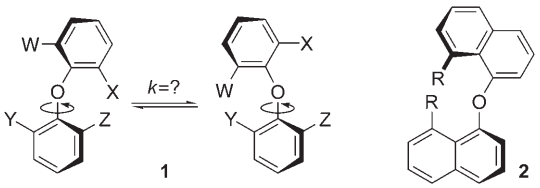

Scheme 1. Atropisomerism in diaryl ethers.

Stereochemistry

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Three Groups Good, Four Groups Bad? Atropisomerism in *ortho*-Substituted Diaryl Ethers**

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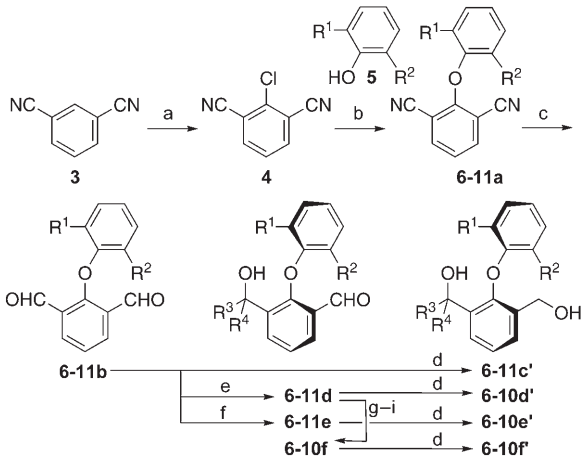
The vancomycin family of antibiotics[1] contains a cyclic peptide aglycone that features three unusual stereogenic features—an atropisomeric biaryl and two atropisomeric diaryl ether units—all incorporated into three fused macrocyclic rings. Atropisomerism is associated principally with single bonds that join a pair of hindered planar groups,[2] and the *ortho*-substituted biaryl atropisomers (of the type present in vancomycin and its acyclic congener actinoidic acid,[3] for example, but also many other compounds) are of course by far the most well known. By contrast, the structural requirements for atropisomerism in diaryl ethers **1** outside of a cyclic framework remain unclear (Scheme 1), despite the presence of diaryl ether units in a range of natural products, including the bastadins for example.[4] McRae et al. in 1954[5a] commented that compounds of type **1** "show, in wooden models, an unusually great degree of steric hindrance about the diphenyl ether linkage". Dahlgard and Brewster[5b] proposed in 1958 that diaryl ethers might exist as separable atropisomers, and some sub-atropisomeric barriers to bond rotations were measured in a small range of compounds **1**,[6,7] but it was not until 1998 that Fuji and co-workers[8] resolved three examples of **2**, the only non-macrocyclic diaryl ethers that have yet proved to be atropisomeric. Herein, we report the synthesis, stereochemistry, stereodynamics, and stereoisomeric separation of a set of simple diaryl ethers and deduce some empirical rules to describe the requirements for chirality in this class of molecule.

Two complementary methods provided the hindered diaryl ethers. Nucleophilic aromatic substitution is generally less sensitive to steric hindrance than the metal-catalyzed coupling reactions commonly used to make diaryl ethers,[9] and we found that the potassium salts of even rather hindered phenols **5** readily displaced the chloride group from **4** (made by lithiation of nitrile **3**[10]) to obtain ethers **6a**–**11a** in good yield. A sequence of addition, protection,[11] oxidation, and reduction reactions yielded the further series of compounds **6**–**11** shown in Scheme 2. Directed *ortho*-metalation is a powerful way of building sterically congested aromatic substitution in a regiocontrolled manner,[12] and the reported[13] sequence of lithiation and oxidation reactions shown in Scheme 3 gave further ethers **14**–**16**. Compounds **7e**, **9e**, **10e**, and **17** were additionally made from 3-bromobenzonitrile by a modification of Scheme 2 (the full experimental details are provided in the Supporting Information).



Scheme 2. Synthesis of diaryl ethers by nucleophilic aromatic substitution. Reagents and conditions: a) 1. LDA, −95 °C, THF; 2. C_2Cl_6; b) **5**, KOH, toluene, Δ, 2 h, then **4**, DMF, 150 °C, 16 h; c) 1. DIBAL, −78→20 °C, 16 h; 2. HCl, H_2O, 1 h; d) $NaBH_4$, THF; e) MeLi, Et_2O, −78 °C, 16 h; f) PhLi, Et_2O, −78 °C, 16 h; g) $(COCl)_2$, Me_2SO, Et_3N, −78 °C, CH_2Cl_2; h) (1*R*,2*S*)-(−)-ephedrine, toluene, Δ, 16 h; i) 1. MeMgI, THF, 0→20 °C, 16 h; 2. HCl, H_2O. DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide.

