest) stoichiometry. This variation of complexation stoichiometry clearly suggests that interaction of **1a** with the small alcohols is more sensitive than that of **1b** to the size of the

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Table III. Summary of Crystal Data and Experimental Parameters

	8	9	10	11	12	13	14	15	16
asymmetric unit	**2a**·MeOH	**3a**·MeOH	$(\mathbf{3a})_2$·2-PrOH	$(\mathbf{4a})_2$·3 MeOH	$(\mathbf{6a})_2$·MeOH	**2b**·2MeOH	**3b**·MeOH	**4b**·1.5MeOH	$(\mathbf{5a})_2$·$(2\text{-PrOH})_2$[a]
M[b]	554.7	570.6	1137.2	1304.8	1267.1	586.8	570.6	652.4	1597.3
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P1$	$C2$	$P2_1/n$	$P2_1/n$	$I2/a$	$C2$
Z	4	4	2	1	4	4	4	8	4
a, Å	10.397 (1)	9.808 (6)	9.833 (4)	12.032 (3)	27.117 (4)	12.256 (4)	9.817 (7)	24.164 (6)	22.544 (3)
b, Å	14.719 (1)	14.624 (2)	24.081 (11)	12.924 (2)	11.248 (9)	14.968 (4)	19.216 (7)	12.879 (8)	14.246 (2)
c, Å	20.982 (1)	20.157 (9)	12.353 (6)	12.934 (7)	19.554 (2)	18.361 (16)	15.853 (6)	25.490 (13)	25.158 (3)
α, deg	90.0	90.0	90.0	110.30 (2)	90.0	90.0	90.0	90.0	90.0
β, deg	90.0	90.0	102.28 (3)	116.12 (2)	92.09 (1)	97.22 (4)	106.17 (5)	126.08 (2)	103.56 (1)
γ, deg	90.0	90.0	90.0	92.80 (2)	90.0	90.0	90.0	90.0	90.0
V_c, Å	3210.9	2891.2	2858.1	1644.4	5960.2	3341.6	2872.3	6411.2	7854.6
D_c, g cm^{-3}	1.147	1.311	1.321	1.318	1.412	1.166	1.319	1.352	1.351
F (000)	1192	1192	1188	678	2600	1264	1192	2712	3280
μ, cm^{-1}	0.701	0.986	0.983	3.984	1.200	0.723	0.992	4.115	1.201
2θ limits, deg	50	50	50	50	50	50	46	50	46
N (unique)	2868	2444	4166	5425	4892	5019	3087	5111	4705
N(obs)[c]	2130	1609	1903	3969	2931	3010	1118	3623	
R_F	0.052	0.054	0.075	0.039	0.053	0.072	0.063	0.046	
R_w	0.052	0.491	0.073	0.039	0.054	0.076	0.059	0.049	
$\lvert\Delta\rho\rvert_{max}$	0.26	0.20	0.40	0.20	0.40	0.46	0.22	0.30	

[a] Structures not fully refined. [b] Molecular weights reflect the contents of the asymmetric unit. [c] For compound 9, $I > 2\sigma(I)$, otherwise $I > 3\sigma(I)$.

alcohol. Moreover, **1a** shows a higher variability of the host:guest stoichiometric ratio for the dipolar-aprotic guest molecules, forming inclusion compounds also in those cases where **1b** is inefficient (see Table II). An exception are the aromatic hydrocarbons for complexation of which **1b** is more effective than **1a**. The inclusion properties of **1a** and **1b** toward amines have been discussed in detail elsewhere.[14,15]

Somewhat unexpectedly, the newly designed host compounds **2–6**, which have one or two substituents of different size and polarity attached to the peripheral aromatic groups, also show a remarkable tendency to form crystalline inclusion complexes with alcohols. This involves both steric forms of **2–6**, the optically resolved and racemic isomers **a** and **b**. Table I summarizes the observed stoichiometric combinations in the various materials. The data in Table I further suggest that polar effects are more important for the inclusion of alcohols than steric effects; e.g., **2b** with four Me substituents forms complexes of indentical constitution to those of the unsubstituted **1b**. On the other hand, unsubstituted **1a** and the tetrafluoro-substituted **3a** are different, although H and F are very similar in size.[19] The same is true for the comparison between **2a** with four Me substituents and the tetrachloro-substituted **4a**; Me and Cl also correspond closely in size,[19] but they differ significantly in polarity of their bonds to aromatic carbon.[20] These polarity effects have a strong influence on the lattice architecture, as is reflected in the different inclusion stoichiometries occurring in the analyzed structures. It can thus reasonably be assumed that the intermolecular arrangement in the different host–guest complexes is determined not only by the relatively strong H-bonding interactions, but also by secondary contacts involving peripheral F and Cl groups of the host molecules.

These contacts may be of repulsive or attractive nature, depending on the interacting fragments in proximity to each other.[5] Consequently, the host:guest stoichiometry differs most from the normal 1:1 ratio for the octafluoro-substituted host compound **6**. An exception seems to be the trifluoromethyl group. Despite the pronounced polarity difference between CF_3 and Me,[20] which, however, correspond in size,[19] the respective hosts, **2** and **5**, exhibit similar behavior (Table I). This is due to the repulsive nature of nonbonding interactions between the Me and CF_3 peripheral groups in the crystal lattice. On the other hand, the single fluoro and chloro substituents of **3** and **4** are more likely to cause attractive contacts of CH···F or Cl···Cl type.[5] The failure to form an EtOH inclusion crystal with the tetrafluoro-substituted host molecule **3b** cannot be explained at this point.

The enclathration capability of **2a–6a** toward amines (Table II) is less extensive in comparison to that of **1a** and **1b**. Furthermore, similarly to the alcohol inclusions, the observed host:guest stoichiometries are not uniformly 1:1 as in the amine complexes with **1a**. The inclusion compounds of **2a–6a** with dipolar aprotic and proton acceptor guests such as THF and dioxane have a particularly complexed host:guest composition of 4:3.[21] A 4:1 (host:guest) stoichiometry of inclusion of THF is also typical of **1a**.

The inclusion behavior of **1a–6a** with hydrocarbon guests is generally poor, involving only benzene and toluene. An efficient complexation of the nonaromatic methylcyclohexane only by **6a** has also been observed.

