Chirality

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C_2-Symmetric Metacyclophanes: A Possible Alternative to *o*,*o*′-Bridged Binaphthyls**

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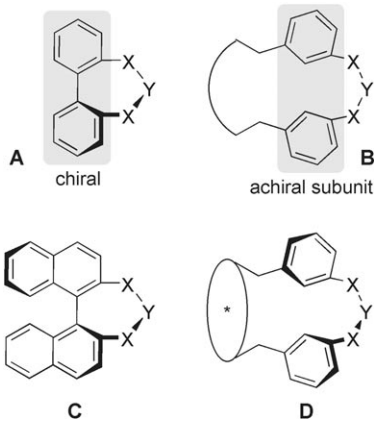
Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday

Among the most prominent examples of compounds containing a chiral axis are bridged biphenyls.[1] Owing to this chirality element, *o*,*o*′-bridged biphenyls **A** are chiral even



though at room temperature, rotation around the phenyl–phenyl bond causes racemization.[2] To prevent racemization or, to be more precise, to fix the molecule at room temperature (298 K) in one of the two conformations, the rotation barrier must be increased. This is realized by the incorporation of further substituents or by the use of *o*,*o*′-bridged binaphthyls **C** instead of biphenyls.[3] Such binaphthyls belong to the most important units in asymmetric synthesis and catalysis. For instance, *o*,*o*′-bridged binaphthyls are either used directly or in derivative form, such as 1,1′-binaphthyl-2,2′-diol (binol)[4] and 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap),[5] and the corresponding *o*,*o*′-bridged binaphthyl–metal complexes are formed in the course of the reaction. The effect of these ligands is based on the fact that one of the possible configurations is favored at the reaction center. The predetermination of a configuration at a center is often also termed chirality transfer. A higher chirality transfer means a stronger predetermination of the configuration.

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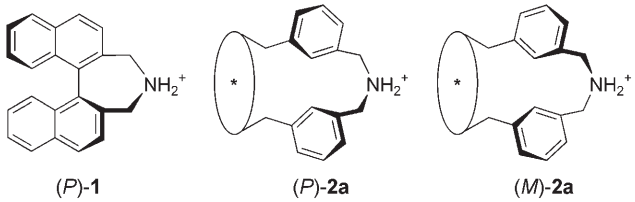
In contrast to the *o*,*o*′-bridged biphenyls, the corresponding metacyclophanes **B**, in which the two aromatic systems are linked by longer chains, are considered achiral.[6] However, it should be possible to stabilize one chiral conformation in a metacyclophane to the extent that it is the sole conformation at room temperature. This process, that is, the introduction of a new chiral element into an achiral subunit, can be termed chirality induction.[7] The stabilization of a chiral conformation in a metacyclophane is interesting not only for its own sake but also because such systems could be used as alternatives to *o*,*o*′-bridged binaphthyls. As a result of their higher steric demand, such C_2-symmetric metacyclophanes should be able to induce higher chiralty transfer. This type of stabilization of a chiral conformation of metacyclophanes has not been described previously.

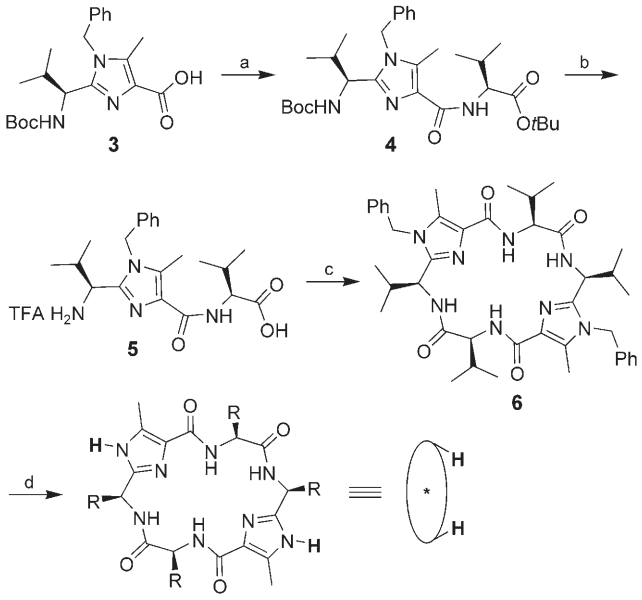
For the preparation of such a conformation-stabilized metacyclophane, we planned to synthesize the ammonium ion (*P*)-**2a**, an analogue of (*P*)-**1**.[8] The key feature in this



