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Tröger's Base Derivatives—New Life for Old Compounds

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Synthetic Tröger's base derivatives are reviewed, including their properties and applications. The rigid V-shaped Tröger's base framework and its inherent chirality have promoted the preparation of diverse receptor systems. Heterocyclic Tröger's base derivatives exhibit affinity for DNA. Metal complexes of Tröger's base are used as catalysts. New applications continue to emerge as synthetic methods are developed.

INTRODUCTION

Tröger's base (TB) **1** (Fig. 1), originally prepared from *p*-toluidine, and its derivatives have been known for over 110 years. Spielman [1], Wagner [2–5], Prelog [6] and coworkers pioneered the chemistry of **1** and its analogs. TB derivatives were initially viewed as anomalous chiral substances with two nitrogen-containing stereogenic centers. Until the 1980s, TB was used mainly for the evaluation of new separation techniques [7]. Interest in TB derivatives has since grown, as the field of supramolecular chemistry, specifically molecular recognition, has evolved. Wilcox and co-workers were the first chemists to envisage the shape and chirality of TB as useful design elements for molecular recognition [8]. Indeed, in the past 15 years there has been renewed interest in TB derivatives [9,10]. Their unique structures have been studied by supramolecular chemists with a view towards the preparation of many novel specific receptors [11,12].

SYNTHETIC APPROACHES

In 1887, Julius Tröger [13] discovered that the condensation of *p*-toluidine and HCHO in the presence of HCl yielded a product of molecular formula $C_{17}H_{18}N_2$. The structure of this compound was the subject of contention for nearly half a century [2]. The correct structure (**1**) was established by Spielman in 1935 [1]. A few months later, Wagner reported the sequence of reactions by which **1** is formed [4] (Scheme 1). This generated much interest, including re-examinations of mechanisms involving aromatic amine and HCHO condensations, over the next three decades [3,5,14].

The formation of the methano-1,5-diazocine skeleton of TB involves an electrophilic substitution reaction. The several electrophilic reactive centers in the starting aromatic amine can, however, promote polymerization. To inhibit polymerization it is necessary for the aniline derivatives to have the *para* position blocked. In principle, the starting aromatic amines can be fully substituted except for an *ortho* position that is required for the desired cyclization reaction. Electronic and steric effects of ring substituents have been reported to influence the regiochemistry [15–20] and yield [18] of this and related reactions.

The general preparation of TB derivatives is based on an acid-induced reaction of an aromatic amine with HCHO [18] or a source of a formaldehyde equivalent, such as paraformaldehyde, hexamethylenetetraamine [21] (HMT) or dimethoxymethane [22]. Methodology selection [22,23] and reaction conditions [24] afford varying yields of TBs. For example, 4-bromo-2-methylaniline furnished the corresponding TB derivative in 85% yield, using paraformaldehyde as a reactive agent. The corresponding yields on replacing paraformaldehyde with HMT or dimethoxymethane were 69% and 43%, respectively. The more common procedure with HCHO afforded no detectable product [23].

Alternative synthetic techniques towards TB derivatives were reported by Becker [25] and Čekavičus [26]. Becker obtained a highly

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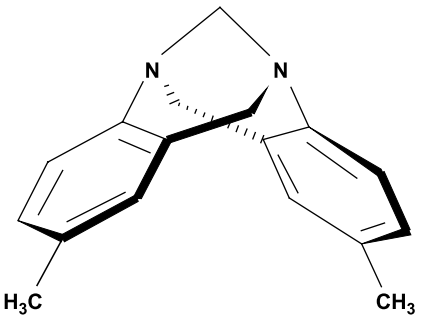

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FIGURE 1 Structure of Tröger's base.

functionalized TB derivative by heating methyl 5-chloro-4-[(ethoxyoxoacetyl)amino]-2-methoxybenzoate in DMSO at 180°C. Čekavičus reported that the novel heterocyclic system **3** arose via the intermolecular Mannich reaction of 1,1-dioxo-1,2-dihydro-benzo[*b*]thiophen-3-one (**2**) (Scheme 2).

A strategy for producing unsymmetrical TB derivatives is based on the Wilcox synthetic protocol (Scheme 3). Starting aromatic amine **4** was reacted with the derivative of isatoic anhydride, 3,1-benzoazine-2,4(1*H*)-dione (**5**), or 2-nitrobenzoic acid (**6**) to afford aminoamide **7** and nitroamide **8**, respectively. The reduction of **7** or **8** is followed by a final cyclization reaction of bisamine **9** to yield unsymmetrical TB derivatives **10** [27].

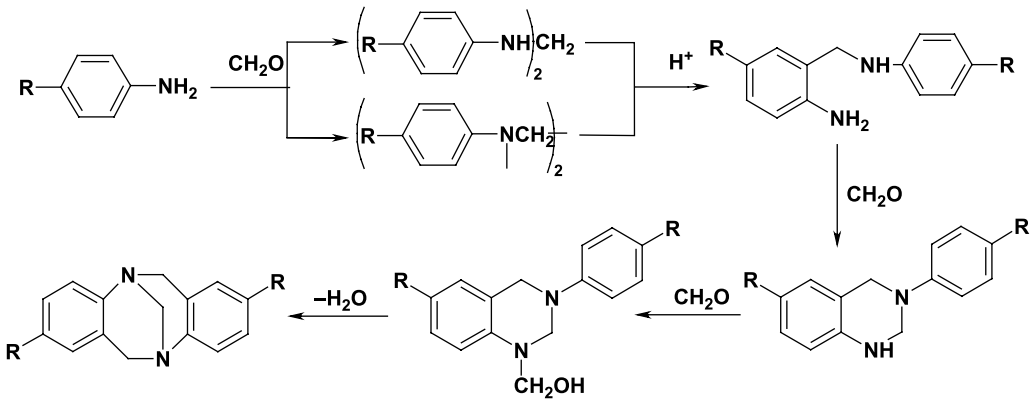
Unsubstituted TB derivative **11a** has not been used directly, or even via the multistep sequence described in Scheme 3. As mentioned previously, the main complication in TB formation from aniline is oligomerization through the unsubstituted *para* position. Cooper and Partridge overcame this problem with the use of intermediate 5,6,11,12-tetrahydrophenomazine **12a** (Scheme 4), which provided **11a** in 85% yield [28]. In addition, 5,6,11,12-tetrahydro-2,8-dimethylphenomazine **12b** was used in the preparation of TB derivatives **11b** substituted at the endomethylene bridge (R′ = alkyl or aryl) [29].

OLIGO-TB DERIVATIVES

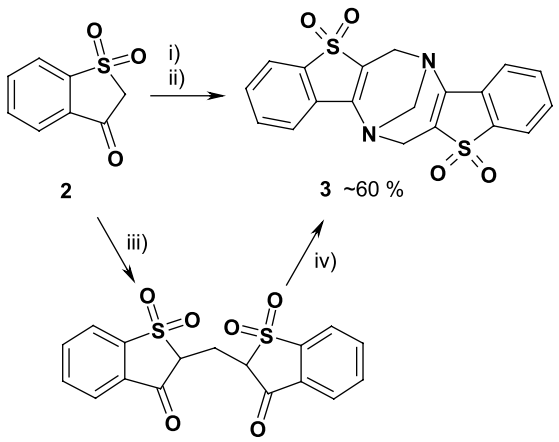
Compounds containing two [30–32] and three [32] TB units have been reported recently. These bis- and tris-TB derivatives were prepared by a synthetic pathway similar to the Wilcox procedure for the synthesis of unsymmetrically substituted TB analogs [27]. An original approach to bis-TBs introduced by Pardos and coworkers was based on the extension of amino TB derivative **13** with an additional TB unit, in a so-called step-by-step methodology [31] (Scheme 5, pathway A).

The synthesis of **13** requires five steps. Thus, the entire process required eight or nine steps. The total optimized yield was 14% (for **14**, $R_1 = CH_3$, $R_2 = NO_2$). We recently described a shorter four-step procedure to prepare bis-TBs **15** and **16**, and also tris-TB **17** from diaminobenzenes **18** and **19**, and 1,3,5-triaminobenzene **20** [32] (Scheme 6). Moreover, the simultaneous formation of the TB units on a central core may also be used towards the preparation of multi-TB systems. It may seem that our methodology is limited only to the preparation of symmetrical oligo-TB derivatives. However, the latest Pardos report demonstrates that the simultaneous approach is also applicable to unsymmetrical bis-TB [30] (see Scheme 5, pathway B). The overall yield in the preparation of **14** ($R_1 = CH_3$, $R_2 = NO_2$) was surprisingly lower than that of the original stepwise method.

The cyclization to form benzene-bridged bis-TBs is regio- and stereoselective. Only one isomer, whose central benzene ring is substituted in positions 1, 2, 3 and 4, of the two possible regioisomers was always obtained [30–32]. In the bis-TB systems, the *syn* configuration ('boat-like') is more attractive than the *anti* ('chair-like'), allowing for the construction of molecular tweezers. Moreover, some isomers of oligo-TB systems can provide 'dish-like' configurations (e.g. *syn*, *syn* equivalent of **17**) resembling calixarenes. Unsubstituted (**15**, **16**) or methyl (**14b**, $R_1 = R_2 = CH_3$) bis- and tris-TB



SCHEME 1 Proposed mechanistic outline of TB formation.



SCHEME 2 Mannich reaction in preparation of TB derivative **3**. Reaction conditions: (i) $(CH_2)_6N_4$, CH_3COONH_4, CH_3COOH or CF_3COOH; (ii) $(CH_2O)_n$, CH_3COONH_4, CH_3COOH; (iii) $(CH_2O)_n$, EtOH; (iv) $(CH_2)_6N_4$, CH_3COONH_4, CH_3COOH.

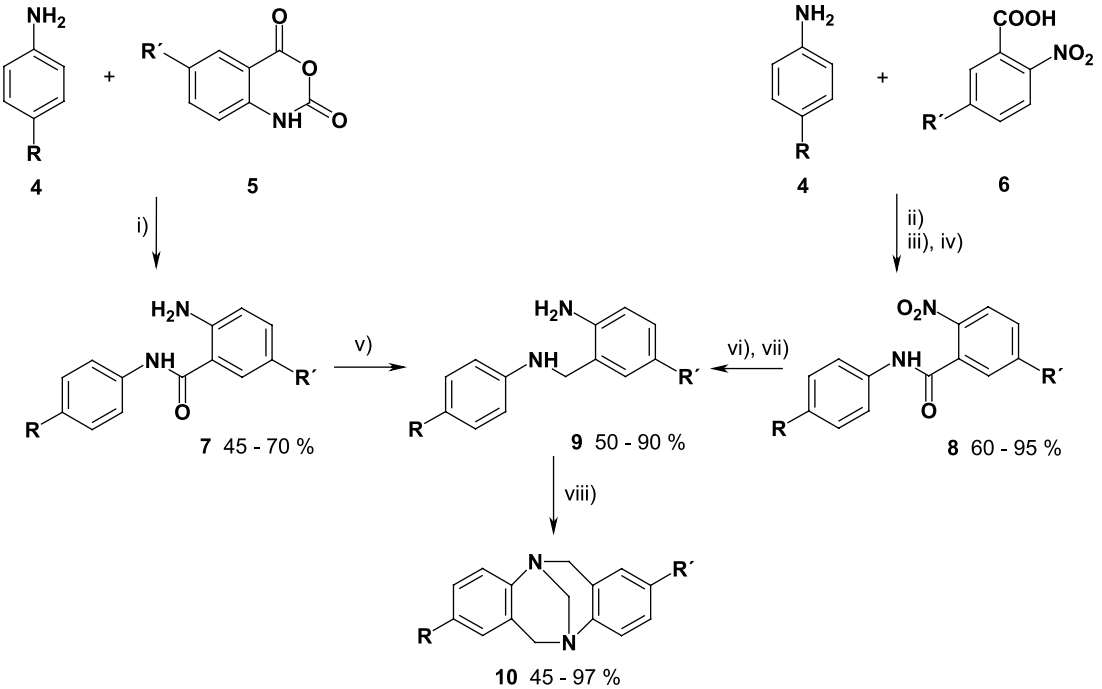
(**17**) derivatives afforded only *anti* or *syn*, *anti* diastereoisomers, whereas nitro bis-TB **14** ($R_1 = NO_2$, $R_2 = CH_3$ or NO_2) derivatives were also obtained in the highly interesting reverse *syn* configuration **14a**.

The relative proportions of the separated diastereoisomers **14a** and **14b** ($R_1 = NO_2$, $R_2 = CH_3$), the only bis-TB derivatives prepared by both synthetic pathways (Scheme 5), were not identical in each of the methods. The 'step-by-step' synthetic approach [31] afforded a 4:1 mixture of isomers **14a** and **14b**. However, in the case of the simultaneous strategy [30], a 1:1 mixture of isomers **14a** and **14b** was obtained under reaction conditions nearly identical to those of the cyclization method. Only the *anti* diastereoisomer **14b** was isolated when the reaction temperature was reduced from 90 to 50°C. This difference in stereoselectivity during the formation of **14** ($R_1 = NO_2$, $R_2 = CH_3$) by similar reactions can only be explained by stereoinduction of byproducts, because in the reaction mixture the diastereoisomers **14a** and **14b** are in thermodynamic equilibrium due to the ready interconversion (racemization) of the methanodiazocine bridges in acid media.