In order to extend our knowledge on the host–guest interaction modes between members of this important compound family and alcohols, and to ellucidate the effects of the host constitution and stereochemistry on the hydroxylic guests binding, we studied the crystal structures of a number of inclusion compounds of **2–6** with MeOH (six examples), EtOH (one example), and 2-PrOH (two examples), namely compounds **8–15**.

X-ray Analysis: Structure Description of Inclusion Compounds 8–15. A numbering scheme of the atoms is given in Figure 1. Views of the packing structures are presented in Figures 2–10 (Figures 5, 7 and 10, see supplementary material). Crystal data are given in Table III (atomic coordinates deposited with the Cambridge Crystallographic Data Centre).

(1) Molecular Structures. The overall structural features of the different host molecules are similar to those discussed in an earlier publication.[15] (Relevant data on the covalent parameters have been deposited.) These molecules are conformationally rigid with the two hydroxyl groups located on the same side of the molecular framework (at distances within the range of 2.62–2.69 Å) and

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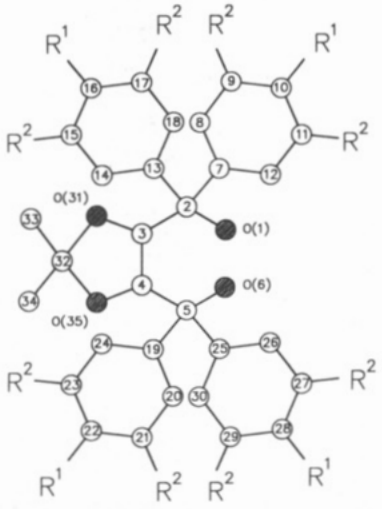

Figure 1. Crystallographic atom labeling scheme of the host framework. The peripheral atoms on the monosubstituted phenyl rings are labeled $R^1(36)$ through $R^1(39)$, while those on the disubstituted phenyl rings $R^2(36)$ through $R^2(43)$. The second independent molecule of the host in the asymmetric units of **10**, **11**, and **12** is marked by primed labels. Consecutively numbered labels in the corresponding structures refer to atoms of the guest moieties.

Table IV. Intramolecular Conformation of H Bonding in the Host Species

	torsion angles, deg				H bond, Å
compd	O(1)–C(2) –C(3)–C(4)	C(2)–C(3) –C(4)–C(5)	O(31)–C(3) –C(4)–O(35)	C(3)–C(4) –C(5)–O(6)	O(1)···O(6)
8	−59.5 (4)	91.0 (5)	−30.6 (4)	−81.5 (4)	2.689 (4)
9	−74.0 (7)	96.9 (7)	−24.6 (6)	−57.4 (7)	2.628 (6)
10	−61.7 (15)	88.0 (18)	−30.9 (13)	−79.0 (17)	2.687 (13)
	−61.1 (17)	95.8 (17)	−26.3 (14)	−68.9 (16)	2.654 (16)
11	−69.4 (6)	89.8 (6)	−31.2 (5)	−65.4 (6)	2.644 (5)
	−84.7 (6)	89.8 (7)	−30.5 (5)	−55.7 (6)	2.639 (5)
12	−73.4 (7)	90.1 (8)	−33.5 (6)	−68.9 (8)	2.652 (7)
	−66.1 (8)	90.9 (8)	−33.4 (7)	−69.6 (8)	2.629 (8)
13	−74.1 (5)	89.2 (5)	−32.6 (4)	−70.2 (5)	2.664 (5)
14	−61.8 (10)	93.7 (11)	−28.0 (9)	−71.5 (10)	2.622 (8)
15	−78.4 (3)	89.8 (3)	−32.7 (3)	−57.7 (3)	2.654 (4)

hydrogen bonding to one another. Selected data referring to the intramolecular conformation and H-bonding are given in Table IV. The polar sites are further exposed in the crystalline phase to interactions with adjacent host species as well as with the polar guest entities. The remaining surface of host molecules in **8** and **13** consists mainly of C–H bonds and is hydrophobic, the host surface in compounds **9–12**, **14**, and **15** being, however, polarized by the peripheral F and Cl substituents.

(2) Packing Relations and Host–Guest Interactions. The two crystalline complexes **8** and **9**, although differing significantly in their packing density, reveal isomorphous structures (Table III). In these crystals the host and guest species are arranged in an alternating manner along continuous H-bonded chains, which extend parallel to the *a*-axis of the unit cell (Figures 2 and 3). The observed intermolecular coordination has a spiral pattern along the crystallographic 2-fold screw axes. The more hindered packing arrangement in crystals involving the larger Me-substituted compound **8** causes a slight distorsion of the H-bonding scheme, including a significant elongation of one of the intermolecular bonds to OH···O = 2.95 Å (Table V).

The continuous mode of host–guest association is disrupted in the 2:1 crystalline complex of **3a** with a bulkier alcohol molecule such as 2-PrOH. In this case (**10**), the H-bonding is confined to trimeric host–host–guest clusters, as the bulky isopropyl group allows access to the guest

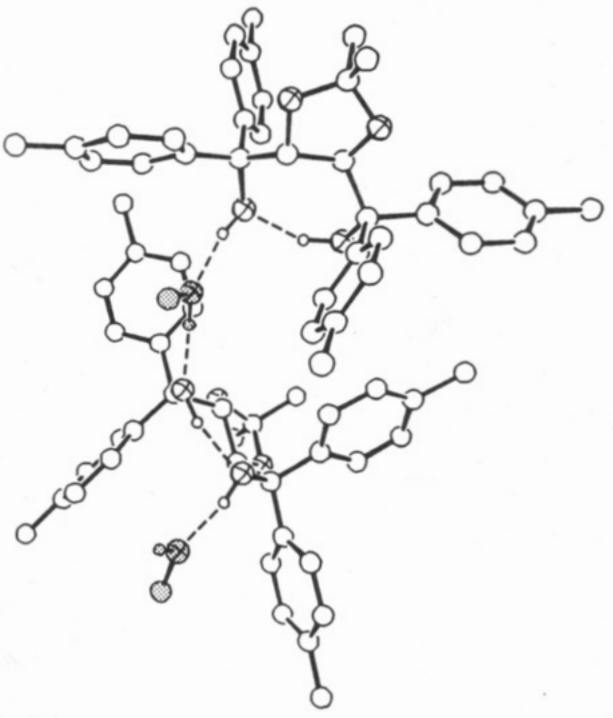

Figure 2. Perspective view of the "linear" H-bonding host–guest association in **8** [**2a**·MeOH (1:1)]. (The MeOH molecules are shaded.) In all figures (2–10), the heteroatoms are marked by crossed circles, and solid and dashed lines represent covalent and hydrogen bonds, respectively.