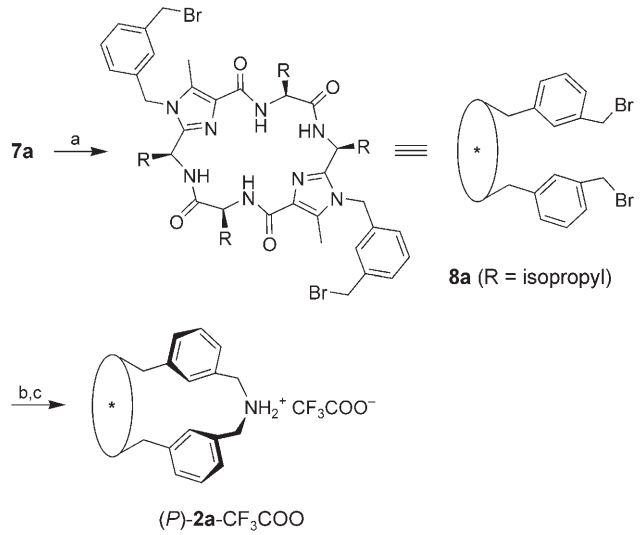
synthesis is the design of a chiral clamp able to stabilize a specific conformer. To be more precise, we planned to energetically destabilize the conformer (*M*)-**2a** substantially relative to the isomer (*P*)-**2a**.

As we had already used cyclic peptides having imidazole units in the backbone for chiralty transfer in C_3-symmetric compounds,[9] we decided to develop a chiral clamp starting from peptidic systems. Molecular modeling studies revealed that the C_2-symmetric compound **7a** (R = isopropyl) should be a suitable clamp (Scheme 1).[10] The imidazole-containing amino acid **3**[11] and L-valine *tert*-butyl ester were converted into the peptide **4** by coupling with pentafluorophenyl phosphinate (FDPP).

The two protecting groups (Boc and *tert*-butyl ester) were removed with TFA (trifluoroacetic acid) in dichloromethane. The resulting free amino acid **5** cyclized to give **6**. Removing the two benzyl protecting groups on the imidazole units yielded the chiral clamp **7a** (R = isopropyl). Two arms were attached to **7** by simple alkylation (Scheme 2). Reaction with ammonia and subsequent protonation with TFA led to the desired C_2-symmetric compound (*P*)-**2a**-CF_3COO.



Scheme 1. Preparation of the chiral clamp **7a** (R = isopropyl). a) FDPP, iPr$_2$NEt, CH_3CN, 89%; b) TFA, CH_2Cl_2, quant.; c) FDPP, iPr$_2$NEt, CH_3CN, 45%; d) H_2, $Pd(OH)_2$, $MeOH/CH_2Cl_2$, 95%.



Scheme 2. Preparation of (*P*)-**2a**-CF_3COO (R = isopropyl). a) 1,3-bis-(bromomethyl)benzene, Cs_2CO_3, CH_3CN, Δ, 56%; b) NH_3, K_2CO_3, CH_3CN, Δ; c) TFA, 50% (two steps).

To prove that as a result of the chiral clamp only the desired diastereomer (*P*)-**2a** is present, NMR and CD analyses as well as molecular modeling calculations were carried out. NMR measurements show that between −80 °C and 120 °C only one diastereomer exists. The signals of the diastereotopic hydrogen atoms next to the NH_2 groups are distinctly separated in this temperature range. Also the comparison of the CD spectra of the chiral scaffold **7a** and (*P*)-**2a**-CF_3COO shows that in (*P*)-**2a** one chiral conformation is stabilized. The two new bands of (*P*)-**2a** at 220 and 199 nm are in a region typical for simple aromatic systems (Figure 1).