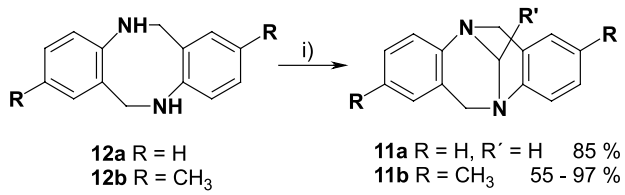
According to the observed results, the *anti* configuration of the bis-TB skeleton with the central benzene ring is probably thermodynamically more stable. Indeed, the thermodynamic stability of the *anti*/*syn* configuration of bis-TB derivatives depends on the polarity of the substituents on the external aromatic rings.

Very recently, we reported novel linear oligo-TB derivatives that exhibit impressive structural features [33]. These compounds possess cavitand-shaped binding sites. Effective new stepwise methodology for linear tris-TB **21** was reported (Scheme 7).

The regioselectivity during formation of these compounds is in accord with the regioselectivity in the preparation of bis-TB. Importantly, for the first time an efficient one-pot reaction was used to prepare the oligo-TB **22** (see Scheme 8). The synthetic process allowed access to tetrameric (**22**, $n = 3$) and higher (**22**, $n > 3$) order TB



SCHEME 3 Preparation of asymmetric TB derivatives. Reaction conditions: (i) EtOH, reflux; (ii) DCC, DMF; (iii) benzene, oxallyl chloride; (iv) DMF, pyridine, rt; (v) BH_3-THF, reflux; (vi) PtO_2 or Pd, H_2, MeOH; (vii) $LiAlH_4$, THF or Et_2O, reflux; (viii) HCHO, HCl.

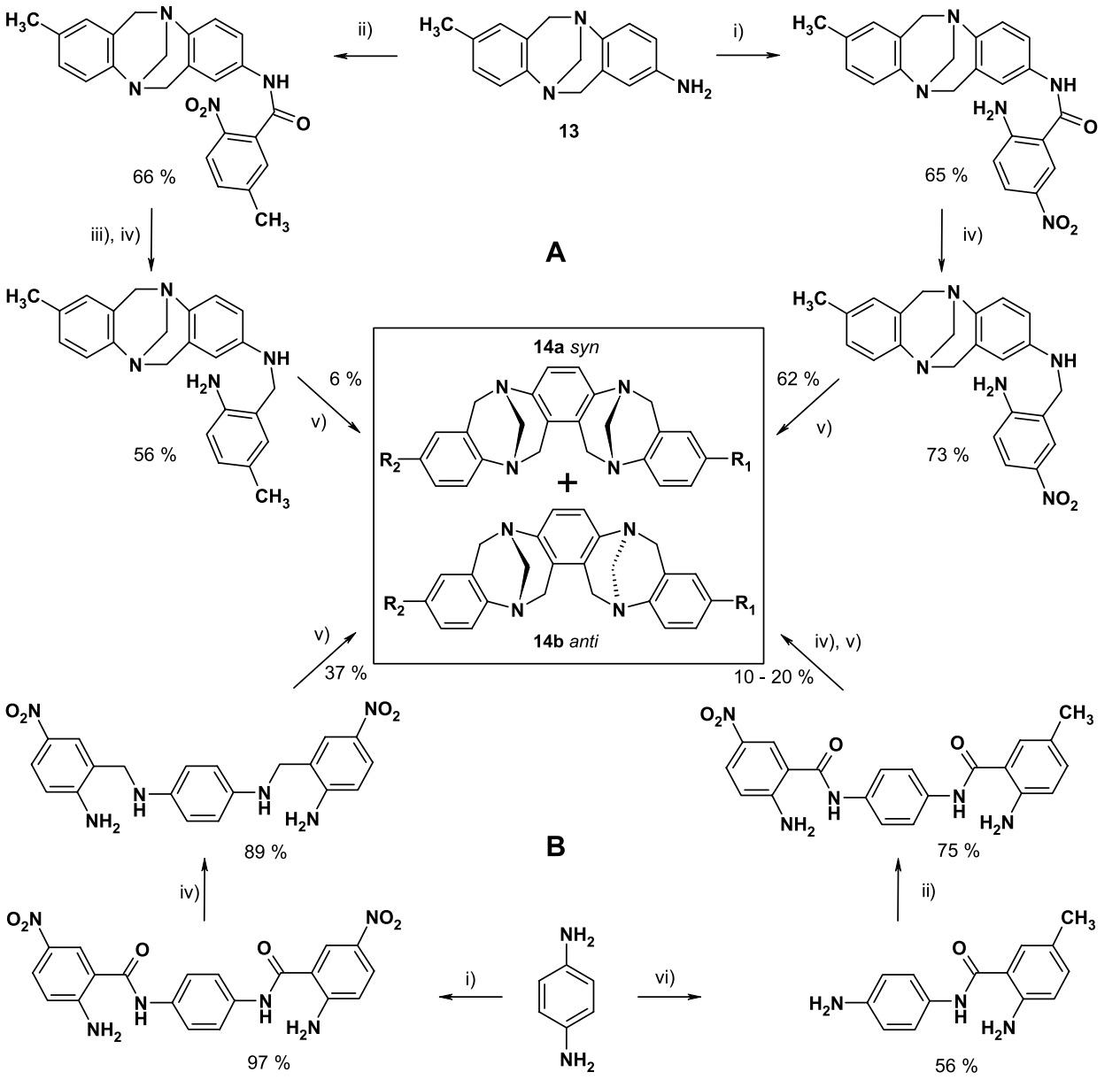


SCHEME 4 Preparation of TB derivative substituted at the endomethylene bridge. Reaction conditions: (i) R′CHO.

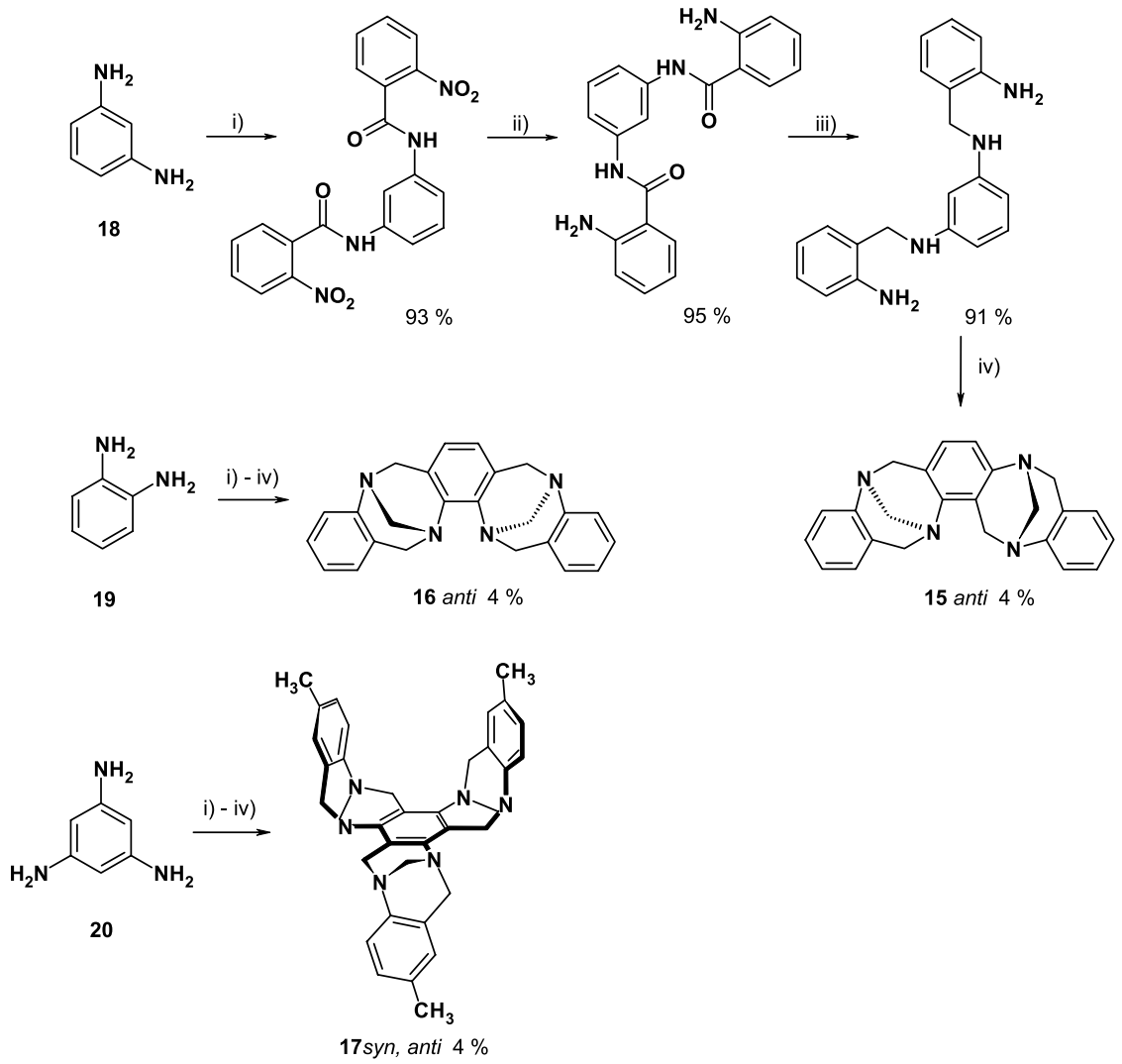
derivatives. This exciting new finding will encourage the design and study of novel chiral materials, with a wide variety of anticipated applications in materials science, organic and bioorganic chemistry.

THE REACTIVITY OF TB DERIVATIVES

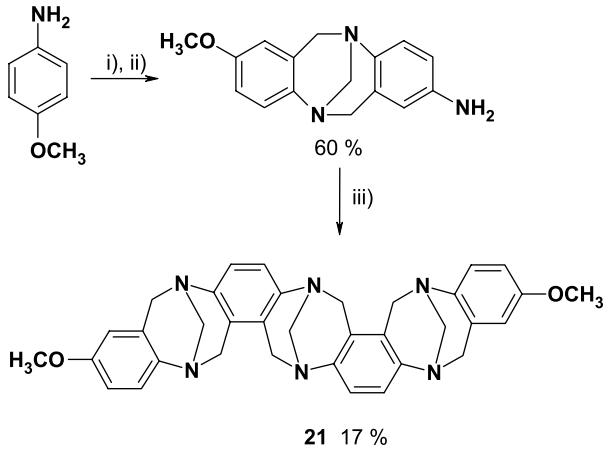
The reactions of TB derivatives can be divided into the chemistry of the aromatic moiety and that of the methanodiazocine bridge. The former is based on the general reactivity of functional groups. Using cross-coupling conditions (Scheme 9), such as the Ullmann [35] (pathway i for **23**), Corriu-Kumada [23] (pathway ii for **24**), Sonogashira [36] (pathway iii for **25**) or Suzuki [35] (pathway iv or v, vi for **26**) reactions, allowed transformation of the 2,8-diiodo- and 2,8-dibromo-substituted TB derivatives **27**. The asymmetric mono- and difunctionalized TB derivatives **28** and **29** were prepared by electrophilic substitution of the lithium salt generated from



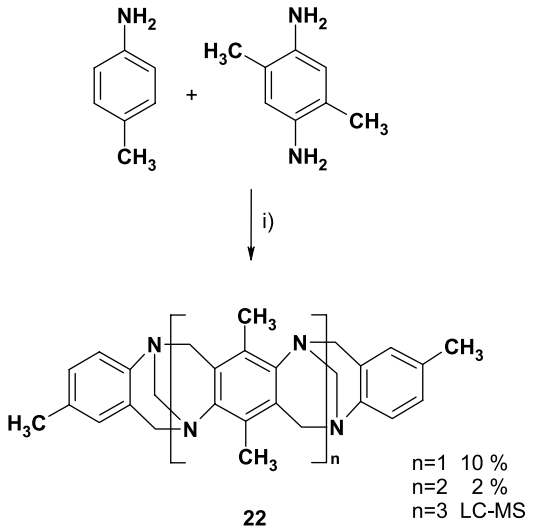
SCHEME 5 Step-by-step and simultaneous preparation of bis-TB derivatives. Reaction conditions: (i) 6-nitroisatoic anhydride, THF; (ii) 5-methyl-2-nitrobenzoic acid, DCC, DMF; (iii) Pd/C, H_2, $CHCl_3$/EtOH; (iv) BH_3-THF, reflux; (v) HCHO, HCl, EtOH; (vi) 5-methyl-2-aminobenzoic acid, DCC, DMF.