Table V. Intermolecular Hydrogen Bonds

	donor	acceptor		donor···acceptor
compd	(at *x*, *y*, *z*)	atom	at site	distance, Å
8	OH(1)	O(40)	*x*, *y*, *z*	2.752 (5)
	OH(40)	O(6)	*x* − 0.5, 0.5 − *y*, 2 − *z*	2.946 (6)
9	OH(40)	O(1)	*x*, *y*, *z*	2.777 (7)
	OH(6)	O(40)	0.5 + *x*, 0.5 − *y*, −*z*	2.667 (8)
10	O(1)	O(1′)	1 − *x*, 0.5 + *y*, 1 − *z*	2.80 (1)
	O(6′)	O(40)	*x*, *y*, *z*	2.73 (2)
11	OH(1)	O(41)	*x*, *y*, *z*	2.653 (7)
	OH(41)	O(43)	*x*, *y*, *z*	2.65 (2)
	OH(43)	O(45)	*x*, *y*, *z*	2.73 (2)
	OH(45)	O(1′)	*x* − 1, *y*, *z*	2.835 (8)
	OH(6′)	O(6)	1 + *x*, *y*, 1 + *z*	2.659 (8)
12	OH(6)	O(44)	*x*, *y*, *z*	2.725 (9)
	OH(6′)	O(1)	*x*, *y*, *z*	2.752 (8)
13	OH(1)	O(40)	*x*, *y*, *z*	2.760 (6)
	OH(40)	O(6)	−*x*, 1 − *y*, 1 − *z*	2.731 (6)
14	OH(40)	O(1)	*x*, *y*, *z*	2.743 (9)
	OH(6)	O(40)	−*x*, −*y*, 1 − *z*	2.688 (8)
15	OH(1)	O(40)	*x*, *y*, *z*	2.775 (4)
	OH(40)	O(42)	*x*, *y*, *z*	2.732 (3)
	OH(6)	O(6)	0.5 − *x*, *y*, −*z*	2.799 (3)

hydroxyl only from one side (Figure 4). Noticeably, however, several CH(phenyl)···F interactions[22] stabilize packing of the trimeric entities in sections parallel to the *ac*-plane of the crystal, as it is reflected in relatively short CH···F nonbonding distances (within 3.09–3.20 Å)[23] between neighboring trimers related by translation along the *a*- and *c*-axes.

A similar aggregation of the host and guest constituents was observed in the crystal structure of the 2:1 complex of host **6a** with EtOH (**12**). The two hosts in every cluster are bound to one another by a single H-bond at an OH···O

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(23) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaka, NY, 1960.

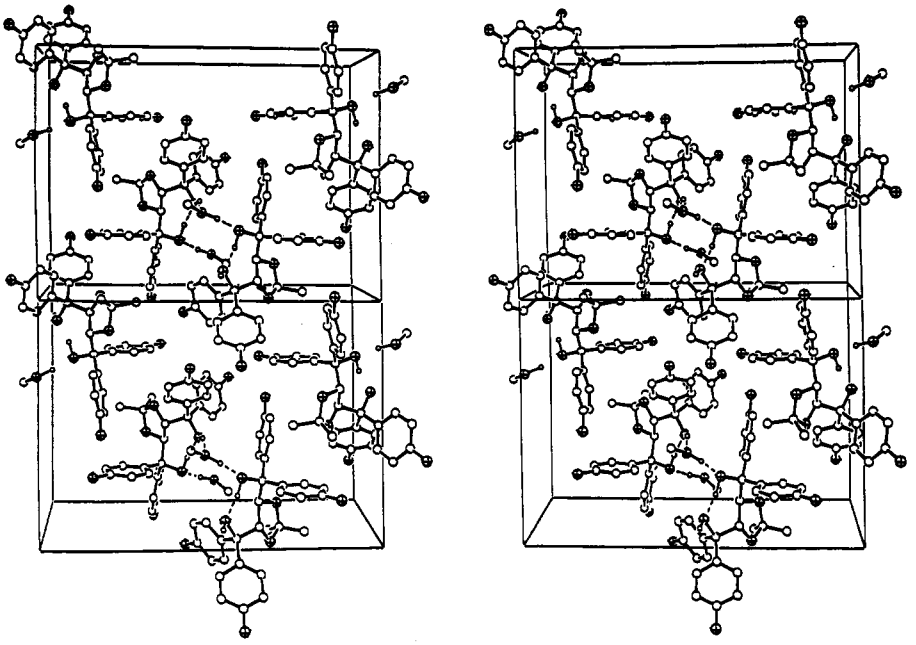

Figure 3. Crystal packing of **9** [**3a**·MeOH (1:1)], stereoviewed down the *a*-axis (*c* is horizontal) and showing two unit cells.

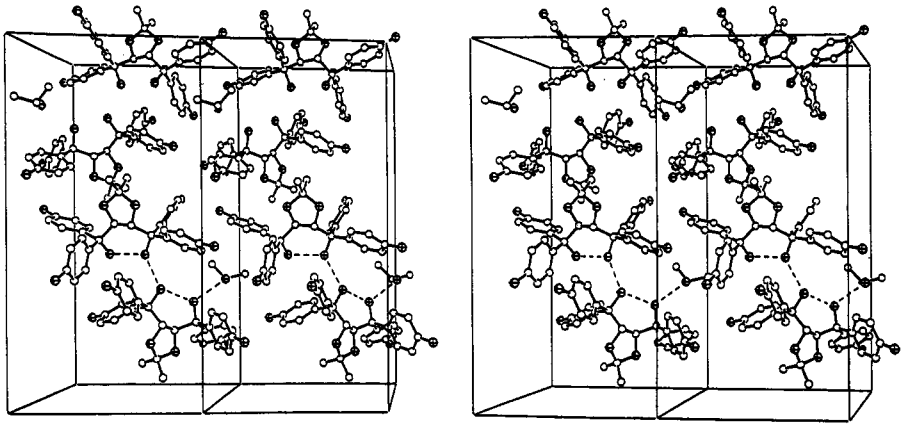

Figure 4. Crystal packing of **10** [**3a**·2-PrOH (2:1)], stereoviewed down the *a*-axis (*c* is horizontal) and showing two unit cells.