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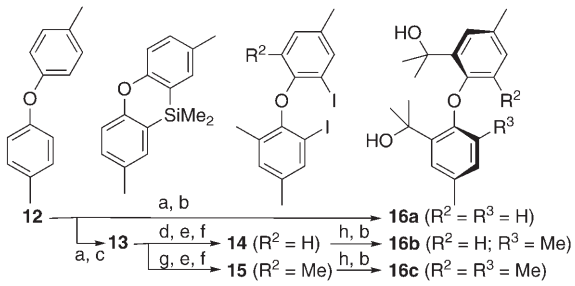


Scheme 3. Synthesis of diaryl ethers by sequential lithiation of di-*para*-tolyl ether.[13] Reagents and conditions: a) *n*BuLi, TMEDA, 20 °C; b) acetone; c) Me_2SiCl_2; d) *sec*-BuLi (×2), TMEDA, Et_2O, 0 °C, 2 h; e) MeI; f) ICl, CH_2Cl_2; g) *s*-BuLi (×3.5), TMEDA, Et_2O, 0 °C, 2 h; h) *n*BuLi, THF, −78 °C. TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine.

Activation parameters for bond rotation were estimated by using dynamic NMR spectroscopy at low and high temperature, following broadening or coalescence of diastereotopic H or Me signals or diastereoisomeric C*H*OH signals, and using an Eyring plot of the corresponding rates of interconversion k obtained by lineshape simulation.[14] Table 1 summarizes the results of these investigations (entries 1–15) and gives $t_{1/2}$ values (the half-life for racemization or epimerization[15] of **6–8**, estimated at 25 °C) and the $\Delta G^{\ddagger}$ value (the free energy of activation for the interconversion of stereoisomers) where appropriate. As expected, the barriers increased with increasing sizes of R^2 and R^3 for each type of substituent R^1 and were higher when the trisubstituted ring bore a tetrahedral CH_2OH group in the place of a trigonal CHO group or a digonal CN group.[16] The half-life for epimerization of **7d** displayed negligible solvent dependence in $CDCl_3$, [D_8]toluene, CD_3OD, and [D_6]DMSO (DMSO = dimethyl sulfoxide). The iodo- and isopropyl-substituted ethers **6** and **7** had broadly similar barriers to rotation (with **6** slightly higher) and in the case of **6f′** (Table 1, entry 4) variable temperature (VT) NMR spectroscopic

Table 1: Rates of isomerization in *ortho*-substituted diaryl ethers.[a]