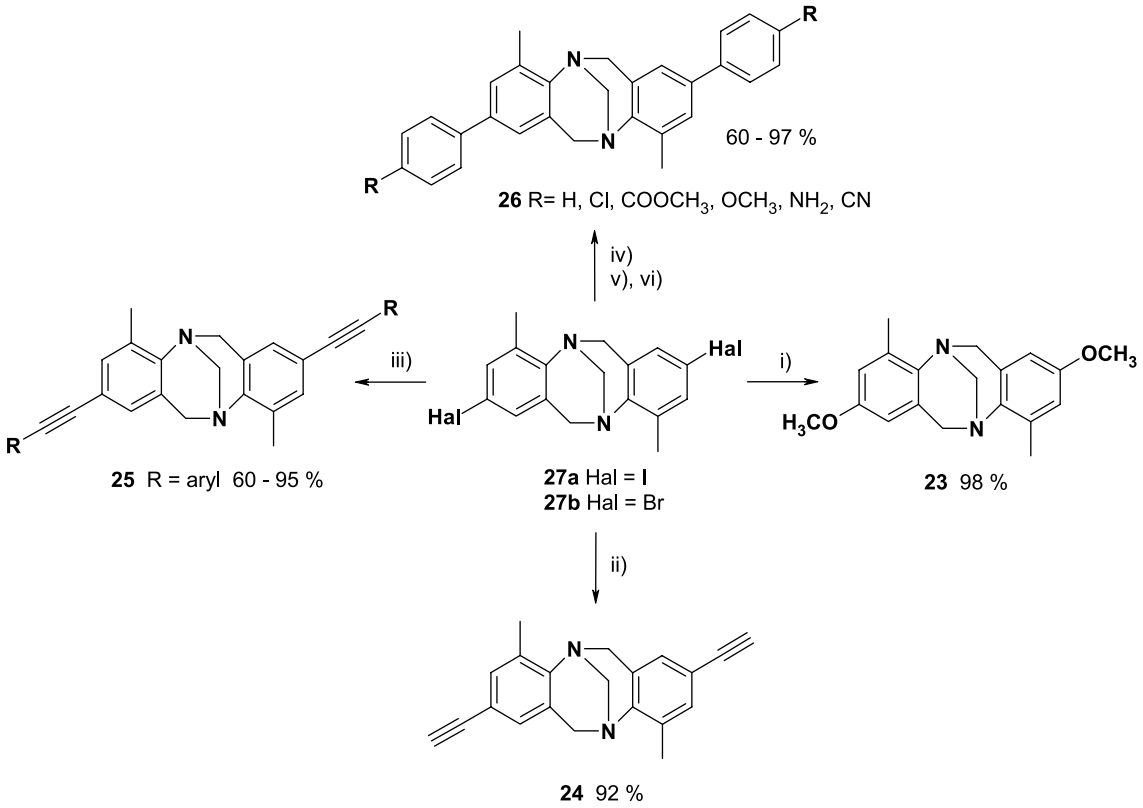
SCHEME 6 Simultaneous formation of bis- and tris-TB derivatives. Reaction conditions: (i) 5-substituted-2-nitrobenzoyl chloride, pyridine, DMF; (ii) Pd/C, H_2, MeOH, DMF; (iii) $LiAlH_4$, dioxane, reflux; (iv) H_2CO, HCl, MeOH.



SCHEME 7 Stepwise preparation of linear tris-TB. Reaction conditions: (i) similarly to conditions described in [34] in three steps; (ii) H_2, Pd/C; (iii) HMT, TFA, 60°C.



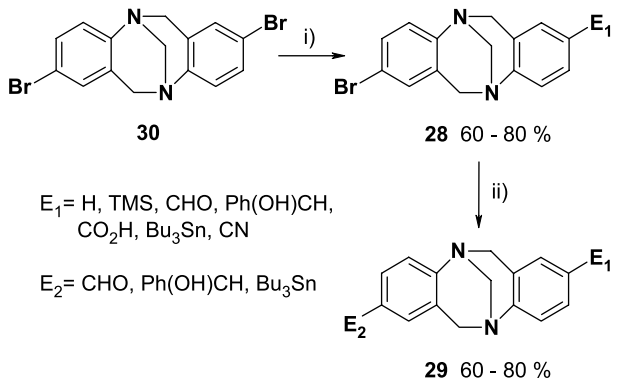
SCHEME 8 One-pot preparation of oligo-TB. Reaction conditions: (i) HMT, TFA, 80°C.



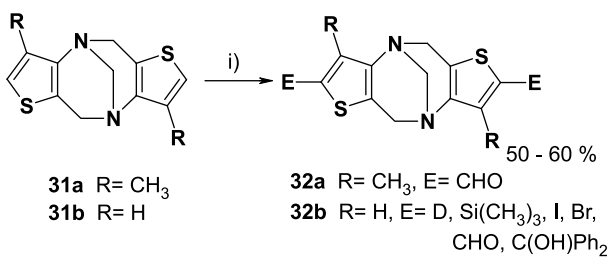
SCHEME 9 Cross-coupling reaction on halogen TB derivatives. Reactions conditions: (i) $NaOCH_3$, CuCl; (ii) ethynylmagnesium bromide, $Pd(PPh_3)_4$; (iii) , $Pd(PhCN)_2Cl_2$, P(*t*-Bu)$_3$, CuI; (iv) Pd[P(*t*-Bu)$_3$]$_2$, CsF, 4-substituted phenylboronic acid; (v) *n*-BuLi, THF, −78°C, then $B(OCH_3)_3$; (vi) Pd[P(*t*-Bu)$_3$]$_2$, CsF, 4-substituted iodobenzene.

the starting dibromo and monofunctionalized bromo **30** and **28**, respectively [37] (Scheme 10). An electrophilic substitution [20] of the lithium salt of **31** was then used to prepare the thiophene difunctionalized TB analogs **32** (Scheme 11). Recently, Sergeyev and Diederich reported a Bingel-type biscyclopropanation in the regioselective preparation of fullerene C_{60} TB cyclic adducts **33** [38] (Scheme 12). The reaction with enantiomerically pure starting TB bismalonate **34** diastereoselectively afforded adduct **33a**. Additionally, other bismalonate TB derivatives exhibited regio- and diastereoselectivity in the Bingel reaction with the fullerene C_{60} [39]. Further reactions of the TB aromatic moiety include nucleophilic substitution [40]; ester hydrolysis followed by ester [41] or amide [12,31,42] protocols; amidolysis [19]; and reduction of the nitro [31], amide [31,42] and benzyl ester [19] groups.

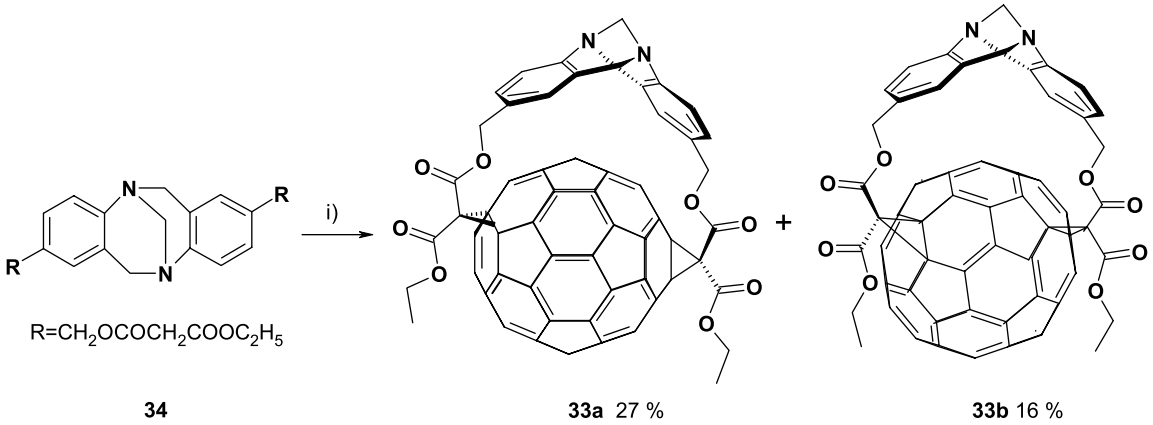
The methanodiazocine bridge of **1** is unaffected by sodium and boiling ethanol, and for the most part by Sn/HCl [1]. It is not oxidized by mercury oxide in Et_2O or by silver nitrate/ammonia. Degradation with HI/red-P at elevated temperature afforded 4-amino-1,3-xylene **35** as a single isolable product (Scheme 13). An improved yield



SCHEME 10 Bromine-lithium exchange followed by electrophile substitution. Reaction conditions: (i) *n*-BuLi, −78°C, electrophile (E_1); (ii) *n*-BuLi, −78°C, electrophile (E_2).



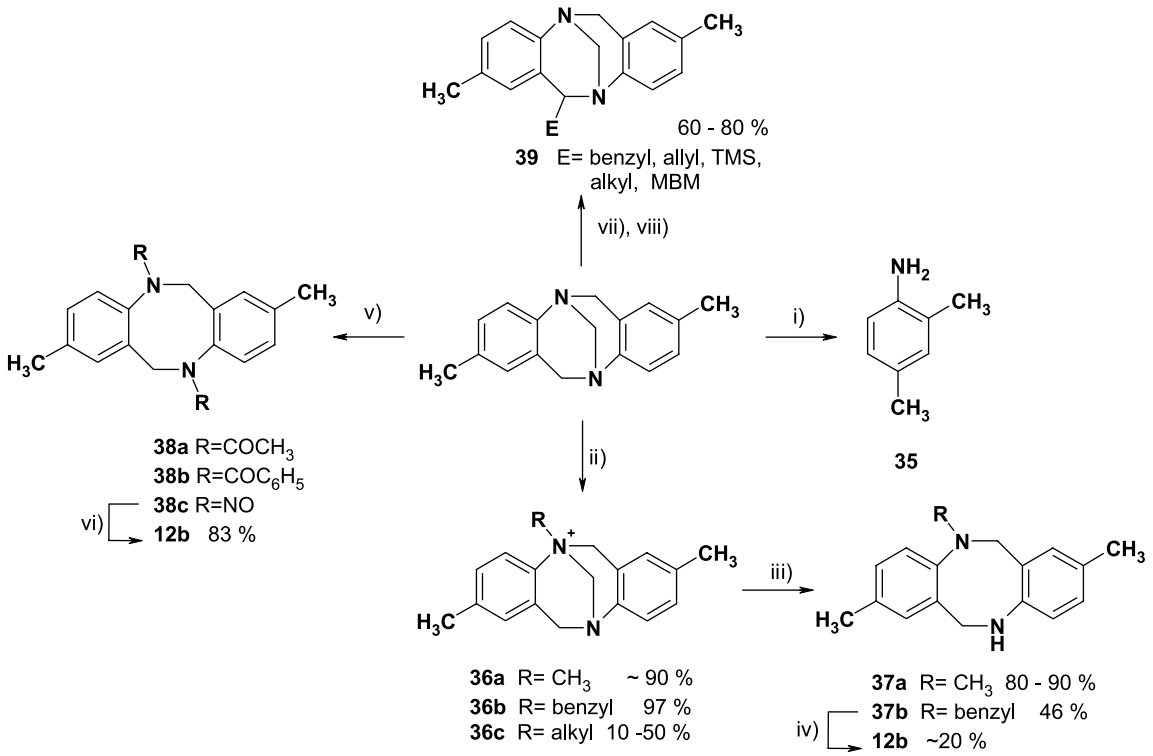
SCHEME 11 Hydrogen-lithium exchange followed by electrophile substitution. Reaction conditions: (i) *n*-BuLi, rt, electrophile.



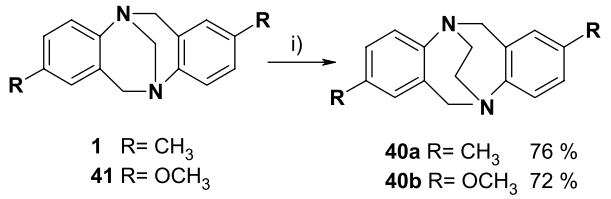
SCHEME 12 Bingel reaction of bismalonate TB derivative **34** with fullerene C_{60}. Reaction conditions: (i) C_{60}, I_2, DBU, 0°C.

of the reduced product was achieved when **1** was first refluxed with HI and then reduced with Sn/HCl [1].