distance of 2.75 Å, with the EtOH guest moiety linked to the host dimer at one end [OH(host)···O(guest) = 2.73 Å] (Figure 5a, supplementary material). The relatively loose binding to the guest species in structures **10** and **12** is reflected in the large-amplitude wagging motion or even partial disorder of these molecules in the crystal lattice. As in **10**, the intermolecular packing of **12** is also stabilized by attractive interactions between adjacent fluorophenyl fragments aligned in an antiparallel manner with respect to one another (Figure 5b, supplementary material). Similar observations apply also to the other examples containing F-substituted host species. In all structures, however, the intermolecular nonbonding F···F contacts are larger than the sum of the corresponding van der Waals radii (2.70 Å)[23] to reflect on the repulsive nature of a direct F···F approach; the shortest F···F distances are >3.18 Å in **9** and **14**, >3.40 Å in **10**, and >2.92 Å in **12** where the density of F atoms on the host surface is particularly high.

The racemic complexes **13** and **14** are characterized by similar features of host–guest association. Their structures can be best described as consisting of H-bonded tetrameric entities of two host and two guest species clustering around the crystallographic centers of inversion. Each MeOH guest is inserted between the hydroxyl groups of two hosts, forming a circular 12-membered $(OH)_6$ motif of hydrogen bonds (Figures 6 and 7; Figure 7, supplementary material). The four distinct intermolecular host–guest OH···O coordination distances are within 2.69–2.76 Å (Table V). Crystal packing of the tetrameric units in both structures is stabilized by van der Waals forces. It is more efficient in the fluoro derivative **14** due to the smaller size of the peripheral substituent and the added contribution of dipolar interactions between neighboring entities in this structure (Figure 7, supplementary material). On the other hand, bulkier methyl substituents in **13** sterically hinder a close packing arrangement of the H-bonded tetramers. Correspondingly, additional uncoordinated molecules of the MeOH solvent are included in the crystal structure in order to fill the intermolecular voids created in it (Figure 6).

A rather unique constitution (host-to-guest ratio of 2:3) and structure characterize the crystalline complexes of both the chiral and racemic forms of the Cl-substitued host, **4a** and **4b**, with methanol (**11** and **15**). As in the corresponding methanol adducts of the F derivative (**9** and **14**), the optically pure compound (**11**) contains a linear arrangement of hydrogen-bonded molecules, while the racemic one (**15**) has a circular motif.

Figure 8 illustrates the intermolecular association in complex **11**. The extended arrays of H-bonded molecules also consists of dimeric host assemblies, which are linked to one another by three linearly arranged molecules of methanol. All the intermolecular H-bonding distances between the oxygen sites range from 2.65 to 2.83 Å (Table

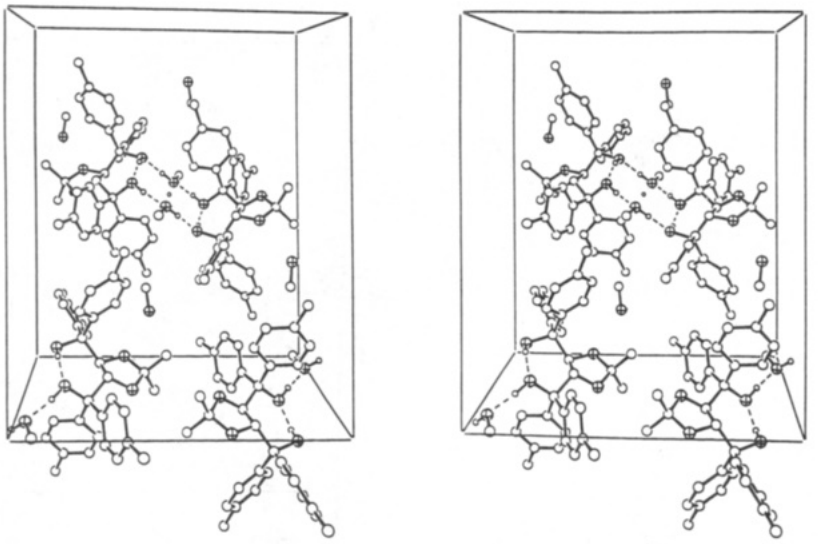

Figure 6. Crystal packing of **13** [**2b**·MeOH (1:2)], stereoviewed approximately down the *b*-axis (*a* is horizontal; the small circle in the hydrogen-bonded ring represents a center of inversion).

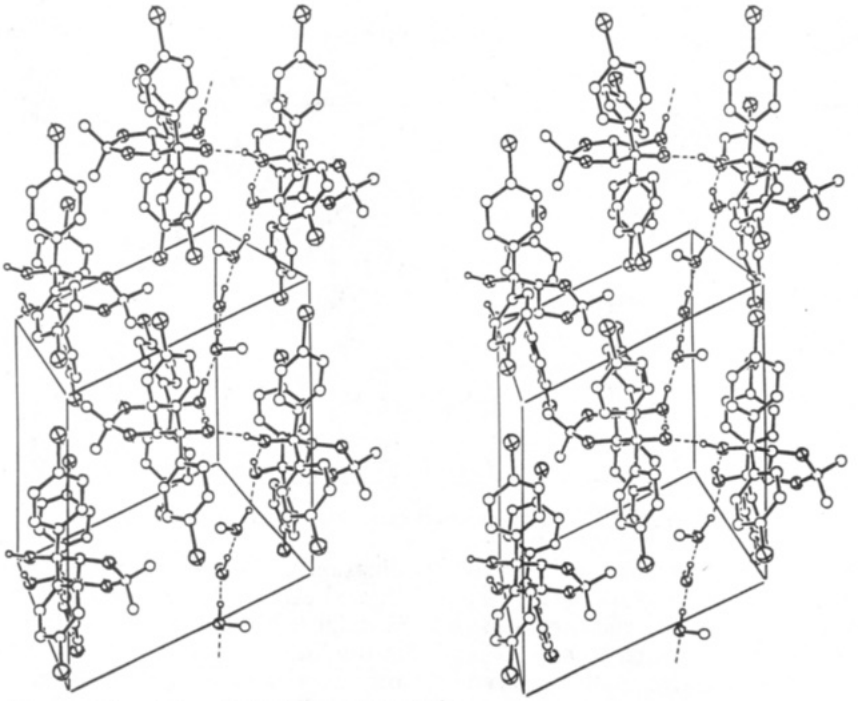

Figure 8. Stereoview of the crystal packing of **11** [**4a**·MeOH (2:3)], showing the continuous arrays of intermolecular hydrogen bonds which extend along the *c*-axis of the crystal.