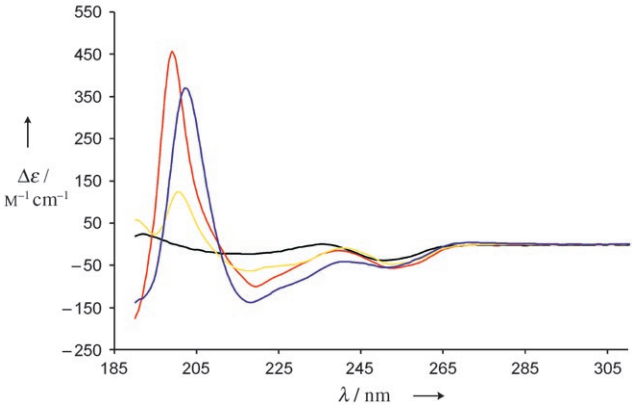


Figure 1. CD spectra of the chiral clamp **7a** (black) and the metacyclophanes (*P*)-**2a**-CF_3COO (red), (*P*)-**11a** (yellow), and (*P*)-**12a**-Br (blue).

Molecular modeling calculations[10] were carried out to determine the extent of the destabilization of the *M* isomer relative to the *P* isomer as a result of the chiral clamp. For the sake of simplification, in some of the calculations the isopropyl groups (R = isopropyl) of the imidazole and valine groups were replaced by simple methyl groups (R = methyl). As all of the isopropyl or methyl groups are orientated opposite to the ammonium unit, the size of the groups is of no importance. The calculated energy differences between the isomers **2a** do not differ essentially from those calculated for the isomers **2b** (Table 1). All calculations regardless of the method and basis set show that the *P* isomers are considerably lower in energy than the *M* isomers. The reason becomes clear when one examines the structures of the two diastereomers (*P*)-**2b** and (*M*)-**2b** (Figure 2).

In the *M* isomer there is a strong repulsive interaction between the methyl groups on the imidazole and the phenyl units of the metacyclophane. Based on the energy difference between the two diastereomers calculated using B3LYP/6-31G**, the ratio of the Boltzmann population between (*P*)-**2b** and (*M*)-**2b** should be approximately 10^{12}:1 at 298 K.[12] The comparison of the chiral metacyclophane (*P*)-**2b** with the binaphthyl derivative (*P*)-**1** shows that the environment of the ammonium group is very similar in the two molecules

Table 1: Calculated energy differences ΔE [kJ mol^{-1}] for pairs of diastereomers.

Method	(*P*)-**2a**/ (*M*)-**2a**	(*P*)-**2b**/ (*M*)-**2b**	(*P,P*)-**10**/ (*P,M*)-**10**	(*P,P*)-**12b**/ (*P,M*)-**12b**
HF/3-21G*[a]	101.9	96.9	4.8	−34.4
B3LYP/3-21G*[a]	94.8	91.4	6.6	−25.5
B3LYP/6-31G*[a]	–	74.9	6.5	−25.9
B3LYP/6-31G**[b]	–	75.3	7.3	−25.5
B3LYP/6-311G**[b]	–	69.0	5.3	−25.6
B3LYP/cc-pVDZ[b]	–	72.2	5.7	−28.3
B971/6-311G**[b]	–	75.0	6.7	−24.7
B971/cc-pVDZ[b]	–	77.6	6.3	−25.0
B3LYP/6-31G**[a]	–	75.2	6.4	–

[a] Full geometry optimization employing the indicated method. [b] Single-point calculations employing the indicated method based on the structure optimized with B3LYP/6-31G*.