Only a few reactions involving modification of the methanodiazocine bridge of TB have been described to date (see Schemes 13 and 14). The pK_a of the TB **1** monoprotonated salt has been determined to be 3.2 in 50% aqueous alcohol [43]. Alkylation of **1** afforded only the monoquaternary product **36** even in the presence of an excess of alkylating agent [29,44–46] (e.g. iodomethane, dimethyl sulfate, allyl and benzyl halides, etc.). Alkali treatment of **36** resulted in the fission of the endomethylene bridge and yielded the alkylamines **37** [29,45]. The catalytic hydrogenation of benzylamine **37b** gave the bis-secondary amine **12b** [45]. The acetylation, benzoylation and nitrosilation of **1** were performed by Spielman in his original determination of the structure of TB **1** [1]. Reaction with acetic anhydride or benzoyl chloride yielded the diacetyl **38a** and dibenzoyl **38b** derivatives, respectively. However, the reactions involved the loss of one carbon atom as HCHO. The dinitroso derivative **38c** was converted to the amine **12b** in high yield upon treatment with CuCl/HCl [29]. Metalation of **1** with *n*-BuLi in the presence of boron trifluoride etherate



SCHEME 13 Reactivity of the methanodiazocine part of TB **1**. Reaction conditions: (i) HI, red-P, 200°C; (ii) RX; (iii) OH^-; (iv) Pd/C, H_2; (v) $CH_3COOCOCH_3$ (for **38a**), C_6H_5COCl (for **38b**), HNO_2, HCl (for **38c**); (vi) CuCl/HCl; (vii) $BF_3{\cdot}Et_2O$, *n*-BuLi, −78°C; (viii) electrophile.



SCHEME 14 Preparation of ethano-TB derivatives. Reaction conditions: (i) $BrCH_2CH_2Br$, Li_2CO_3, 105°C.

afforded an organolithium TB functionalized at a benzylic methylene position. Subsequent reaction with electrophiles furnished alkylation products **39** without loss of stereochemical integrity [47,48].

Hamada and Mukai synthesized the ethano-TB analog **40** by the reaction of **1** and its methoxy derivative **41** with 1,2-dibromethane. The endo-methylene bridge was converted to endoethylene in greater than 70% yield [49].

GEOMETRIC CONSIDERATIONS

The rigid V-shape of the TB skeleton, formed by methanodiazocine bridging of the aromatic rings of the molecule, has played a considerable role in supramolecular chemistry. The X-ray structure of racemic **1** was reported by Wilcox in 1985 [50]. The aromatic rings of TB analogs are oriented roughly at right angles to each other. The dihedral angle between the aromatic rings depends on the substitution pattern of the aromatic rings. In the compounds examined to date, the dihedral angle ranges from 81° to 104° [18,51,52]. The (*R*,*R*)/(*S*,*S*) absolute configuration assigned to (−)/(+)-**1** by a combination of vibrational circular dichroism (VCD) spectroscopy and *ab initio* density functional theory (DFT) [53] was in accord with results obtained from X-ray crystallography of monoprotonated TB salts containing chiral anions [54]. The opposite absolute configuration of **1**, deduced from CD measurements, was reported earlier by Mason *et al.* [55]. The structure, VCD and IR spectra predicted using *ab initio* DFT were in excellent agreement with the X-ray structure and the experimental spectra obtained in CCl_4 and CS_2 solutions of **1** [56].

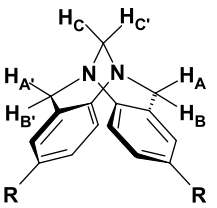


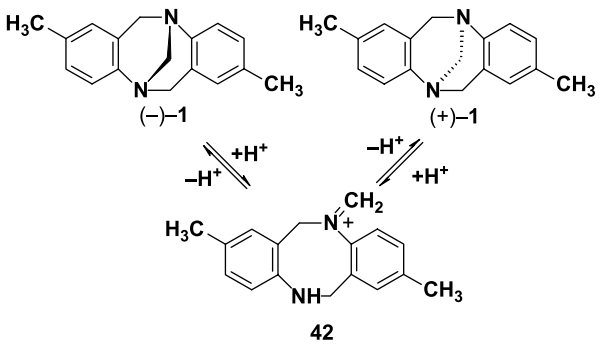
FIGURE 2 Detail structure of TB for the NMR studies.

The geometry of TB derivatives was also studied by nuclear magnetic resonance (NMR). The ^1H NMR spectrum exhibits, in addition to the aromatic peaks, an AA′BB′CC′ spin system for the methanodiazocine unit (see Fig. 2). The assignment of the *exo* ($H_AH_{A'}$) and *endo* ($H_BH_{B'}$) protons is mostly carried out by selective NOE irradiation of the bridging methylene protons ($H_CH_{C'}$). This resulted in enhancing the intensity of the *exo* protons. In the aromatic and most heteroaromatic TB derivatives, the lower field doublet was assigned to the *exo* and the higher field doublet to the *endo* protons [16,17,34,40,57–59]. The chemical shift of the *endo*/*exo* protons are strongly influenced both by the nature and the geometry of the constituent rings. This effect was most pronounced for the *endo* protons [17].

CHIRALITY

The enantiomers of asymmetrically substituted compounds containing trivalent nitrogen could not be completely resolved because of rapid pyramidal inversion at room temperature. Prelog and Wieland postulated that the inversion of **1** through the nitrogen atoms could be sterically discriminated by imposing ring strain [6]. Their effective resolution of (±)-**1** by liquid chromatography using a D-lactose column was one of the first examples of a chiral substance resolved chromatographically and the first example of the resolution of an amine, wherein the chirality is solely due to stereogenic N-atom(s) with a very high inversion barrier. Although, the resolution of (±)-**1** resulted only in a 5.5% isolation of both enantiomers from the racemate, optically active **1** was made available for study. The enantiomers (+)-**1** and (−)-**1** were found to be stable to the extent that they could be sublimed without any observable racemization.

However, racemization of TB is acid catalyzed. The mechanism of TB racemization was suggested by Prelog and Wieland [6] to proceed through the intermediacy of iminium ion **42** (see Scheme 15).



SCHEME 15 Proposed acid-catalyzed racemization of TB.

The Gibbs free energy $\Delta G^{\#}$ of acid racemization was estimated to be in the range 79.1–94.6 kJ/mol [60]. This result is in accord with the inversion barrier [61] of diacyl **38a** and dibenzoyl **38b**, reasonable models for the iminium intermediate **42**.

Greenberg *et al.* examined the mechanism of acid-promoted racemization by NMR and UV spectroscopy at room temperature [60]. However, only protonated forms of **1**, instead of the expected iminium ion **42**, were detected in acidic solutions of **1**. The fact that the NMR spectrum of monoprotonated **1** reflects C_2 symmetry indicates rapid proton exchange between the two bridgehead nitrogens on the NMR timescale. On the other hand, the 13,13-dimethyl derivative of **1**, which easily loses acetone in dilute acid, was found to form an iminium ion in concentrated acid. The authors attributed this observation to the fact that the iminium ion **42** might be present in undetectable amounts during the acid racemization process involving **1**.

An enantioselective dynamic electrokinetic chromatography technique was used by Trapp *et al.* for determination of rate constants, enantiomerization barriers ($\Delta G^{\#}$ at 298 K = 100.9 ± 0.5 kJ/mol) and activation parameters ($\Delta H^{\#}$ at 298 K = 89.5 ± 2.0 kJ/mol, $\Delta S^{\#}$ at 298 K = − 42 ± 10 J/mol K) of **1** at pH 2.2 [62]. Introduction of a permanent positive charge in TB **1** significantly decreased the enantiomerization barrier, which is not in conflict with the iminium-based theory.

CHIRAL RESOLUTION OF TB 1

TB **1** is one of the classic compounds used for studying the separation properties of chiral sorbents. As mentioned earlier, enantiomers of **1** were first separated by liquid chromatography on an α-D-lactose stationary phase in 1944 [6]. Very good resolution of (±)-**1** was achieved on a cellulose triacetate (CTA) system [63–67]. The thermodynamics of the adsorption [66] and mass transfer kinetics [65] of **1** on this phase with EtOH as the solvent were investigated by Guichon and coworkers using frontal analysis. For both enantiomers, the adsorption enthalpies and entropies decrease with increasing temperature in the interval 30-40°C. The opposite trend holds true for Gibbs free energies [66]. Recently, the separation of (+)-**1** and (−)-**1** on CTA was applied by Morbidelli and coworkers as a model system for simulated moving bed (SMB) chromatography [67–71].

Methods leading to the enantioseparation of (±)-**1** were also developed by using (+)-poly(triphenylmethylmethacrylate) [72,73], *trans*- and *cis*-tris(4-phenylazophenylcarbamate) [7] and a steroidal glycoside [74] as chiral selectors in high-performance liquid chromatography (HPLC) or capillary electrochromatography (CEC), respectively. The application of supercritical fluid chromatography (SFC) and gas chromatography (GC) techniques to modified cyclodextrins (Chirasil-β-Dex) [75,76] and the SMB separation of (+)- and (−)-**1** on amylose carbamate derivatives (Chiralpak-AS) [77] have also been reported. High levels of resolution (enantioselective factor $\alpha = 4.8 \pm 0.2$) of **1** was achieved by molecular imprinting of (+)- and (−)-**1** to methacrylic acid-ethylene glycol dimethylcrylate copolymers. The polymers prepared in the presence of (+)- or (−)-**1** demonstrated a distinct preference for (+)- and (−)-**1**, respectively. In the case of the reference polymer, involving copolymerization with (±)-**1** as a template, no enantioselectivity was observed [78].

For many years it was asserted that the resolution of enantiomers of **1** by diastereomeric salt formation with chiral acids was not feasible because of the ready racemization of the partially resolved salts in acidic media. The first success in resolving (±)-**1** with an acidic resolving agent was described by Wilen *et al.* in 1991 [54]. Reaction of (±)-**1** with (−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate (**43**) in EtOH yielded the diastereomeric salt (+)-**1**·(−)-**43** in a surprising 93% yield; 186% based on the amount of (+)-**1** in the racemate. The authors interpreted this finding as involving conversion of the (−)-**1** to (+)-**1** during formation of the precipitated diastereomeric salt (+)−**1**·(−) − **43**, which is in accord with the facile racemization of TB derivatives in acid medium [6]. In other words, the resolution was attended by a crystallization-induced asymmetric transformation of the diastereomeric salt.

CHIRAL RESOLUTION AND CHIRAL INDUCTION OF TB ANALOGS

Although TB analogs are chiral and their formation is not enantioselective, there have been relatively few reports of their resolution. Hamada and Mukai enantioseparated (±)-ethano-TB **40a** by diastereomeric salt formation using optically active di-*p*-toluoyltartaric acid in acetone. The attempted resolution of its methoxy derivative **40b** failed under the same as well as modified conditions [49]. Application of this procedure to resolve the naphthyl TB derivative proved successful only under anhydrous conditions [79]. The resolution of a proflavine TB analog was achieved by crystallization with dibenzoyl tartaric acid. The enantiomeric excess (*ee*) of the separation was *ca.* 80% (determined by NMR) [80]. Crossley and coworkers resolved the dizinc(II) bisporphyrin TB analog by chromatography over preabsorbed L-histidine benzyl ester on silica gel [11].

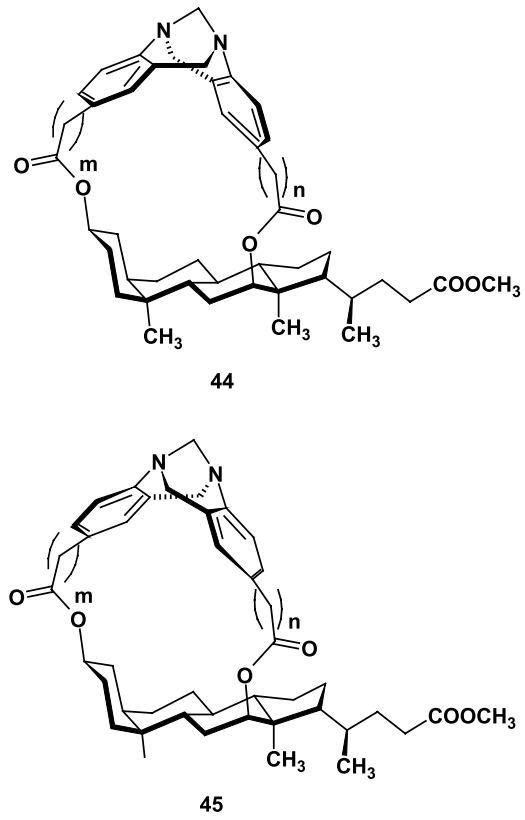


FIGURE 3 Diastereoisomers of steroid TB derivative.

An elegant synthesis to form optically pure TB analogs by diastereoselective cyclization of a chiral precursor was described by Webb *et al.* [21]. Maitra and coworkers reported chiral induction of a 7-deoxycholic acid template in the preparation of diastereoisomers **44** and **45** (Fig. 3) [51,81]. As the two diastereoisomers have different orientations in space, the authors expected that the spacer lengths linking the two aniline fragments to the steroid would influence the stereoselectivity during the preparation of **44** and **45**. Systematic alteration of the spacer lengths provided the most affected isomer, (*S*,*S*)-**44c**, in 75% yield with 70% diastereoselectivity [51]. However, it was impossible to separate the diastereoisomeric mixture by chromatography, even using a C_{18} HPLC column. Only slow crystallization of the mixture from EtOH afforded a small amount of the pure diastereoisomer **45a** [81].

An excellent example of the use of the TB moiety as a chiral auxiliary in asymmetric synthesis is the preparation of the above-mentioned fullerene TB derivative **33a**. The high asymmetric induction in the addition of **34** to fullerene C_{60} was attributed to the relatively large distance between the two reacting fullerene bonds spanned by the TB tether [38].