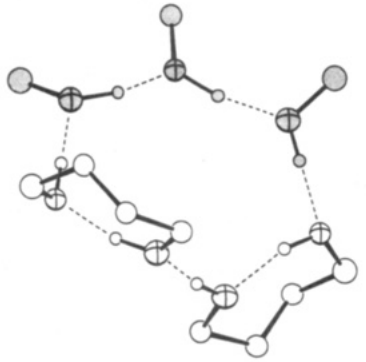

Figure 9. Crystal structure of **15** [**4b**·MeOH (2:3)]: illustration of the 14-membered $(OH)_7$ ring of hydrogen-bonded moieties. (For clarity, only the 1,4-dihydroxybutane fragments of the hosts are shown; the MeOH molecules are shaded.)

V). The Me groups of the three guests lie in proximity to, and point at, the host phenyl rings; the terminal methyls in the methanol cluster to hosts in the same chain, while the central one to the concave surface between the aryl rings of an adjacent chain.

The interaction scheme in **15** is shown in Figures 9 and 10 (Figure 10, supplementary material). It involves 14-membered $(OH)_7$ rings located on crystallographic symmetry of 2-fold rotation, the central MeOH thus being disordered about the symmetry axes. Consequently, the direction of the hydrogen bonds in each circle is not uniquely defined; rather, it varies at the different sites of the crystal in a random manner (see the Experimental Section). In the pentameric clusters the two hosts are linked to one another by a single H-bond, and are of the same chirality. Their outer ends are bridged by three MeOH guest species.

Both structures (**11** and **15**) contain numerous intermolecular Cl···Cl contacts within the range of 3.39–3.60 Å (the higher value indicating the nomal Cl···Cl van der Waals distance),[5] formed between the ends of neighboring

C–Cl bonds which approach one another roughly at right angles. It appears that the structural requirements associated with an optimization of these interactions induce interhost voids which are sufficiently large to accommodate at each site a cluster of three MeOH moieties.

Structure **16** of the complex between tetrakis(trifluoromethyl)-substituted host **5a** and 2-PrOH consists of localized H-bonded 1:1 host–guest entities.

Conclusions

Derivatives of the topical host compound **1** (**a**, **b**) with attached peripheral substituents of different size and polarity have proved to be a source of new crystalline inclusion hosts with novel structures. They form crystalline inclusions with a variety of uncharged organic molecules ranging from protic dipolar to apolar compounds (143 different examples, Tables I and II). Composition of the inclusion materials depends primarily on structural parameters of the host, its optical form (optically resolved or racemic), and the type (polarity, size) and position of the attached substituents.

These parameters also determine the mode of interaction between host and guest, as clearly indicated by crystallographic data obtained for nine cases of selected alcohol inclusions. A general account suggests the following.

(1) In host–guest adducts involving MeOH guests, the optically resolved host species with Me and F substituents form linear (spiral) host–guest H-bonded chains (cf. **8**, **9**), while the racemic species yielded circular motifs of H-bonds (**13**, **14**).

(2) In the chiral structures, continuous arrangements are formed only with MeOH. In the presence of larger guest alcohols, such as 2-PrOH, a finite noncyclic H-bonded cluster occurs (cf. **10** and **16**).

(3) The crystal packings in structures **11** and **15**, composed of tetrachloro-substituted hosts **4a** or **4b** and MeOH guests, are affected to a significant extent by specific Cl···Cl nonbonding interactions.[5]

(4) The intermolecular arrangements of inclusion compounds containing fluoro-substituted hosts (e.g. **10**, **12**) are stabilized by CH(phenyl)···F interactions,[22] as it is reflected in relatively short nonbonding distances between the corresponding fragments.

The observed correlation between the structural features of the MeOH inclusions with hosts differently substituted at the para position of the phenyl rings (**2**–**4**; R^1 = Me, F or Cl), is surprising to some extent. Evidently, there is more similarity between the structures involving the Me- and F-substituted derivatives, which differ most in size (van der Waals radii of covalently bound F, Cl, and Me are 1.35, 1.8, and 2.0 Å, respectively)[23] and polarity, than between those involving more equally sized Me and Cl derivatives or more evenly polarized F and Cl moieties. This observation can be attributed primarily to the different nature of nonbonding interactions between the peripheral substituents. Thus, direct F···F and Me···Me intermolecular contacts involving "harder" end atoms are mostly of a repulsive nature (for either electrostatic or steric reasons). On the other hand, the Cl···Cl nonbonding interaction between the "softer" chlorine atoms with an appropiate directional geometry provides an attractive contribution to the lattice stabilization energy. The significant role that such contacts can play in determining crystalline arrangements of organic compounds has recently been described.[5] In the present case they induce interhost voids sufficiently large to accommodate clusters of three H-bonded MeOH moieties in structures **11** and **15**.

To our knowledge, complexation of small alcohol clusters inside a crystalline cavity has not been reported before. Recently, such clusters attracted considerable attention as models for theoretical calculations.[24] The control of chiral crystalline arrangements by weak nonbonding interactions of Cl···Cl or CH···F type, demonstrated in this study, has been found important in the design of nonlinear optical materials[25] and of solid-state reactive materials.[3-5] Moreover, the optically resolved hosts are promising as chiral NMR shift reagents.[26]

Experimental Section

General. Starting compounds and all other reagents were purchased from Janssen. Spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analytical data for all new compounds are given in the supplementary material (Tables VI–X).

(4*R*,5*S*)- and (4*RS*,5*RS*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylates (7a,b) were obtained by trans-ketalization of the corresponding tartaric acid diesters with 2,2-dimethoxypropane and *p*-toluenesulfonic acid according to literature procedures.[1]

2,2-Dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL Host Compounds) 1a–6a, 1b–4b, and 6b. General Procedure. Grignard reaction as described for **1a**.[16,17] Purification of the compounds by recrystallization from MeOH or EtOH yielded the solvates (crystalline inclusion compounds; see Table I). The solvent-free compounds (all colorless powders) were obtained by heating the solvates to 60 °C at 15 Torr for 24 h. Specific details are given for each compound.