Entry	R^1	R^2	R^3	R^4	Ether	Aldehydes **6–11**		Alcohols **6′–11′**	
						$\Delta G^{\ddagger}$[b] [kJ mol^{-1}]	$t_{1/2}$[b]	$\Delta G^{\ddagger}$[b] [kJ mol^{-1}]	$t_{1/2}$[b]
1	I	H	H	H	**6c**	–	–	78.8[c]	4 s[c]
2	I	H	Me	H	**6d**	[d]	0.02 s[e]	[d]	7 s
3	I	H	Ph	H	**6e**	[d]	0.06 s[e]	[d]	7 s
4	I	H	Me	Me	**6f**	76.8	3 s	95.7	1 h
5	*i*Pr	H	H	H	**7c**	–	–	71.5[c]	0.2 s[c]
6	*i*Pr	H	Me	H	**7d**	[d]	0.02 s[e]	[d]	2 s
7	*i*Pr	H	Ph	H	**7e**	[d]	0.02 s[e] 0.006 s[e,f]	[d]	0.4 s
8	*i*Pr	H	Me	Me	**7f**	78.5	3 s	90.9	8 min
9	*t*Bu	H	H	H	**8c**	–	–	88.0[c]	2 min[c]
10	*t*Bu	H	Me	H	**8d**	[d]	30 s	105.0 102.0[g]	20 h
11	*t*Bu	H	Ph	H	**8e**	[d]	2 min	[d]	> 10 h[h]
12	*t*Bu	H	Me	Me	**8f**	> 97[h]	> 2 h	113.5[i,j]	50 days[k]
13	CMe_2OH[l]	H	H	–	**16a**	–	–	71.0	0.1 s
14	CMe_2OH[l]	H	Me	–	**16b**	–	–	114.0[m]	40 days[k]
15	CMe_2OH[l]	H	CH_2OMe	–	**17**	–	–	108.7[l]	7 days
16	Me	Me[n]	H	H	**9c**	–	–	< 36[o]	< 1 μs
17	Me	Me[n]	Me	H	**9d**	< 36[o]	< 1 μs	< 36[o]	< 1 μs
18	Me	Me[n]	Me	Me	**9f**	< 38[o]	< 1 μs	< 38[o]	< 1 μs
19	*i*Pr	*i*Pr	H	H	**10c**	–	–	< 37[o]	< 1 μs
20	*i*Pr	*i*Pr	Me	H	**10d**	< 36[o]	< 1 μs	< 37[o]	< 1 μs
21	*i*Pr	*i*Pr	Me	Me	**10f**	< 38[o]	< 1 μs	< 38[o]	< 1 μs
22	*t*Bu	Me	H	H	**11c**	–	–	86.8[p]	–
23	*t*Bu	Me	Me	H	**11d**	[d]	6000 years[q,r]	–	–
24	*t*Bu	Me	Ph	H	**11e**	[d]	50000 years[q,r]	–	–
25	CMe_2OH[s]	Me	Me	–	**16c**	–	–	> 128[t]	> 50 years[r]

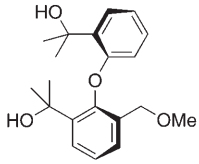
[a] Barriers to bond rotation determined by VT-NMR spectroscopic analysis at > 25 °C in [D_6]DMSO unless otherwise indicated. [b] Free energy of activation (±0.5–1.0 kJ mol^{-1}) for bond rotation and half-life for interconversion of rotamers (generally racemization or epimerization to equilibrium mixture) calculated at 25 °C.[15] [c] Rotamers are not stereoisomers in this case. [d] Bond rotation leads to epimerization. [e] Determined by VT-NMR spectroscopic analysis at < 25 °C in $CDCl_3$ (**6d**, **e**), [D_8]toluene (**7e**), CD_3OD (**7e**-CN), and in each of $CDCl_3$, [D_8]toluene, CD_3OD, and [D_6]DMSO (**7d**). [f] Half-life for the corresponding nitrile. [g] Barriers for two diastereoisomers determined by separation (HPLC) and equilibration at 40 °C in hexane/*i*PrOH (98:2). [h] No coalescence up to 150 °C. [i] Determined by resolution (HPLC, β-GEM, hexane/*i*PrOH (98:2)) followed by racemization in hexane/*i*PrOH (98:2) at 70 (**8f′**), 40 (**16b**), 60, and 80 °C (**17**). [j] Barrier at 70 °C. [k] Half-life estimated by assuming $\Delta S^{\ddagger} = 0$. [l] For comparison with **8**; $R^{2,3}$ refer to structure **16**. [m] Barrier at 40 °C. [n] Carries a *p*-Me substituent as well. [o] VT-NMR spectroscopic analysis in CD_3OD at −90–+20 °C.[20] [p] Determined by VT-NMR spectroscopic analysis in [D_6]DMSO at 25–150 °C; barrier probably corresponds to bond rotation that does not lead to racemization.[21] [q] Determined by flash column chromatography of diastereoisomers (**11d**: R_f = 0.58, 0.71 petrol/EtOAc (5:1)) and equilibration at 90 °C in [D_8]toluene (**11d**) or 115 °C in [D_6]DMSO (**11e**). [r] Half-life estimated by assuming $\Delta S^{\ddagger} = 0$. [s] For comparison with **11**; $R^{2,3}$ refer to structure **16**. [t] Determined by resolution (HPLC, β-GEM, hexane/*i*PrOH (98:2)) followed by attempted racemization in hexane/*i*PrOH (98:2) at 60 °C.

analysis indicated that the separation of atropisomeric stereoisomers might be possible at ambient temperature.[17] The results confirm that acyclic diaryl ethers have much lower barriers to rotation than those constrained within a macrocyclic ring.[18]

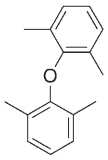
Nonetheless, many of the *tert*-butyl-substituted ethers **8** and related compounds **16b** and **17** showed no coalescence, even at 150 °C in [D_6]DMSO (Table 1, entries 9–15), which is indicative of barriers to rotation beyond those required for atropisomerism. Indeed, atropisomeric diastereoisomers **8d′** and atropisomeric enantiomers **8f′**, **16b**, and **17** were separable by HPLC. Each isomer showed a first-order decay to an equilibrium mixture when incubated in hexane/*i*PrOH between 40 and 70 °C, and we derived the half-lives reported in entries 10, 12, 14, and 15 (Table 1) from the rate of this decay.