MOLECULAR RECOGNITION

The methanodiazocine bridge of TB has been incorporated into receptor designs to afford chirality and a rigid V-shaped geometry. Wilcox, Crossley, Maitra, Demeunynck, Lhomme and their coworkers have made use of the properties of TB in the construction of molecular torsion balances, chiral solvating agents, water-soluble cyclophanes, hydrogen- and metal-ligand-bonding receptors as well as DNA binders.

Wilcox and coworkers designed molecular torsion balances **46**–**48** to study edge-to-face aromatic interactions (see Fig. 4, **46**) [41] and CH-π interactions (see Fig. 4, **47**, **48**) [82], properties that play key roles in protein folding and molecular recognition. The energetic barrier (*ca* 2 kJ/mol in these experiments) of two possible conformational folded-unfolded states was calculated from equilibrium constants determined by NMR spectroscopy. The experiments supported the conclusion that the electrostatic potential of the aromatic rings is not a dominant aspect of the aryl-aryl interaction. Experimental data of edge-to-face interactions were subsequently compared to the molecular mechanics calculations by Nakamura and Houk [83].

PORPHYRIN TB DERIVATIVES

Crossley *et al.* covalently linked two tetraarylporphyrins through the methanodiazocine bridge of TB to prepare well-defined chiral cleft-containing molecules **49** and **50** (Fig. 5), whose molecular recognition properties could be monitored by electronic changes in the porpyhrin system [52]. Condensation of 2-amino-5,10,15,20-tetraarylporphyrin with HCHO afforded the bisporphyrin TB **49a**. Subsequent metalation of the porphyrin moieties of **49a** afforded zinc, palladium [52], cobalt and copper [11] complexes (**49b**–**e**) with M–M distances of 8.4–9.0 Å, as extrapolated from the X-ray structure analysis of **50b**. The binding properties of **49b** to compounds that can exploit the two metal binding sites, such as α,ω-diaminoalkane [52] and histidine and lysine esters [84], were studied by ^{1}H NMR and UV–Vis spectroscopy. 1,2-Diaminoethane displayed the greatest affinity ($K_a = 1.9 \times 10^8\,M^{-1}$) for the α,ω-diaminoalkane tested. The affinities were found to be reduced upon extension of the alkyl chain. In the case of histidine and lysine benzyl esters, the L-form of the guests preferred the (+)-enantiomer of the host **49b** by factors of 9.2 and 2.8, respectively. L-Lysine benzyl ester was bound less tightly to (+)-**49b** and (−)-**49b** than the benzyl and methyl esters of L-histidine [84]. The enantioselective recognition studies were later used for the resolution of racemic **49b** by chromatography on an L-histidine benzyl ester presaturated silica gel column. Surprisingly, the

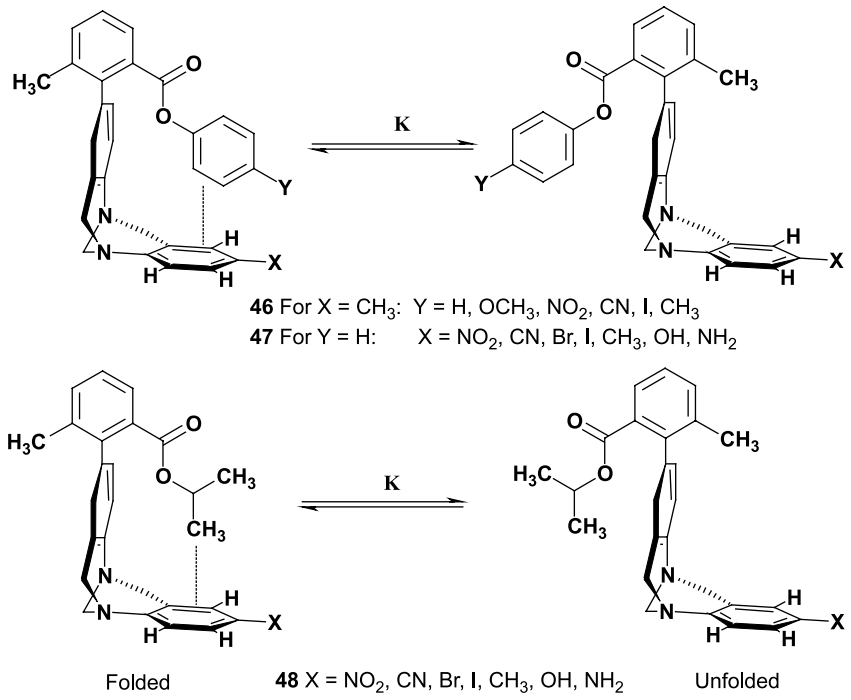


FIGURE 4 Conformational states (folded and unfolded) for 'Wilcox' molecular torsion balance.

enantiomer (+)-**49b**, which has a stronger binding interaction with the L-histidine benzyl ester, eluted from the column before (−)-**49b**. Moreover, the eluting fractions of the separated enantiomers (+)-**49b** and (−)-**49b** had different colors than the injected racemic material **49b**. The significant color change for (+)-**49b** indicated that (+)-**49b** was eluting as the (+)-**49b**·histidine complex, whereas (−)-**49b** consisted mainly of the free compound. This suggestion is also in accord with the rate of elution of (+)-**49b** and (−)-**49b** from the column, as the (+)-**49b**·histidine complex has a weaker interaction with the solid phase than free (−)-**49b.** This resolution technique was highly specific only for **49b** and the attempts to resolve **49c–e** by using this column proved unsuccessful [11].

The configuration of **49b** makes it a suitable model for primary donor–primary acceptor (D–A) pairs of

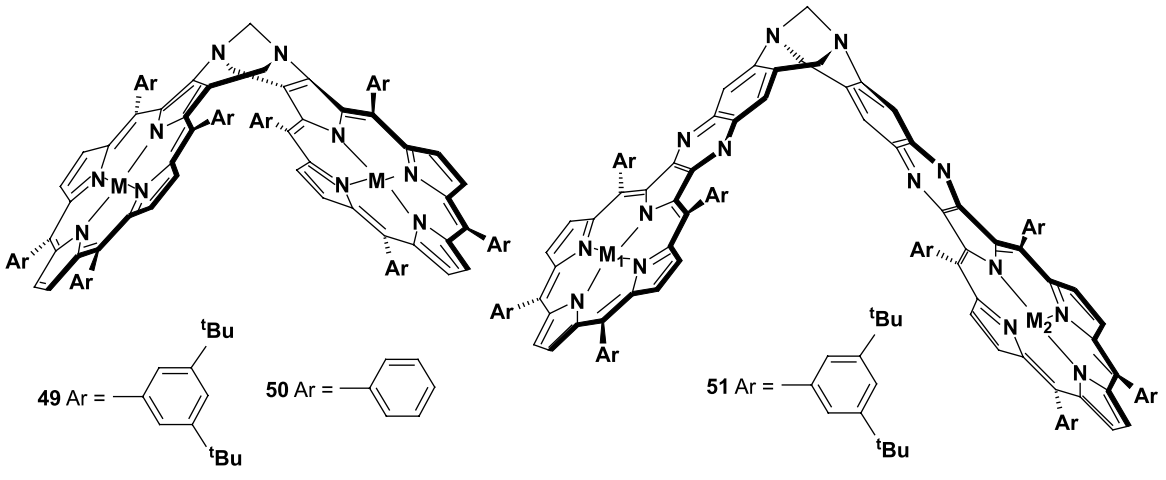


FIGURE 5 Porphyrin TB analogs and their metal complexes.

a bacterial photosynthetic reaction center (PRC). However, the center-to-center distance of **49** is less than 9.0 Å, instead of the required 16.5 Å. To mimic the geometry of the D-A pair of a PRC more closely, the porphyrin rings were separated by a quinoxaline-expanded bridge. The proper cavity size was achieved by the quinoxaline extension of the porphyrin rings to give the quinoxalinoporphyrin TB derivative **51**. The center-to-center distance and also an intermolecular edge-to-edge shortest distance in the zinc(II) complex **51b** were obtained by molecular modeling and conformed to distances found in the PRC by X-ray structural analysis [15]. The photophysical characterization, intermolecular electronic energy transfers between the rigidly linked free-base porphyrins of **51a** and from the zinc(II) porphyrin to the free-base porphyrin of **51c** were investigated by steady-state absorption and emission spectroscopy, time-resolved fluorescence spectroscopy and semiempirical calculations [85].

Like **49b**, compound **51b** was also found to bind ditopic α,ω-diaminoalkanes strongly. However, 1,7-diaminoheptane was the smallest guest that interacted with the receptor in a ditopic manner, forming a 1:1 complex. The binding strength of larger guests was significantly higher. The affinity of **51b** to long ditopic ligands suggested the use of the quatropic ligand *N*,*N*,*N*′,*N*′-tetrakis-(3-aminopropyl)-butane-1,4-diamine for the preparation of a molecular capsule with a tetraamine guest inside the spherical dimer of **51b**. UV–Vis monitoring of the titration of **51b** with the tetraamine, as well as ^{1}H NMR studies, confirmed the initial formation of the expected 2:1 complex, which dissociated to two 1:1 complexes (two Zn-amine bonds and two free amine groups per complex) at higher ligand concentrations [86].

HETEROCYCLIC TB DERIVATIVES

The intercalating ability of heterocyclic polyaromatics to DNA prompted the preparation and binding studies of methanodiazocine-derivatized phenanthroline and acridine derivatives. These compounds are of great promise as DNA probes because of their different possible modes of interaction with DNA and their chiral properties. The geometry of the TB unit affords these molecules a helical shape, which can be similar or opposite to the helicity of DNA [80]. Yashima *et al.* described for the first time the preparation of such a TB derivative (**52**) by the acid-induced reaction of 5-amino-1,10-phenanthroline with HCHO. A study of interactions with DNA revealed significantly higher changes in CD upon the addition of **52** as compared to the parent 1,10-phenanthroline. Moreover, the copper(I) complex of **52** caused nearly complete conversion of covalently closed circular pUC18 plasmid to open circular DNA [59].

Demeunynck and coworkers have investigated this aspect of TB chemistry in detail. The benzophenathroline **53** [87], asymmetric and symmetric acridine **54** [17,87,88] and acridino-phenanthroline **55a** [17] analogs were prepared and studied extensively by ^{1}H NMR spectroscopy (Fig. 6). This served to show the opposite relative chemical shifts of the *endo*/*exo* protons of the cyclic diazocine unit [17] (see Fig. 2).

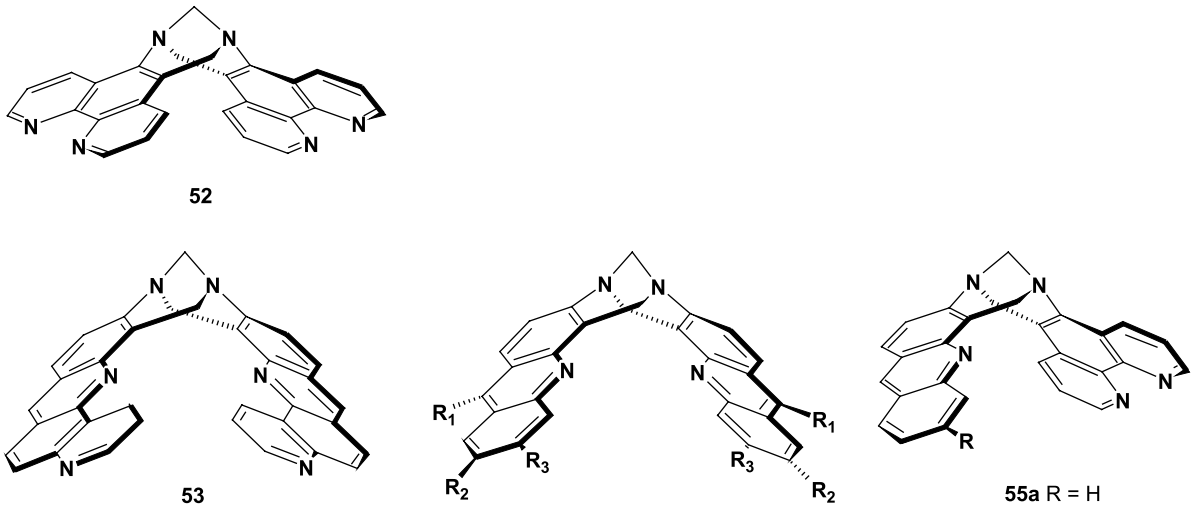


FIGURE 6 Heterocyclic polyaromatic TB analogs containing phenanthroline or acridine.