1a: from diester **7a** with bromobenzene; 74%; mp 192–193 °C (lit.[16] mp 193.5–195 °C); $[\alpha]^{20}_D$ –64.6° (*c* 1, in $CHCl_3$) [lit.[16] $[\alpha]^{20}_D$ –65.1° (*c* 1, in $CHCl_3$)].

1b: from diester **7b** with bromobenzene; 66%; mp 202–207 °C (lit.[15] mp 202–207 °C).

2a: from diester **7a** with 4-bromotoluene; 49%; mp 103–105 °C (lit.[12a] mp 103–105 °C); $[\alpha]^{20}_D$ –52° (*c* 1, in $CHCl_3$) [lit.[12a] $[\alpha]^{20}_D$ –47° (*c* 0.12, in $CHCl_3$)].

2b: from diester **7b** with 4-bromotoluene; 63%; mp 104–106 °C.

3a: from diester **7a** with 4-fluorobromobenzene; 36%; mp 169–170 °C; $[\alpha]^{20}_D$ –65.6° (*c* 1, in $CHCl_3$).

3b: from diester **7b** with 4-fluorobromobenzene; 55%; mp 190–192 °C.

4a: from diester **7a** with 4-chlorobromobenzene; 25%; mp 124 °C; $[\alpha]^{20}_D$ –62.9° (*c* 1, in MeOH).

4b: from diester **7b** with 4-chlorobromobenzene; 22%; mp 112–113 °C.

5a: from diester **7a** with 4-(trifluoromethyl)bromobenzene; 33%; mp 205–206 °C; $[\alpha]^{20}_D$ +114.2° (*c* 1, in $CHCl_3$).

6a: from diester **7a** with 3,5-difluorobromobenzene; 48%; mp 145–147 °C; $[\alpha]^{20}_D$ –76.2° (*c* 1, in $CHCl_3$).

6b: from diester **7b** with 3,5-difluorobromobenzene; 49%; mp 193–195 °C.

Preparation of the Crystalline Inclusion Compounds. General Procedure. They were obtained by recrystallization of the corresponding host compound from a minimum amount of the respective guest solvent. The crystals which formed were collected by suction filtration and dried (1 h, 15 Torr, room temperature). Host–guest stoichiometry was determined by ^{1}H NMR integration. Data for each compound are given in Tables I and II.

Crystallography. (a) Sample Preparation and Data Collection. Suitable crystals for X-ray diffraction were prepared by slow cooling of a solution of the corresponding host compound in the respective guest solvent.

The X-ray diffraction experiments were carried out at room temperature (ca. 298 K) on automated CAD4 and Picker dif-

(24) Brink, G.; Glasser, L. *S. Afr. J. Chem.* **1982**, *35*, 105.

(25) *Nonlinear Optical Properties of Organic Molecules and Crystals*; Chemla, D., Zyss, J., Eds.; Academic Press: New York, 1987; Vols. 1 and 2.

(26) (a) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K.; Fuji, K. *Chem. Lett.* **1988**, 131. (b) Toda, F.; Toyotaka, R.; Fukada, H. *Tetrahedron: Asymmetry* **1990**, *1*, 303.

fractometers equipped with a graphite monochromator. Intensity data were collected by the ω–2θ scan mode with a constant speed of either 3 or 4 deg/min, using Mo Kα (λ = 0.7107 Å) radiation. The analyzed crystals were sealed in Lindemann thin glass capillaries or covered by a thin layer of epoxy resin to prevent desorption of the guest component during data collection. Possible deterioration of the crystals during the measurements were tested by detecting periodically the intensities of three standard reflections from different zones of the reciprocal space. For all compounds, except 14, it was found negligible; the standard intensities of 14 exhibited a linear decrease (of about 15% over the entire experiment), which required an approriate correction of this set of data. No corrections for absorption or secondary extinction effects were applied. The cell constants and pertinent details of the experimental conditions are summarized in Table III.

Structure Analysis and Refinement. The crystal structures were solved by a combination of direct methods and Fourier techniques (MULTAN 80 and SHELX 86).[27,28] Their refinements were carried out by large-block least-squares (SHELX 76),[29] including the positional and anisotropic thermal parameters of the non-hydrogen atoms. Final calculations were based only on those observations that satisfied the conditions $I > 2\sigma(I)$ in 12 and $I > 3\sigma(I)$ in the other structures.

The structural model of 16 could not be refined with an adequate precission due to rotational disorder of the trifluoromethyl substituents about the C(phenyl)–CF_3 bond. Anisotropic least-squares calculations with the corresponding non-hydrogen atom molecular fragments converged at $R = 0.20$, indicating clearly that the obtained description of this structure, although generally correct, is still incomplete. Efforts to improve the result, incorporating various models of the host disorder, were unsuccessful, and the detailed structural study of this compound was not concluded. On the other hand, standard crystallographic refinements of compounds 8–15 converged smoothly at reasonably low R values (Table III), allowing a reliable description of the atomic parameters of host and guest constituents and of the intermolecular interaction scheme. However, the guest components in 13 and 15 as well as one the two MeOH guest species in 8 were found to exhibit large-amplitude "wagging" motion or possible disorder and were included in the calculations with isotropic thermal parameters only. Moreover, due to an excessive thermal motion and a low data-to-parameters ratio in 13, the phenyl rings of the host and the 2-PrOH guest were refined with restrained geometry in order to avoid unreliable distortions of bond lengths and bond angles.

Most hydrogen atoms were introduced into the structure factor computations in calculated positions, the methyl substituents being treated as rigid groups. Approximate positions of the hydroxy H atoms were found directly in difference Fourier maps. All OH hydrogens of the host and guest species could be located in compounds 9–12, only those of the host molecules in compounds 8, 14 and 15, and none in 13. Peaks corresponding to two alternative positions for each hydroxyl H atom were found in 10, indicating a 2-fold directional disorder of the H-bonding pattern.

