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In-Line Proximity Effects in Extended 7-Azanorbornanes. 1. A New Concept for Modifying Effector Group Separation Based on the Control of *N*-Invertomer Geometry

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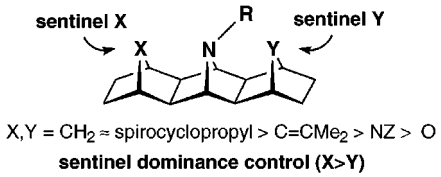
ABSTRACT



Control of *N*-substituent geometry in fused 7-azanorbornane systems is based on the dominance of one proximate bridge (sentinel X) over the other (sentinel Y) relative to the *N*-bridge; the *N*-inversion equilibrium can effectively be displaced in favor of a single invertomer. This study has used a combination of synthesis, crystallography, and molecular modeling to establish stereostructures.

The ability of nature to maximize host/guest interactions using conformational changes within the host is a well-established tenet in enzyme substrate selectivity. A series of leading articles covering the concepts of supramolecular science has recently appeared.[1−5] Host flexibility has been advocated as a necessary feature in unnatural host design,[5] and several examples have been reported which support this concept. Changes in shape which involve methylene chain conformations are usually too imprecise, and improvement has been gained by using conformational changes within six-membered rings.[6−8] Similarly, guest flexibility can play a role in some host/guest interactions, e.g., bis-intercalating agents. The role of nitrogen in determining conformation in *N*-alicyclic systems has been well established.[9] However, our present study demonstrates that *N*-invertomer preferences can be controlled and thereby adds a new element into the design and use of fused 7-azanorbornanes.

Recently, we described a new class of "windscreen wiper" molecules having two 7-azanorbornanes linked together by a rigid carbocyclic frame.[10] Such molecules have the potential to exhibit a significant degree of substituent mobility associated with nitrogen inversion. Since the rest of the

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carbocyclic frame of the molecule is rigidly fused, displacements at nitrogen occur within a plane bisecting the long axis of the molecule (Figure 1). This inversion process, if

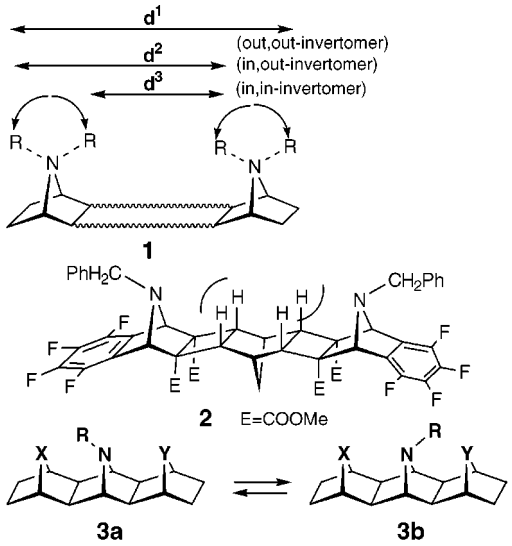
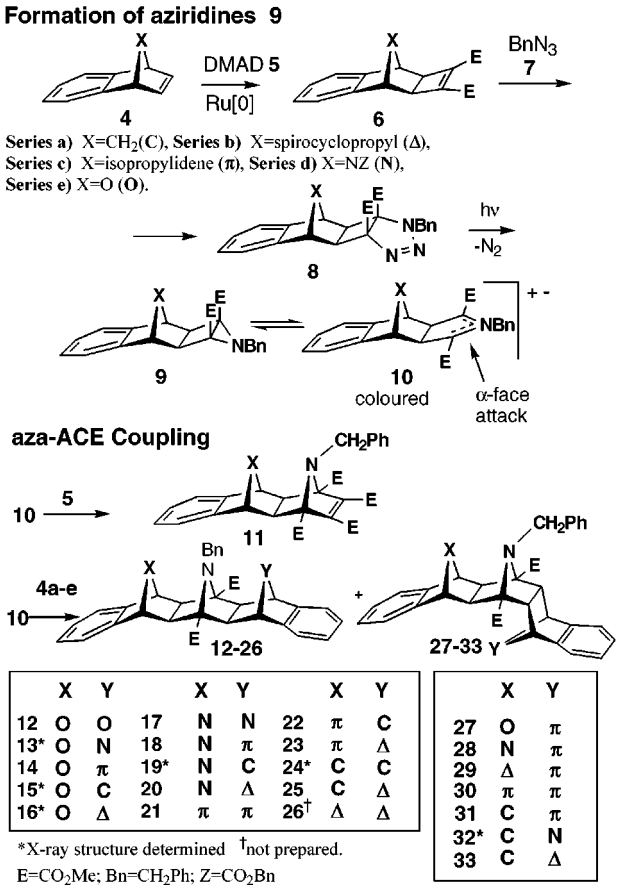