The UV–Vis spectrum of **54b** in the presence of calf thymus DNA recorded changes that varied as a function of pH [80]. The authors noted that the interaction with DNA should be accompanied by protonation of the acridine moiety. The same conclusion was drawn from an analysis of the CD spectra of **54b** recorded in the presence of calf thymus DNA and in 3 M HCl solution. The liquid-liquid partitioning of racemic **54b** between an aqueous solution of calf thymus B-DNA and BuOH revealed that (−)-**54b** preferentially associates with calf thymus DNA. After vigorous stirring and phase separation, the BuOH layer afforded a CD spectrum similar to (+)-**54b**. The spectrum of the aqueous phase was similar to that of (−)-**54b** [80]. Thermal denaturation studies confirmed the enantioselective binding of (−)-**54b** to DNA [89]. The stabilization of poly(dA-dT)$_2$ and poly(dI-dC)$_2$ (which contains inosine residues instead of guanosines because of the very high stability of poly(dG-dC)$_2$) by the (−)-isomer during thermal denaturation studies was significantly greater than that by the (+)-isomer or the racemic (±)-**54b** mixture. Although acridine derivatives are known as strong DNA intercalators, electronic linear dichroism (ELD) indicated that the acridine rings of **54b** are not intercalated into DNA. In addition, unlike conventional intercalators, the ligand had almost no effect on the relaxation of DNA induced by human topoisomerases. The lack of interference with the methylation of N7-guanidine residues of DNA suggested that the ligand interacts within the minor groove of the double helix.

Sequence selectivity was investigated by DNasa *I* footprinting. The (+)-antipode of **54b** failed to inhibit DNase *I* cleavage, even at high concentrations. However, the (−)-isomer strongly protected certain sequences against cleavage by this nuclease [89]. Compound (−)-**54b** recognized preferentially sequences containing both A·T and G·C base pairs, such as the motifs 5′-GTT·AAC, 5′-ATGA·TCAT and 5′-GACGTTGT·ACAACGTC. The symmetric structure of **54b** greatly complicated the analysis of the DNA binding data and mechanism. On the other hand, the DNA cleavage properties observed for the copper(I) complex of **52** [59] prompted the synthesis of an asymmetric acridine-phenanthroline TB analog **55b** [90]. The spectroscopic data from the CD and ELD experiments were compatible with a bimodal binding process, implicating intercalation of an acridine ring coupled with groove binding of the phenanthroline moiety. The DNasa *I* footprinting detected with the ligand **55b** was closer to that of the phenanthroline analog **52** than to the parent acridine **54b**. The triplet sequences 5′-GTC-5′-GAC were deduced as providing an optimal binding site for compound **55b** [90].

The affinity for DNA observed for the phenanthroline TB derivative **52** inspired Pardo and colleagues to develop heterocyclic TB analogs containing azole rings as substituents on the aromatic moiety (**56-59**), or analogs bearing heterocyclic aromatics (e.g. **60**–**62**, **63a**,**b**) [16,57,58]. All of the π-excessive amino heterocycles studied, including the amino derivatives of carbazole, pyrazoles, indazoles and benzothiazole, afforded the corresponding TB derivatives (**60**–**62**, **63a**,**b**), as would be inferred from the reaction mechanism. The cyclization was always regioselective and occurred towards the *ortho* position contiguous to the heterocyclic ring; presumably, this represents the most reactive site towards electrophilic reagents [16] (see Fig. 7 for compounds **60**–**62**).

The pyridine-extended TB derivative **64** developed by Johnson *et al.* exhibited very interesting results in the inhibition of the enzyme thromboxane A_2 synthase (TxA_2). The ED_{50} value (30 ng/mL) obtained for this compound was comparable to ED_{50} values for TxA_2 synthase inhibitors (sodium furegrelate, dazoxiben and OKY-1581) that had been extensively studied before [91]. Recently, Abonia *et al.* described the synthesis of pyrrazole **63c**–**g** and pyrimidine **65** TB derivatives and suggested the mechanism of their formation from isolated intermediates [92]. In this case, C-alkylation served to initiate the reaction instead of Schiff-base formation as proposed by Wagner (Scheme 15) [4].

The TB analog **66** (Fig. 8), bearing a heterocyclic ring with functional groups, allowed for the construction of more advanced and selective systems [19]. In this work, which was described by our group, amino-*N*-methylpyrroles were chosen as starting materials. This choice was made because the species constitute building blocks of the natural antibiotics, e.g. distamycin and netropsin. These latter compounds bind in the minor groove of DNA with high affinity and specificity. The incorporation of the methanodiazocine scaffold into oligo *N*-methylamidopyrrole derivatives resulted in TB analogs of natural antibiotics (**67**) that were obtained from dicarboxylic acid **66c** through an amide protocol. Preliminary experiments showed that the bisguanidine derivative **66e** and also bisacylguanidinium **66f** exhibit affinity for DNA.

APPLICATION OF TB DERIVATIVES AS ARTIFICIAL RECEPTOR SYSTEMS

The TB scaffold has been used extensively for the construction of molecular receptors following the initial studies of Wilcox and coworkers [8,40,42,93–95].

Chiral Solvating Agents

Wilen *et al.* observed that ^{1}H NMR spectra of $CDCl_3$ solutions of racemic alcohols (Ph-CR_1R_2OH) showed anisochrony of at least one set of peaks in

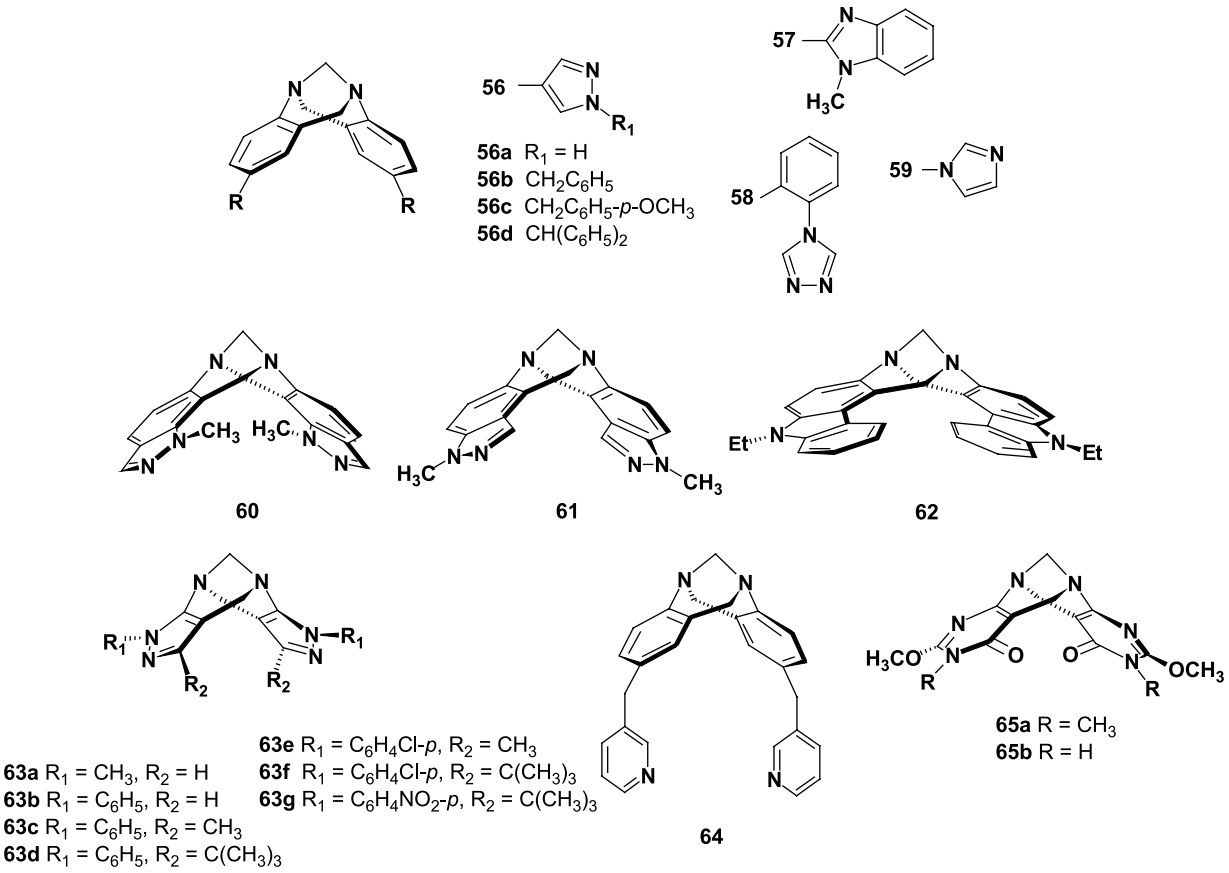


FIGURE 7 TB derivatives bearing heterocyclic aromatics (**56**–**62**, **64**) and TB derivatives of pyrrazole (**63**) and pyrimidine (**65**).

the presence of (+)-**1**. These results were best interpreted in terms of the participation of **1** as a chiral solvating agent that serves to effect discrimination between diastereomers. Enantiopure (+)-**1** generated intrinsically nonidentical chemical shifts in specific nuclei of the associated diastereomeric complex formed between (+)-**1** and an enantiomeric alcohol [54].

Water-soluble Cyclophanes

The ability of water-soluble cyclophanes to form inclusion complexes with aromatic, aliphatic and alicyclic substrates inspired Wilcox and colleagues to developed macrocyclic analogs of TB as rigid chiral receptors for small, neutral organic molecules [8,21,40,42,95].

The first examples of the cyclophane TB family included a bis[*p*-(alkoxy)phenyl]methane system containing two secondary ammonium groups (**68**; Fig. 9). Their binding properties were studied by NMR titrations carried out in DCl/KCl buffer (pD 1.9 ± 0.1). The association of hosts **68** to tested benzenoid substrates did not reach 350 M^{-1} and no significant selectivity was observed (see Table I). Nevertheless, the diphenylmethane unit provided a host **68a** with consistently better guest binding

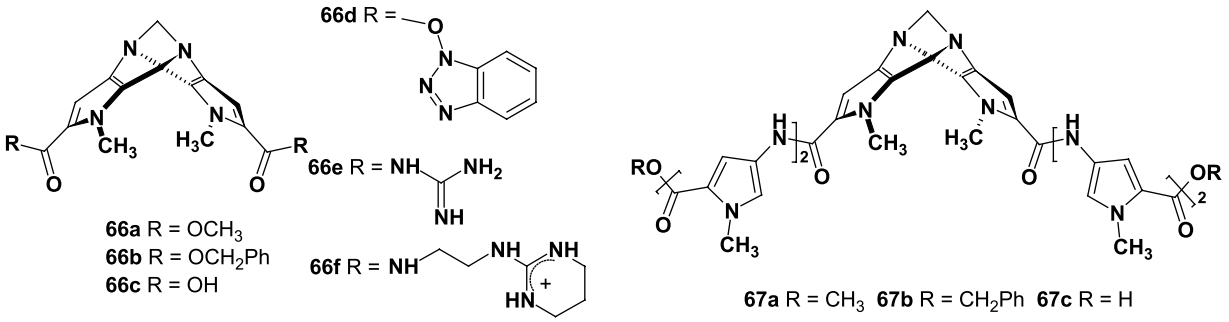


FIGURE 8 TB analogs of amino-*N*-methylpyrroles (**66**) and oligo *N*-methylamidopyrroles (**67**).

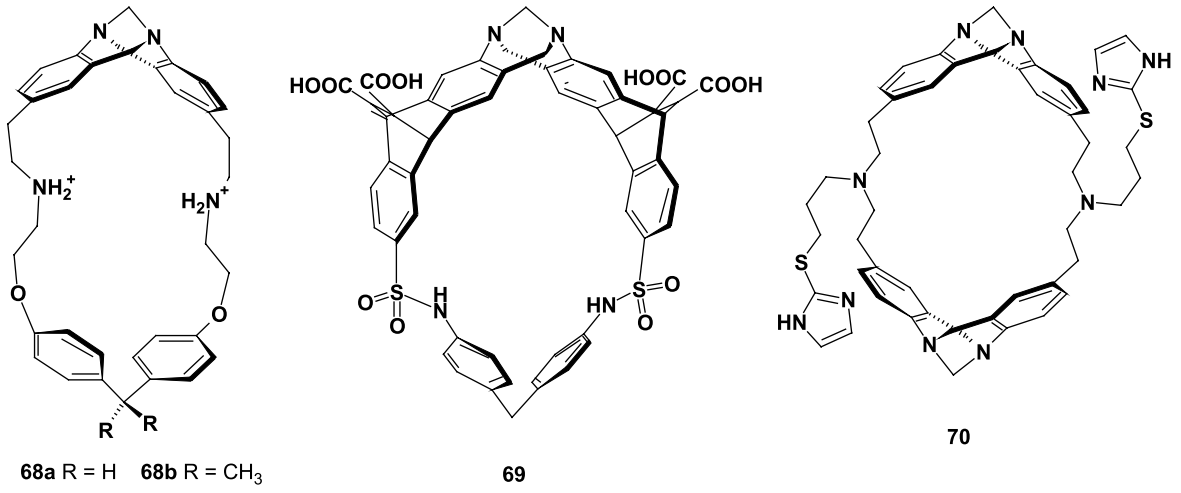


FIGURE 9 Water-soluble TB cyclophanes.

properties than the comparable host **68b** derived with diphenylpropane. The authors interpreted this finding by proposing that the geminal dimethyl group in host **68a** destabilizes the occupied host more than it destabilizes the unoccupied host [8,40].