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Registry No. 1a, 93379-48-7; 1a·MeOH (1:1), 144109-23-9; 1a·EtOH (1:1), 144126-57-8; 1a·*t*-BuOH (1:2), 144109-24-0; 1a·1-$PrNH_2$ (1:1), 126524-76-3; 1a·$(1\text{-Pr})_2$NH (1:1), 129670-12-8; 1a·$(1\text{-Pr})_3$N (1:1), 126525-04-0; 1a·c-$HexNH_2$ (1:1), 126524-82-1; 1a·morpholine (1:1), 144109-25-1; 1a·piperidine (1:1), 126524-96-7; 1a·pyridine (1:1), 126525-06-2; 1a·acetone (1:1), 144109-26-2; 1a·cyclohexane (1:1), 144109-27-3; 1a·acetonitrile (3:2), 144109-28-4; 1a·nitromethane (3:2), 144109-29-5; 1a·DMF (1:1), 144109-30-8; 1a·DMSO (1:1), 144109-31-9; 1a·THF (4:1), 144109-32-0; 1a·dioxane (1:2), 144109-33-1; 1a·benzene (2:1), 144109-34-2; 1b, 93222-42-5; 1b·2-PrOH (1:1), 144109-35-3; 1b·*t*-BuOH (1:1), 144109-36-4; 1b·c-HexOH (1:1), 144109-37-5; 1b·MeOH (1:1), 144109-38-6; 1b·EtOH (1:1), 144109-39-7; 1b·1-$PrNH_2$ (2:3), 144109-40-0; 1b·$(1\text{-Pr})_2$NH (1:1), 144109-41-1; 1b·$(1\text{-Pr})_3$N (1:1), 126525-11-9; 1b·c-$HexNH_2$ (1:1), 126552-63-4; 1b·morpholine (1:1), 144109-42-2; 1b·piperidine (1:1), 126525-02-8; 1b·pyridine (1:1), 126525-13-1; 1b·DMF (1:1), 144109-43-3; 1b·DMSO (1:1), 144109-44-4; 1b·benzene (1:1), 144109-45-5; 1b·toluene (2:1), 144109-46-6; 1b·xylene (2:1), 144109-47-7; 2a, 144109-48-8; 2a·EtOH (1:1), 144109-49-9; 2a·2-PrOH (1:1), 144109-50-2; 2a·1-$PrNH_2$ (1:1), 144109-51-3; 2a·$(1\text{-Pr})_2$NH (1:1), 144109-52-4; 2a·piperidine (1:1), 144109-53-5; 2a·pyridine (1:1), 144109-54-6; 2a·acetone (2:1), 144109-55-7; 2a·cyclohexanone (1:1), 144126-58-9; 2a·acetonitrile (2:1), 144109-56-8; 2a·nitromethane (2:1), 144109-57-9; 2a·DMF (1:1), 144109-58-0; 2a·DMSO (1:1), 144109-59-1; 2a·THF (4:3), 144109-60-4; 2a·dioxane (1:1), 144109-61-5; 2a·toluene (1:1), 144109-62-6; 2b, 144177-79-7; 2b·EtOH (1:1), 144177-80-0; 2b·2-PrOH (1:1), 144177-81-1; 2b·*t*-BuOH (1:1), 144177-82-2; 2b·c-HexOH (1:1), 144177-83-3; 3a, 144109-63-7; 3a·EtOH (2:1), 144109-64-8; 3a·*t*-BuOH (3:2), 144109-65-9; 3a·c-HexOH (2:1), 144109-66-0; 3a·1-$PrNH_2$ (1:1), 144109-67-1; 3a·$(1\text{-Pr})_2NH_2$ (1:1), 144109-68-2; 3a·$(1\text{-Pr})_3$N (2:1), 144126-59-0; 3a·c-$HexNH_2$ (1:2), 144109-69-3; 3a·morpholine (2:3), 144109-70-6; 3a·pyridine (2:1), 144109-71-7; 3a·acetone (2:1), 144109-72-8; 3a·cyclohexanone (1:1), 144109-73-9; 3a·acetonitrile (3:2), 144109-74-0; 3a·nitromethane (3:2), 144109-75-1; 3a·DMF (1:1), 144109-76-2; 3a·DMSO (1:1), 144109-77-3; 3a·THF (2:1), 144109-78-4; 3a·dioxane (4:3), 144109-79-5; 3b, 144177-84-4; 3b·2-PrOH (1:1), 144177-85-5; 3b·*t*-BiPJ (1:1), 144177-86-6; 3b·c-HexOH (1:1), 144177-87-7; 4a, 144109-80-8; 4a·EtOH (1:2), 144109-81-9; 4a·2-PrOH (1:2), 144109-82-0; 4a·*t*-BuOH (1:2), 144109-83-1; 4a·c-HexOH (1:1), 144109-84-2; 4a·1-$PrNH_2$ (1:1), 144109-85-3; 4a·$(1\text{-Pr})_2$NH (1:1), 144109-86-4; 4a·c-H3xNH_2 (1:2), 144109-87-5; 4a·pyridine (2:1), 144109-88-6; 4a·acetone (2:1), 144109-89-7; 4a·cyclohexanone (2:3), 144109-90-0; 4a·acetonitrile (2:1), 144109-91-1; 4a·nitromethane (2:1), 144109-92-2; 4a·DMF (1:1), 144109-93-3; 4a·DMSO (1:3), 144109-94-4; 4a·dioxane (1:1), 144109-95-5; 4a·benzene (2:1), 144109-96-6; 4b, 144177-88-8; 4b·EtOH (2:3), 144177-89-9; 4b·2-PrOH (1:1), 144177-90-2; 4b·*t*-BuOH (1:1), 144177-91-3; 4b·c-HexOH (1:1), 144238-46-0; 5a, 144109-97-7; 5a·MeOH (1:1), 144109-98-8; 5a·EtOH (1:1), 144109-99-9; 5a·*t*-BuOH (1:1), 144110-00-9; 5a·1-$PrNH_2$ (1:1), 144110-01-0; 5a·$(1\text{-Pr})_2$NH (1:1), 144110-02-1; 5a·$(1\text{-Pr})_3$N (1:1), 144126-60-3; 5a·c-H3xNH_2 (1:1), 144110-03-2; 5a·morpholine (3:2), 144110-04-3; 5a·pyridine (1:1), 144110-05-4; 5a·acetone (2:1), 144110-06-5; 5a·cyclohexanone (1:1), 144110-07-6; 5a·acetonitrile (2:1), 144110-08-7; 5a·nitromethane (1:1), 144110-09-8; 5a·DMF (2:1), 144110-10-1; 5a·DMSO (1:1), 144110-11-2; 5a·THF (2:1), 144110-12-3; 5a·dioxane (1:1), 144110-13-4; 5a·benzene (1:1), 144110-14-5; 6a, 144110-15-6; 6a·MeOH (3:1), 144110-16-7; 6a·2-PrOH (2:1), 144110-17-8; 6a·*t*-BuOH (3:2), 144110-18-9; 6a·c-HexOH (3:2), 144110-19-0; 6a·1-$PrNH_2$ (1:1), 144110-20-3; 6a·$(1\text{-Pr})_2$NH (1:1), 144110-21-4; 6a·$(1\text{-Pr})_3$N (1:1), 144126-61-4; 6a·c-$HexNH_2$ (1:1), 144110-22-5; 6a·pyridine (1:1), 144110-23-6; 6a·acetone (2:1), 144110-24-7; 6a·acetonitrile (2:1), 144110-25-8; 6a·DMSO (1:2), 144110-26-9; 6a·THF (1:1), 144110-27-0; 6a·dioxane (4:3), 144110-28-1; 6a·benzene (2:1), 144110-29-2; 6a·methylcyclohexane (2:1), 144110-30-5; 6b, 144177-92-4; 6b·MeOH (2:3), 144177-93-5; 6b·EtOH (2:3), 144177-94-6; 6b·2-PrOH (1:1), 144177-95-7; 6b·*t*-BuOH (1:3), 144177-96-8; 6b·c-HexOH (2:3), 144177-97-9; 7a, 37031-29-1; 7b, 116499-08-2; 8, 144110-31-6; 9, 144110-32-7; 10, 144110-33-8; 11, 144110-34-9; 12, 144110-35-0; 13, 144177-98-0; 14, 144177-99-1; 15, 144178-00-7; 16, 144110-36-1; ClC_6H_4-*p*-Br, 106-39-8; BrC_6H_4-*p*-Me, 106-38-7; FC_6H_4-*p*-Br, 460-00-4; BrC_6H_5, 108-86-1; BrC_6H_4-*p*-CF_3, 402-43-7; 3,5-difluorobromobenzene, 461-96-1.