Figure 1. Windscreen wiper molecule **1** and fixed invertomer systems in (linked) 7-azanorbornanes.

the molecule can be forced to adopt one of the conformations, opens up the opportunity to form three distinct isomers with R,R separations corresponding to d^1 (out,out-invertomer), d^2 (in,out-invertomers), and d^3 (in,in-invertomers). In practice, the *N*-substituents in **2** are forced to assume the out,out-configuration owing to the steric interaction with the H-substituents on the inside of the frame,[11] so we sought alternative ways to control the *N*-invertomer preference and report herein the role of sentinel groups on either side of the 7-azanorbornane to achieve this goal.

To allow individual control of "in" or "out" invertomer positioning, it was important to have an understanding of the geometry and mobility of *N*-substituents in 7-azanorbornanes. Preliminary molecular modeling (AM1) indicated that placement of proximate groups (sentinel bridges X or Y) on each side of the *N*-bridge within a [3]polynorbornane frame XNY[12] offered such an opportunity (Figure 1). The constraints that the sentinel bridges exert in the dynamic XNX series are also supported by molecular modeling (see discussion in the accompanying Letter[13]). This effect manifests itself in the motion of the substituent on the *N*-bridge such that the distances between the inner and outer limits reduce as X becomes larger and tend more and more toward that expected for a planar nitrogen system.

Scheme 1



In this Letter, we report the synthesis of *syn*-facial aza-[3]polynorbornanes **12**−**25** in which five different sentinel groups (spirocyclopropyl, methylene, isopropylidene, aza, and oxa) have been incorporated as X,Y bridges about the central *N*-benzyl-7-azanorbornane. We also discuss how the sentinel groups X and Y affect *N*-substituent conformations, e.g., invertomer **3a** versus invertomer **3b**, using a combination of X-ray, modeling, and ^{1}H NMR techniques.

The synthesis of 14 different *N*-bridged [3]poly norbornanes **12**−**25**[14] was achieved by application of our recently

(11) The out,out-sterochemistry in **2** has been established by X-ray crystallography.[10]

(12) We describe the particular [3]polynorbornanes using a three-letter prefix as a shorthand notation to designate the bridges (see Scheme 1 for the one-letter abbreviations for each bridge type), i.e., CNC[3]poly norbornane refers to the symmetrical product **24** in which the aza bridge is flanked by methylene bridges, whereas the ONπ[3]polynorbornane indicates an unsymmetrical product **14** in which the aza bridge is flanked by an oxygen bridge on one side and a 7-isopropylidene group on the other. For the bent isomers **27**−**33**, the bent bridge is designated in parentheses, e.g., the CN(N) adduct **32** has the carbon and the *N*-benzyl bridge syn-related and the second NZ bridge on the underside of the [3]polynorbornane.

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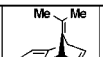
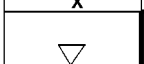
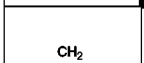
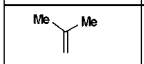
(14) Physical properties of representative new compounds: **11e** 57%; mp 158−159 °C; ^{1}H NMR δ 2.50 (2H, s), 3.51 (6H, s), 3.78 (6H, s), 3.82 (2H, s), 5.83 (2H, s), 7.12−7.18 (3H, m), 7.25−7.29 (4H, m), 7.46 (2H, d, J = 7.45 Hz); ^{13}C NMR δ 48.83, 52.38, 52.43, 55.15, 79.75, 80.91, 119.58, 126.51, 126.77, 127.68, 127.99, 139.02, 144.42, 146.66, 164.24, 167.35, HRMS calcd for $C_{29}H_{27}O_9N$ 533.1686, found 533.1685. **12** 43%; mp 299−300 °C; ^{1}H NMR δ 2.13 (4H, s), 3.71 (6H, s), 4.16 (2H, s), 5.38 (4H, s), 7.06−7.08 (4H, m), 7.11 (1H, t, J = 7.85 Hz), 7.16−7.18 (4H, m), 7.25 (2H, t, J = 7.85 Hz), 7.70 (2H, d, J = 7.85 Hz); ^{13}C NMR δ 51.87, 52.45, 56.67, 75.00, 79.64, 119.18, 125.04, 126.73, 127.21, 127.26, 144.11, 146.29, 170.75; HRMS calcd for $C_{33}H_{29}O_6N$ 535.1994, found 535.1998. **25** 4%; mp 221−222 °C; ^{1}H NMR δ 0.01 (2H, t, J = 7.85 Hz), 1.12 (2H, t, J = 7.85 Hz), 1.17 (1H, d, J = 8.88 Hz), 1.89 (2H, s), 2.27 (2H, s), 2.85 (2H, s), 3.16 (3H, m), 3.89 (6H, s), 4.38 (2H, s), 6.92−6.95 (4H, m), 7.00−7.03 (4H, m), 7.21 (1H, t, J = 7.51 Hz), 7.31 (2H, t, J = 7.51 Hz), 7.54 (2H, d,