Optically pure, water-soluble macrocyclic TB tetraacid **69** has been examined as a receptor for terpenes. A ^{1}H NMR study in an ND_4Cl/ND_3 buffer at pD 9.0 in D_2O showed that host **69** binds the isomeric menthols with reasonable selectivity [(−)-menthol $K_a = 2.5 \pm 0.2 \times 10^3\,M^{-1}$, (+)-menthol $K_a = 2.0 \pm 0.2 \times 10^3\,M^{-1}$, (+)-isomenthol $K_a = 1.0 \pm 0.2 \times 10^3\,M^{-1}$] [21]. This indicates that the axial groups on the cyclohexane nucleus may not fit in the host cavity. This notion is consistent with the results obtained by studying the interaction of **69** with 4-*tert*-butylcyclohexanol. In this latter case, the guest bearing an axial substituent (*cis*-isomer, $K_a = 8.6 \times 10^3\,M^{-1}$) was accommodated less well in this shape-selective cavity **69** than its *trans*-isomer ($K_a = 4.1 \times 10^4\,M^{-1}$) [95].

A recent contribution includes the synthesis and study of cyclophane bis-TB derivative **70** bearing mercaptoimidazole groups on the alkyl bridge. These receptors were designed to bind biologically relevant phosphates in their natural environment. The mercaptoimidazole groups were introduced to promote electrostatic interactions and to enhance solubility. Studies of the complexes formed from **70** and *O*-phosphorylethanolamine, 4-nitrophenyl phosphate and 4-nitrophenyl were performed using NMR spectroscopy in 0.1 M KCl/DCl buffer at pD 1.4, below the critical micelle concentration of **70**. Experiments showed that **70** interacted with 4-nitrophenyl phosphate ($K_a = 830\,M^{-1}$) 10 times more readily than with its nonphosphate analog 4-nitrophenol [42].

TABLE I Association constants K_a (M^{-1}) of receptors **68** with benzenoides.

Substrate	**68a**	**68b**
2,4,6-Trimethylphenol	100	70
4-Methoxyphenol	60	–
4-Toluensulfonic acid	330	250
4-Methylphenol	50	40
4-Cyanophenol	170	70
4-Nitrophenylacetate	140	–
1,3-Dihydroxynaphthalene	330	200

Hydrogen-bonding Receptors

Wilcox *et al.* described carboxylic acid TB derivatives such as **71** (Fig. 10) as hosts for cyclic urea and adenine derivatives [93,94]. The receptor design was based on formation of four hydrogen bond donor-acceptor pairs between two properly arranged carboxylic acids of **71a** and the targeted urea or adenine base moieties. Binding affinities for the interaction of **71a** with 9-ethyladenine, biotin methyl ester and several other guests were determined by NMR and UV/fluorescence spectroscopy techniques. Support for the suitability of **71a** to recognize adenine derivatives was provided by comparing the binding of 9-ethyladenine to **71a** ($K_a = 140\,M^{-1}$), benzoic acid ($K_a = 30\,M^{-1}$) and 2,6-diphenic acid ($K_a = 20\,M^{-1}$) in THF-d_8, as well as by noting the relative weak binding of **71a** to 6-*N*-methyl-9-ethyladenine ($K_a = 14\,M^{-1}$), a guest that cannot form four concurrent hydrogen bonds with the host.

To increase the measured association constants, it was considered feasible to carry out analytical experiments in $CHCl_3$ instead of THF. However, host **71a** was poorly soluble in $CHCl_3$, and therefore the more soluble hosts **71b** and **71c** were prepared. Association constants for these hosts with several guests were determined in $CDCl_3$ [93] (Table II).

The dicarboxylic acids **71b–d** were used for determining the effect of H_2O on hydrogen bonding in these systems. The experiments showed that small

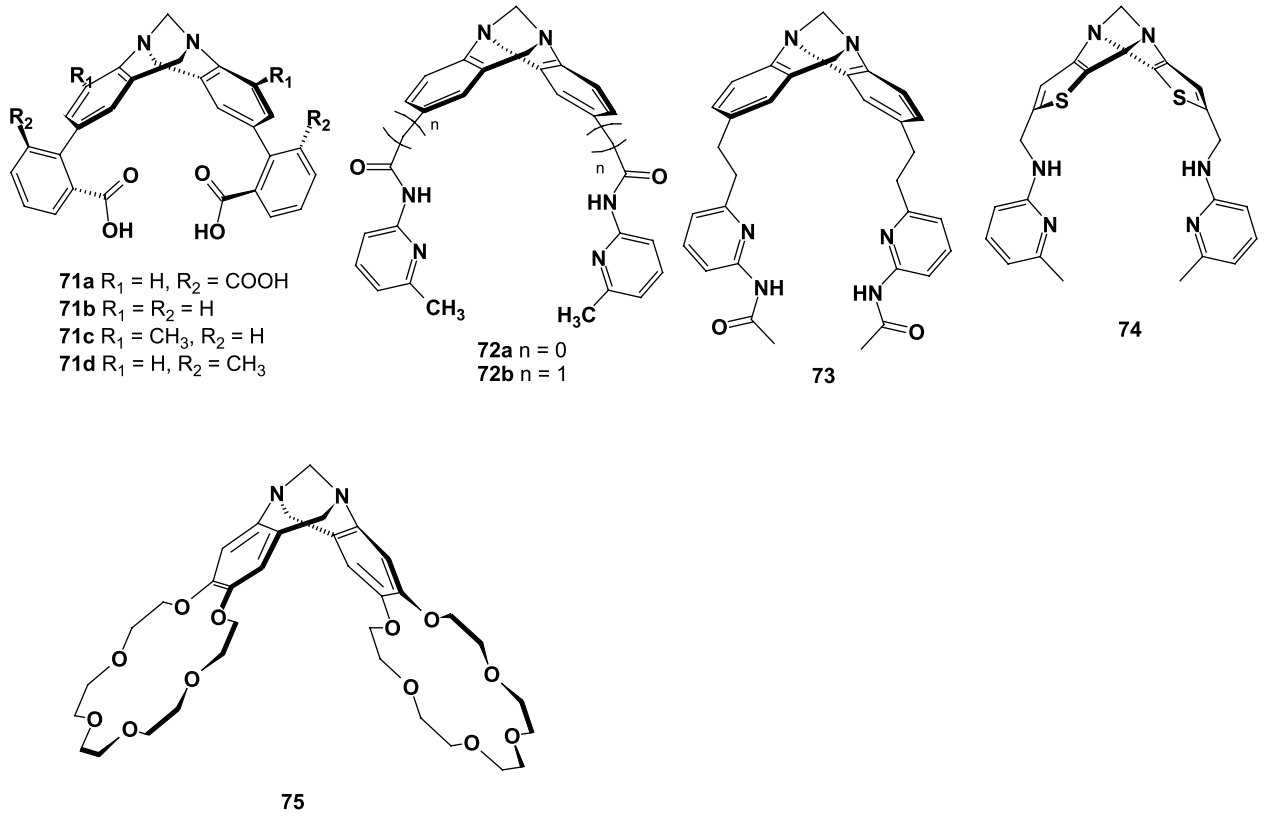


FIGURE 10 TB derivatives as hydrogen-bonding receptors.

amounts of water can have a very large effect on the entropy and enthalpy changes associated with a binding event. The more tightly self-enclosed diacid **71d** was less affected by water as it is far less susceptible to hydration than the more opened hosts **71b** and **71c** [94].

The design and synthesis of amidopyridine TB receptors **72** to recognize dicarboxylic acids with precise chain lengths were reported by Goswami and Ghosh [96]. The receptors include two amidopyridine units that are angularly displayed by the TB spacer on a concave face to bind dicarboxylic acids. The complexation study, based on ^{1}H NMR spectroscopic titrations carried out in $CDCl_3$ containing 2% DMSO-d_6, with a series of dicarboxylic acids showed that the cavity of TB analog **72a** is selective for suberic acid [96] (see Table III). Strong complexation of **72a** with suberic acid was also observed by fluorescence detection, which afforded a binding constant ($K_a = 2.5 \times 10^4\,M^{-1}$) close to the value observed in the ^{1}H NMR titration experiments [12]. The more flexible receptors **72b** and **73** exhibited weaker binding to the same dicarboxylic acids than **72a**. A marginal increase in K_a was observed for suberic and sebacic acids. However, the stoichiometry of the these complexes determined from the breaks in the titration curve ($\Delta\delta$ vs. C_{guest}/C_{host}) was 1:2 (guest: host) rather than 1:1 [12].

Studies of the binding of dicarboxylic acids to the TB analogs **72** included the observation of chiral recognition, using (+)-camphoric acid as a chiral diacid guest, as it was expected to provide a close match to the cavity dimensions of **72**. The NMR spectra showed two different sets of amide protons upon titration of (±)-**72a** with (+)-camphoric acid. The authors explained the chemical shift variation by the different stabilities of the diastereomeric associates of the enantiomers in solution. Attempts to resolve racemic **72a** by crystallization and

TABLE II Association constants K_a (M^{-1}) of **71b** and **71c** with biotin and adenine related compounds.

	71b	**71c**
9-Ethyladenine	$(4.5 \pm 1.7) \times 10^4$	$(5.1 \pm 1.0) \times 10^5$
Biotin methyl ester	$(1.7 \pm 0.3) \times 10^4$	–
Dimethylenurea	$(2.1 \pm 0.4) \times 10^4$	$(4.4 \pm 0.5) \times 10^4$
2-Aminopyrimidine	$(2.6 \pm 0.5) \times 10^3$	$(9.4 \pm 0.4) \times 10^3$

TABLE III Association constants K_a (M^{-1}) of receptors **72**–**74** with dicarboxylic acids.

Diacid	**72a**	**72b**	**73**	**74**
Glutaric	1.0×10^3	2.4×10^2	1.1×10^2	2.5×10^2
Adipic	1.7×10^3	3.5×10^2	5.3×10^2	3.6×10^2
Suberic	1.5×10^4	4.8×10^2	1.0×10^3	2.1×10^2
Sebacic	3.1×10^3	5.8×10^2	6.5×10^3	3.9×10^2

chromatographic separation with (+)-camphoric acid as a chiral template failed [12].

Kobayashi and Moriwaki [97] recently described the thiophene TB derivative **74** bearing two pyridylamino groups, whose hydrogen-bonding mode is similar to receptors **72** reported by Goswami and Ghosh [96]. The complexation properties of **74** were studied by ^{1}H NMR spectroscopic titration methods in $CDCl_3$ containing 0.5% DMSO-d_6. The targets guests were aliphatic and aromatic dicarboxylic acids. The stoichiometry and association constants were determined from titration curves generated by following the chemical shift of the 3′-H of the pyridine ring. All dicarboxylic acids studied, except for malonic acid and phthalic acid, were suggested to form complexes with 1:1 stoichiometry. The thiophene receptor **74** binds these dicarboxylic acids nonselectively with approximately the same binding affinity as receptor **72b** (see Table III). On the contrary, significantly higher selectivity was determined for malonic ($K_a = 1.9 \times 10^5\,M^{-1}$) and phthalic ($K_a = 7.0 \times 10^4\,M^{-1}$) acids, which bind to receptor **74** with a 1:2 (guest:host) stoichiometry [97].

Hansson *et al.* [98] also investigated the use of the TB scaffold in the design of hydrogen-bonding receptors. Their TB analogs were based on the methanodiazocine bridging of two benzo-18-crown-6 ethers, entities that are widely appreciated as being strong primary ammonium ion complexation partners. Condensation of 4-aminobenzo-18-crown-6 with formalin afforded only the linear symmetric derivative **75** of the three possible geometrical bis(18-crown-6) isomeric TB analogs that could potentially have been produced. Its complexation properties were tested with bisammonium salts of α,ω-diaminoalkane by NMR spectroscopy in a 1:1 mixture of MeOH-d_4 and $CDCl_3$ (see Table IV). The experiments revealed that bisammonium salts with $n = 6–8$ bind with an affinity almost equal to that of host **75**. However, a slight preference for heptane-1,7-diylbis(ammonium chloride) was observed. The enantiomeric discrimination of receptor **75** for chiral bisammonium salts was examined using racemic **75** and L-cystine methyl ester dihydrochloride. The ^{1}H NMR spectrum at a 1:1 ratio revealed that the aromatic protons as well as the protons of the methylene bridge were doubled compared to free **75**.

TABLE IV Association constants K_a (M^{-1}) of the complexation of **75** bisammonium salts of α,ω-diaminoalkane.