Simplistically, we expected that—as with biaryl compounds[2,19]—two 2,6-disubstituted rings (namely, four *ortho* substituents) would provide much higher barriers to rotation for a variety of substitution patterns. However, dynamic NMR studies of the tetrasubstituted ethers **9** and **10**, in which $R^1 = R^2$, painted a very different picture (Table 1, entries 16–21). For all of these compounds, diastereotopic or diastereoisomeric signals of groups carried by the unsymmetrical ring remained unresolved even at −90 °C in CD_3OD, thus suggesting[20] barriers to racemization or epimerization at least as low as 36–38 kJ mol^{-1}.[21] The corresponding half-life for racemization or epimerization for these compounds is probably[20] less than 10^{-6} s, a factor of 100 000 shorter than for even the fastest racemization of the comparable ethers **7** bearing only one isopropyl group at R^1 and comparable with the rate of Ar–OAr rotation in thyroxine,[7] a di-*ortho*-substituted diaryl ether.

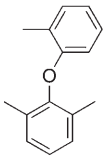
Molecular mechanics studies of some simplified analogues allow us to propose a reason for this huge discrepancy. Figure 1a,b shows two-dimensional plots generated by a macromodel (MM2*)[22] of the energy of simple tri- and tetrasubstituted model compounds **18** and **19**. The calculated



17



18



19

ground-state conformations of **18** and **19** are consistent with previous proposals:[23] the two rings are more or less perpendicular in **19** (conformations C and D in Figure 1), with the H atom "*endo*", whereas the two rings lie skew to one another in **18** to avoid steric interactions with the *ortho* substituents (conformations A and B in Figure 1).[24]

The "valleys" in Figure 1a,b run diagonally, which indicates that the lowest energy pathways for conformational interconversion in both **18** and **19** involve concerted (geared) rotation[25] of the two O–Ar bonds. For ethers **18** and any simple tetrasubstituted diaryl ether with at least one symmetrically substituted ring, such a process allows transition from one global minimum A to a mirror-image global minimum B. Ether **18** is symmetrical, but interconversion between mirror-image structures can take place along the dotted line in Figure 1a via transition state *x*.