reported aza−ACE coupling reaction[15] that employs the [4π + 2π] addition of benzonorbornadienes **4a**−**4e** to the 1,3-dipoles **10a**−**10e** formed by ring opening of the appropriate aziridinocyclobutenes **9a**−**9e** (Scheme 1). The 15th possible *syn*-facial aza[3]polynorbornane ΔNΔ **26** could not be prepared by this method. The required aziridines **9a**−**9e** were synthesized in three steps from the appropriate benzonorbornadiene **4a**−**4e** using the sequence: (i) conversion to the related cyclobutene 1,2-diester by ruthenium-catalyzed addition of dimethyl acetylenedicarboxylate (DMAD) **5**; (ii) addition of benzyl azide **7** to the resultant cyclobutenes; (iii) photoinduced deazetization of the triazoline adducts (see Scheme 1 and Table 1).

Table 1. Yields and Melting Points of XNY **12**−**25**[a]

increasing dipolarophilicity →

X ↓					
	** 0[†] not obtained	0 4% melt **221-222**[‡]	9+34* **277-278**	26 **201-202**	74 **256-257**
	1	6 26% melt **214-315**	22 **230-231**	44 **174-175**	51 **254-255**
	0	0	8+24* **202-203**	67 **130-131**	94 **145-146**
NZ Z=CO_2CH_2Ph	0	0	8+0.5*	42 **225-226**	46 **208-209**
O	0	6	12+18*	62	43 **299-300**

[a] Yields are isolated and formed by the benzene reflux method unless stated otherwise. * = bent-frame isomer. ** = symmetrical XNX compounds are on diagonal and are boxed in bold.

Formation of the extended-frame aza[3]polynorbornanes **12**−**25** was achieved by thermal reaction of the aziridino cyclobutenes **9a**−**9e** with the benzonorbornadienes **4a**−**4e** [benzene at reflux or heating the reagents neat at 120 °C (melt method)]. In several reactions a second stereoisomer was formed in which the attacking dipolarophile has its bridge located in an *anti*-relationship to the others, viz **27**−**33**. This bent-frame stereoisomer was always formed as well as the extended-frame isomer when 7-isopropylidene benzonorbornadiene **4c** was used as the dipolarophile, but rarely with the others. The two-bridged systems **11a**−**11e**[14] were prepared by heating the appropriate aziridine **9a**−**9e** with excess DMAD **5** at 120 °C.

Each of the XNY products could be formed in two ways, since the X bridge could be part of the aziridine **9** and reacted with the Y-bridged dipolarophile **4** or the Y bridge could be incorporated into the aziridine reagent **9** and reacted with the X-bridged dipolarophile. Table 1 shows that the different modes of coupling gave vastly different yields for the same product in several cases. Two factors contribute to this difference: (a) the dipolarophilicity of the benzonorbornadienes **4** (O > NZ > $\pi \gg CH_2 > \Delta$); (b) the relative stability of the 1,3-dipoles toward a competitive fragmentation process (O, π, NZ, others stable).[16]

The stereostructures of the [3]polynorbornanes was established by X-ray crystallography (Figure 2) or by spectral data. The NOE between the *endo*-bridgehead protons Ha and Hb (Figure 3) was used to confirm the extended-frame