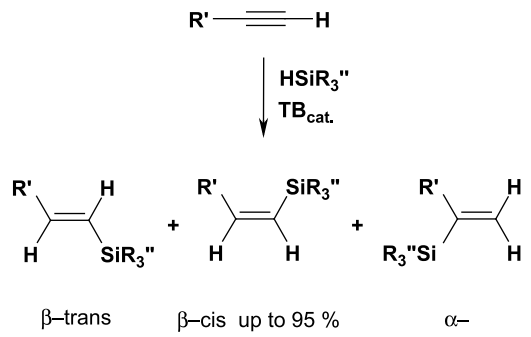
Ammonium salt	n	K_a
Butane-1,4-diylbis(ammonium chloride)	4	5.0×10^5
Pentane-1,5-diylbis(ammonium chloride)	5	7.0×10^5
Hexane-1,6-diylbis(ammonium chloride)	6	2.6×10^6
Heptane-1,7-diylbis(ammonium chloride)	7	7.8×10^6
Octane-1,8-diylbis(ammonium chloride)	8	3.7×10^6

This is consistent with the formation of two diastereomeric complexes, L-(−)-**75** and L-(+)-**75**. The diastereoselectivity calculated from the ^{1}H NMR spectrum was found to be 62:38. Related experiments with L-lysine methyl ester dihydrochloride did not reveal any enantiomeric discrimination [98].

TB CATALYTIC ACTIVITES AND TB METALLOCOMPLEXES

Despite its chirality, little has been done to exploit TB as a chiral ligand. Xu *et al.* tried to use (−)-**1** as a chiral ligand in 1,4-addition of aryllithium reagents to α,β-unsaturated *tert*-butyl esters [99]. Harmata and Kahraman recently reported asymmetric induction of (+)-**1** in the addition of diethylzinc to aromatic aldehydes. However, the enantioselectivity was poor (*ee* 7–22%). The higher *ee* of the product (up to 86%) was achieved by the modified TB chiral ligand (+)-**39** (E = CH_2OCH_2-CPh_2OH) [48].

The nitrogen atom of TB is able to form a donor-acceptor bond with heavy metals such as rhodium, iridium [100] and mercury [101] via the nonbonding sp^3 orbital. Goldberg and Alper reported that addition of an ethanolic solution of **1** to a solution of rhodium(III) or iridium(III) chloride in EtOH at room temperature resulted in the formation of a pink solid and a dark violet powder, respectively. ^{1}H NMR spectra and elemental analysis showed that both nitrogen atoms are coordinated to metal atoms, resulting in the formation of complexes of the general formula **1**·2MCl_3 [100]. Both complexes were air stable and nonhydroscopic. Their catalytic activity was tested on the hydrosilylation of terminal alkynes. This reaction can afford the normal *syn*-addition product (β-*trans*-alkenylsilane) and the thermodynamically less stable *anti*-addition product (β-*cis*-alkenylsilane), as well as the α-isomer (Scheme 16). The rhodium(III) complex readily catalyzed the addition of various silanes to terminal alkynes. The *anti*-addition product was formed in some cases with selectivities up to 95% [100].



SCHEME 16 Hydrosilylation of terminal alkynes catalyzed by **1**·2MCl_3 complex.

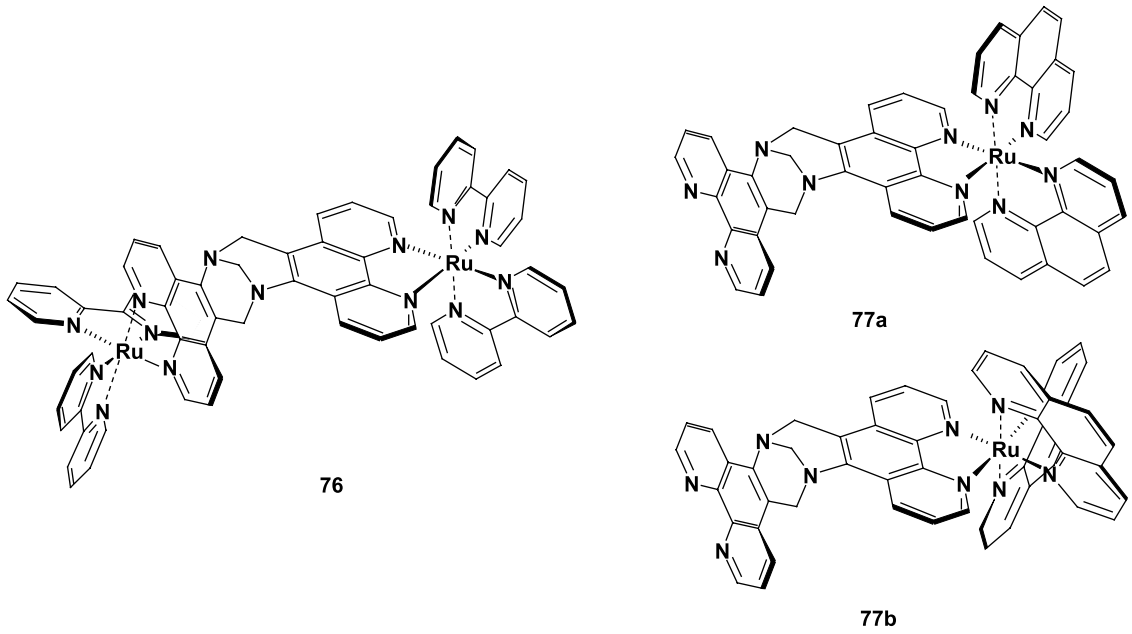


FIGURE 11 Ruthenium(II)-bipyridyl-TB phenanthroline complexes.

The TB (+)-**1** adduct of methyltrioxorhenium ((+)-ReO_3CH_3), characterized by its crystal structural and spectroscopic data, was reported by Herrmann *et al.* The catalytic properties of this complex were tested in the epoxidation of olefins and the oxidation of sulfides. However, no enantioselective reactions of the pro-chiral olefins and sulfides were observed [102].

Elimination of the endomethylene bridge in **1** leads to the eight-membered cyclic diamine **12b** with the vibrational freedom of the two methylene carbons restricted by their being a part of the aromatic rings. Although the axial positions in the bis-complex of this amidine are open for five and six coordination, only four-coordinated complexes with copper(II), palladium(II), nickel(II), platinum(IV) and zinc(II) were prepared [103–105].

Another method of TB complex formation involves using the TB periphery as a binding site. To this end, the bismetallocomplexes of porphyrin TB conjugates **49a** and **51a** were used as diamine receptors [52,86]. The phenanthroline TB analog **52** has been used as a bridging ligand for the preparation of a bimetallic ruthenium(II) complex **76** (Fig. 11). Because of the chirality of the ruthenium(II) precursors, $Ru(Bpy)_2Cl_2$, and also of the TB unit, this complex (**76**) was obtained as a mixture of diastereomers [106]. The diastereomer formation was evident from the complexity of the NMR spectra. It was found that stereoisomer formation could be reduced by the use of a mononuclear species that forms only two diastereoisomers. Recently, the mononuclear ruthenium(II) complex of phenanthroline TB **52** was synthesized and both its diastereomeric forms **77a** and **77b** were separated and subsequently characterized by 1D and 2D NMR techniques [107]. The identical emission properties of **77a** and **77b** indicated an absence of the influence of stereoisomerism on the photophysical properties of **77**. As mentioned above, the copper(I) complex of **52** was used to effect the cleavage of DNA [59].

Ibrahim *et al.* [108] and Manjula and Nagarajan [109] simultaneously described TB macrocycles **78** (Fig. 12), products that contain a crown ether framework for cation binding. The ability of these systems to complex alkali metal cations was investigated using Cram's picrate extraction method. The data showed that the macrocycles have good extraction capabilities and display high binding affinities ($K_a \approx 10^5$ M^{-1}) for all of the cations studied. However, they display little in the way of selectivity [109]. Subsequently, Miyahara *et al.* prepared the dibenzodiazocine **79** by removing the endomethylene bridge in **78a** [110]. Generally, the enantiomers of dibenzodiazocine derivatives **12**

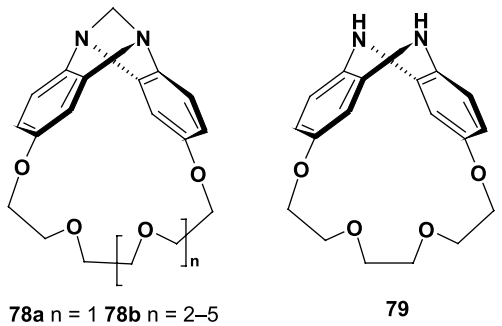


FIGURE 12 TB macrocycles with crown ether framework.

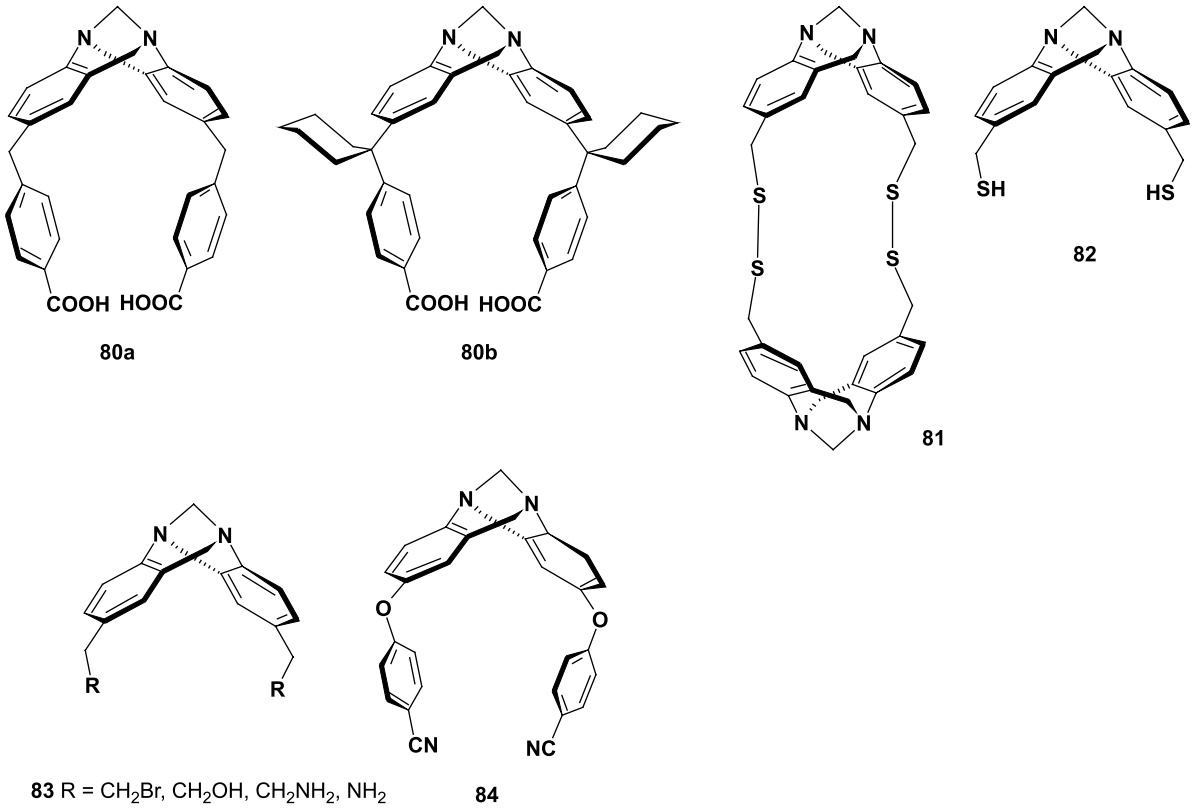


FIGURE 13 TB derivatives reported.

cannot be resolved because of rapid interconversion of the enantiomers. However, the polyether tether present in **79** was short enough to prevent such inversion processes. Its optical resolution was achieved by HPLC separation using a cellulose-based Chiralcel OJ column. Preliminary complexation studies showed that diamine **79** is good ligand for metal salts, in a manner that is reminiscent of the corresponding open-chain **12b** [105]. For example, the $(\mathbf{79})_2{\cdot}NiCl_2$ complex was readily obtained as orange crystals [110].

Studies involving TB derivatives are ongoing, with many potentially important properties remaining to be discovered and explored. For example, dicarboxylic TB derivatives **80** [111] that are more flexible than the described receptors **71** [95] have been synthesized (Fig. 13). Mercapto **81** and dithia **82** derivatives prepared by Bag and Kiedrowski [112,113] could prove useful in organic and bioorganic chemistry for studying biologically important thiol and disulfide groups. The TB derivatives **83** and **84** [50] could also play an important role in chiral molecular recognition. Considerable effort is currently focused on exploiting TB derivatives as novel materials, as well as analyzing their use in the development of analytical methods. TB analogs are also promoting investigations of second harmonic reflections from chiral surfaces [114]. Meanwhile, novel sulfone derivatives have been shown to serve as novel aromatic chelates [115]. New analogs of TB that are fluorescent via excited state intramolecular proton transfer and exhibit large Stokes shifts have recently been described [116]. These systems could have use as sensors.

In conclusion, TB derivatives are highly useful synthetic building blocks. They embody chiral tectons exhibiting a wide range of applications. These properties include biomimetic molecular recognition processes as well as complex interactions with important biomolecules. Emerging directions offer exciting new possibilities for the synthesis and applications of novel oligo-TB systems.

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