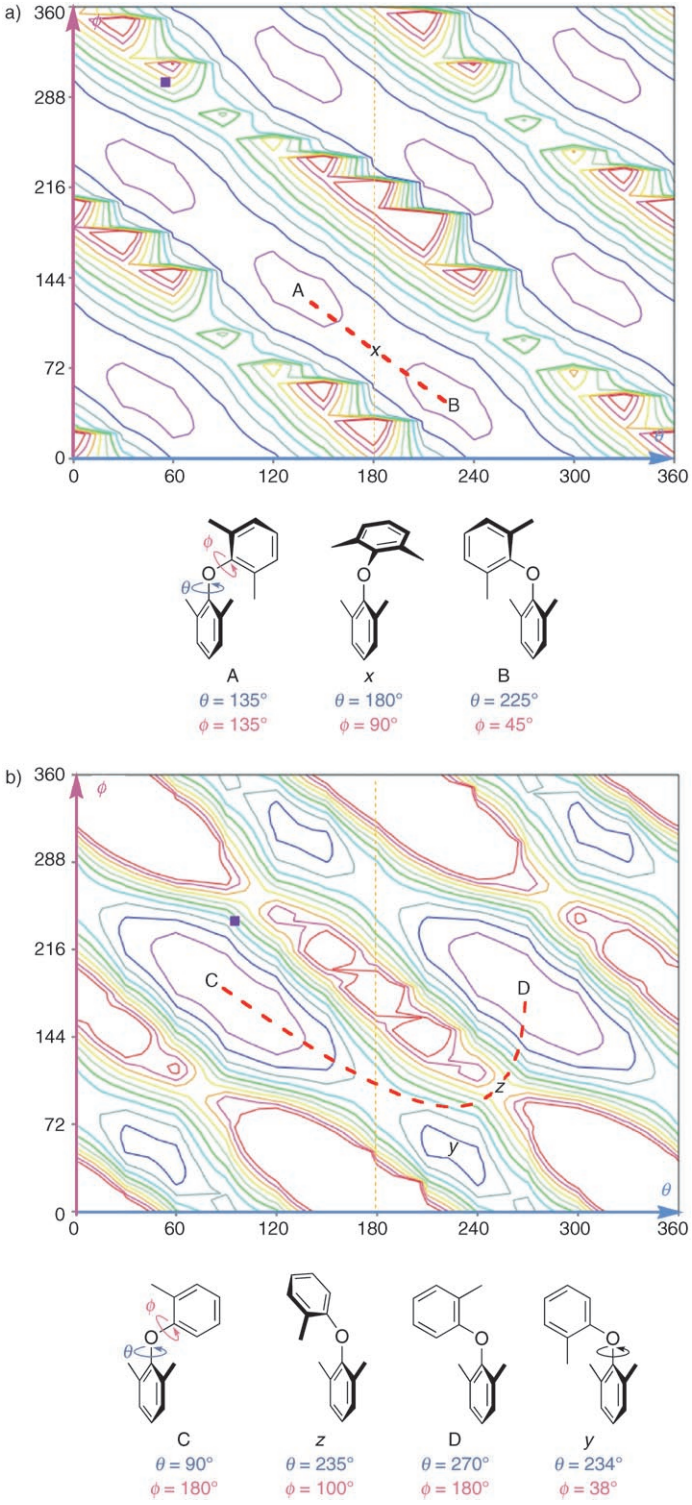


Figure 1. Potential-energy plots for bond rotation in **18** and **19**. a) Concerted bond rotation in **18.** b) Decoupled bond rotation in **19**.

Concerted rotation cannot interconvert the global minimum of one stereoisomer with that of its mirror image for the trisubstituted ether **19** (Figure 1b); concerted rotation from C instead passes through local minimum *y*, with the methyl group "*endo*". One of the two rings must decouple and undergo an independent rotation to racemize and yield D via transition state *z*. Mirror-image minima lie separated by the ridges on the potential-energy surface illustrated in Figure 1b, and their interconversion must follow the pathway represented by the dotted line.

If the proposal that the huge difference in rates of racemization between **6–8** and **9** and **10** arises from a change in mechanism of isomerization is correct, then any diaryl ether, whether trisubstituted or tetrasubstituted, that cannot isomerize by a low-energy concerted pathway (namely, in which both rings are unsymmetrically substituted) has the potential to display atropisomerism. We tested this hypothesis with the unsymmetrically tetrasubstituted ethers **11** and **16c** (Table 1, entries 22–25). Chromatographic separation of atropisomers was achieved for **11d**, **11e**, and **16c**, and incubation of the diastereoisomers of **11d**, **11e**, and **16c** at raised temperatures in toluene showed only slow isomerization, even over a period of weeks. We estimate that the half-lives for epimerization of **11d** and **11e** at room temperature reach well into millennia. Hindered 2,6,2′,6′-tetrasubstituted diaryl ethers with two unsymmetrically substituted rings are stable chiral compounds.

From this data, we draw the following conclusions about the potential for atropisomerism in acyclic diaryl ethers:

a) Atropisomerism in diaryl ethers depends less on the total number of substituents than the substitution pattern.
b) Diaryl ethers in which one of the rings is symmetrically substituted do not exhibit atropisomerism because their stereoisomers may interconvert by concerted bond rotation. This behavior means that even diaryl ethers with four *ortho* substituents may racemize rapidly.
c) Diaryl ethers in which both rings are unsymmetrically substituted may exhibit atropisomerism, as long as at least one of the substituents is as large as a *tert*-butyl group. This condition can hold even for diaryl ethers with only three *ortho* substituents.

In summary, the feature most favorable to high rotational barriers in diaryl ethers **1** is heavy, but unsymmetrical, substitution: for stable chirality **1** requires $(W,X,Y,Z \neq H)$, $(W \neq X)$, $(Y \neq Z)$, $(W \geq t\text{Bu})$, and $(Y \geq t\text{Bu})$.

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