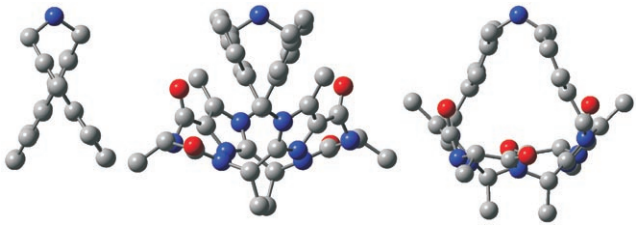
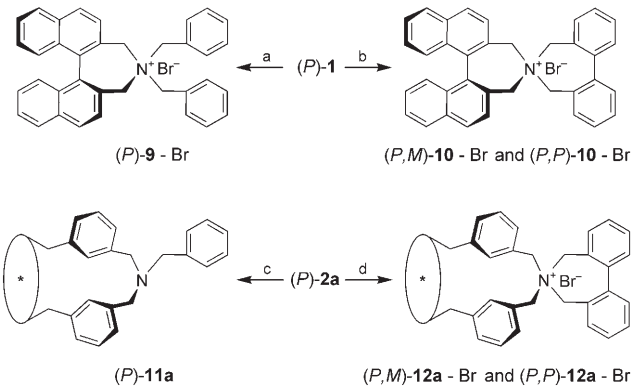


Figure 2. Molecular structures of (*P*)-**1** (left), (*P*)-**2b** (R = methyl; middle) and (*M*)-**2b** (R = methyl; right) calculated using B3LYP/6-31G**. C gray, N blue, O red. Hydrogen atoms have been omitted for clarity.

(Figure 2). In (*P*)-**2b**, however, the NH_2 unit is deeper in the cavity formed by the two phenylene groups, whereas in the case of the binaphthyl it is more exposed. The angle between the carbon atoms to which the two methylene groups are bound and the NH_2 unit is 127° in the case of (*P*)-**2b**, whereas in case of the binaphthyl (*P*)-**1** it amounts to only 75°. Accordingly, the steric demand of the aromatic units of (*P*)-**2b** is greater than that of (*P*)-**1**.

The greater steric demand of the aromatic units of (*P*)-**2a** also has ramifications in its chemical reactivity. For instance, in the benzylation of (*P*)-**2a** with benzyl bromide, only the tertiary amine (*P*)-**11a** can be isolated (Scheme 3). The corresponding quaternary ammonium compound can be detected only in traces. In contrast, the reaction of (*P*)-**1** affords the respective ammonium compound (*P*)-**9**.[13]

The reaction of (*P*)-**1** and (*P*)-**2a** with 2,2′-bis(bromomethyl)-1,1′-biphenyl yields in both cases the respective quaternary ammonium compounds (*P*)-**10**[14] and (*P*)-**12a** because one biphenyl group is sterically less demanding than two benzyl groups. As the newly introduced biphenyl unit contains a further chirality element, the extent of the chirality transfer of the two systems on the new unit can now be investigated. The NMR spectra of the two compounds show that the conformers are in equilibrium with each other at room temperature.[14] The CD spectrum of (*P*)-**12a**-Br is distinctly different from that of (*P*)-**2a**-CF_3COO (Figure 1). The extent of the energetic preference of one of the two conformations at the biphenyl unit can best be determined



Scheme 3. a) Benzyl bromide, K_2CO_3, CH_3CN, Δ, 53%;[13] b) 2,2′-bis(bromomethyl)-1,1′-biphenyl, K_2CO_3, CH_3CN, Δ;[14] c) benzyl bromide, K_2CO_3, CH_3CN, Δ, 90%; d) 2,2′-bis(bromomethyl)-1,1′-biphenyl, Cs_2CO_3, CH_3CN, Δ, 50%.

with molecular modeling studies. Table 1 compiles the energy differences between the diastereomers. It can be seen that independent of the method and basis set used the metacyclophane shows a larger chirality transfer, which means that it stabilizes one of the two possible configurations at the biphenyl unit better than the binaphthyl. Interestingly, in case of (*P*)-**10**, the homochiral conformer is more stable, while in case of (*P*)-**12b** it is the heterochiral conformer.

In conclusion, we have shown that it is possible to stabilize a chiral conformation of a metacyclophane by using a chiral clamp. This process can be understood as the induction of chirality. The resulting conformation resembles that present in binaphthyl units. Because in the metacyclophane the bridge is much deeper in the cavity of the aromatic rings, the chirality transfer onto a new chirality element is distinctly greater. The relatively simple preparation of the metacyclophanes—coupling of a chiral clamp to achiral units—opens up the possibility of synthesizing a vast number of new metacyclophanes and investigating their properties as asymmetric units in catalysis and synthesis.

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