Supplementary Material Available: Spectroscopic (IR, ^1H NMR, ^{13}C NMR, MS) and elemental analytical data of the new

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compounds (Tables VI–X) and Figures 5, 7, and 10 (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The author has deposited atomic coordinates for the structures of Table III with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Directed Ortho-Lithiation of Phenylcarbamic Acid 1,1-Dimethylethyl Ester (*N*-Boc-aniline). Revision and Improvements

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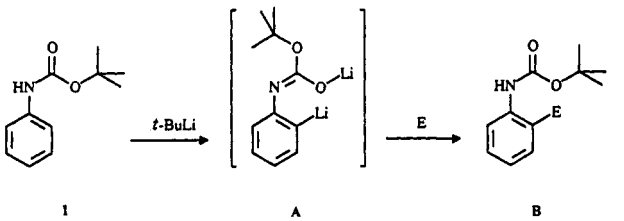
Evaluation of the results of a study, undertaken to examine the influence of the main reaction parameters (lithiation temperature, concentration, lithiating agent, and solvent) on the course of the title reaction, subsequently led to the development of an improved and more generally-applicable lithiation procedure. Hitherto unpublished stability data for solutions of *t*-BuLi and *n*-BuLi/TMEDA in diethyl ether and THF are reported for various temperatures.

The methodology of directed or heteroatom-facilitated lithiation has evoled—especially during the past decade—to an extremely powerful tool in the field of organic synthesis.[1] In particular, the development of new strategies for the buildup of polysubstituted aromatics and heteroaromatics was strongly influenced by this technique,[2] as substitution patterns difficult to obtain by standard substitution tactics became easily accessible starting with educts bearing suitable directed metalation groups (DMG's). In the meantime, an ever-increasing number of various functional groups, known to be applicable as ortho-directors,[2] became available to the synthetic chemist. Particularly among the known N-related DMG's, the *t*-BuOCONH[3] and the *t*-BuCONH functionalities[4] are of special value as they offer the advantage of an easy regeneration of the free amino function somewhere in the course of a multistep synthesis. Due to the fact that deprotection can be achieved under milder conditions, the carbamate structure seems favorable.

The first paper, where the *t*-BuOCONH group was applied as an ortho-director, was published by Muchowski and Venuti[3] in 1980. Dilithiation of 1 and subsequent reaction of the intermediate A with various electrophiles yielded a series of 2-substituted products B demonstrating the ortho-directing potential of this attractive functionality (Scheme I). The lithiation conditions recommended in this paper (addition of 2.4 equiv of *t*-BuLi to a 8% solution of 1 in THF at −78 °C and then stirring for 2–2.5 h at −20 °C) were referred unchanged in most cases where this DMG later was used in directed ortho-lithiations.[5] On the other hand, it is noteworthy that the yields reported in all these papers vary inexplicably over a wide range, reaching those of the initial paper (59–91%) only in two cases.[5j,k]

Scheme I



1 A B

Table I. Directed Ortho-Lithiation of 1 with *t*-BuLi/THF, 2.5 h at −20 °C, Me_2S_2 as Electrophile

entry	equiv of *t*-BuLi/concn[a] of 1	yield[b] of 2 (%)
1[c]	2.4/80	60–90
2	2.4/50	<10
3	2.4/100	52
4	2.4/200	65
5	5.0/100	66

[a] Concentration of 1 in mg/mL of THF. [b] Isolated yields of pure material. [c] Conditions in ref 3, reported yields obtained by using various electrophiles.

In the course of our own research work, we intended to exploit the ortho-directing power of the *t*-BuOCONH-group for the synthesis of some benzoannelated heterocyclic systems. Due to disappointing results obtained in our first attempts to lithiate 1 according to the cited standard conditions we became motivated to study this reaction in more detail. In particular, the influence of changes of the lithiation temperature, the applied concentration of 1, the kind and amount of the lithiating agent, and the solvent on the course of the title reaction had to be considered. To follow the progress of the lithiation reaction, samples of the reaction mixture were taken periodically and quenched with Me_2S_2. The conversion was then easily determined by comparing the integrals of the *t*-Bu groups of the educt 1 and the resulting 2-SMe product 2 in the ^{1}H-NMR.

Concerning the reaction temperature, it was observed that, below −40 °C, the rate of the ortho-lithiation of 1 is very low. Consequently, the lithiation must proceed mainly in the temperature range between −40 and −20 °C. Since no details are given in the literature about the time

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