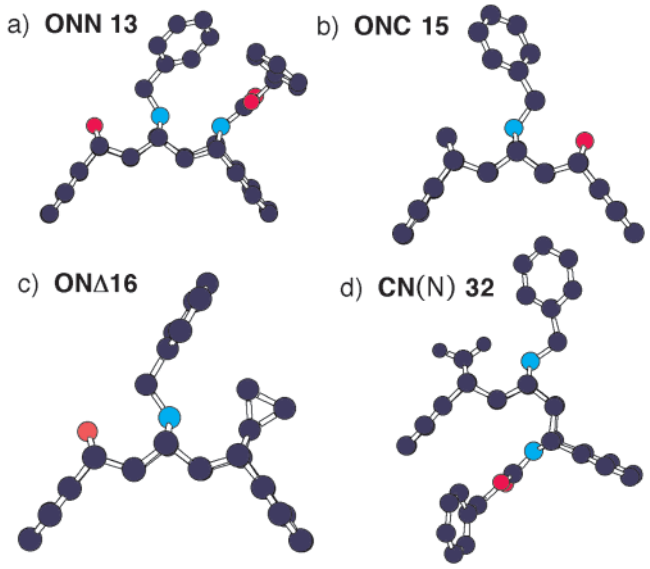


Figure 2. X-ray structures of extended-frame adducts **13**, **15**, and **16** and bent-frame adduct **32** (X-ray data for these structures, together with CNN **19** and CNC **24**,[13] are available from the author).

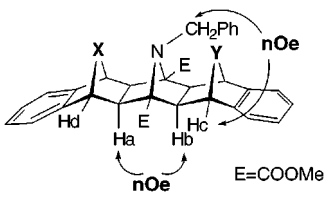


Figure 3. NOE measurements used in the structure determination and invertomer position fo r[3]poly norbornanes **12**−**25**. Similar NOEs were used to assign invertomer geometry to **36** and **38**.

J = 7.51 Hz); HRMS calcd for $C_{37}H_{35}O_4N$ 557.2566, found 557.2559. **29** 34%; mp 210−211 °C; ^{1}H NMR δ 0.14 (2H, t, J = 7.83 Hz), 1.01 (6H, s), 1.12 (2H, t, J = 7.83 Hz), 2.10 (2H, s), 2.57 (2H, s), 2.85 (2H, s), 3.55 (6H, s), 3.71 (2H, s), 3.77 (2H, s), 7.00−7.07 (6H, m), 7.16 (2H, m), 7.15−7.21 (3H, m), 7.26 (2H, t, J = 7.34 Hz), 7.34 (2H, d, J = 7.34 Hz); HRMS calcd for $C_{40}H_{39}O_4N$ 597.2879, found 597.2880. **35** 90%; mp 157−159 °C; ^{1}H NMR δ 2.75 (4H, s), 3.75 (12H, s), 3.95 (4H, s), 5.64 (4H, s), 7.26−7.34 (10H, m); ^{13}C NMR δ 42.73, 50.16, 53.39, 59.00, 73.81, 81.92, 128.44, 128.54, 129.43, 136.91, 167.15, 167.36; HRMS calcd for $C_{40}H_{34}N_2O_{13}$ 726.2061, found 726.2061. **36** 54%; mp 280−282 °C; ^{1}H NMR δ 1.43 (4H, s), 1.99 (2Hs, s), 2.25 (4H, s), 2.86 (2H, s), 3.70 (12H, s), 3.91 (4H, s), 5.32 (4H, s), 7.12−7.43 (18H, m); ^{13}C NMR δ 30.94, 42.37, 52.34, 54.09, 58.24, 58.60, 76.78, 80.03, 120.09, 126.47, 127.47, 127.95, 129.28, 143.75, 147.30, 171.47; HRMS calcd for $C_{53}H_{50}N_2O_{10}$ 874.3465, found 874.3452. **38** 35%; mp 274−275 °C; ^{1}H NMR δ 0.87 (2H, d, J = 8.1 Hz), 1.71 (4H, s), 2.56 (4H, s), 2.61 (4H, s), 3.12 (2H, d, J = 8.1 Hz), 3.74 (12H), 3.76 (4H, s), 5.08 (4H, s), 6.07 (4H, s), 7.15−7.40 (10H, m).

geometry of the XNY adducts having different sentinel groups. For the C_{2v}-symmetrical compounds XNX, the simplicity of the ^{1}H NMR spectra provided the required support.

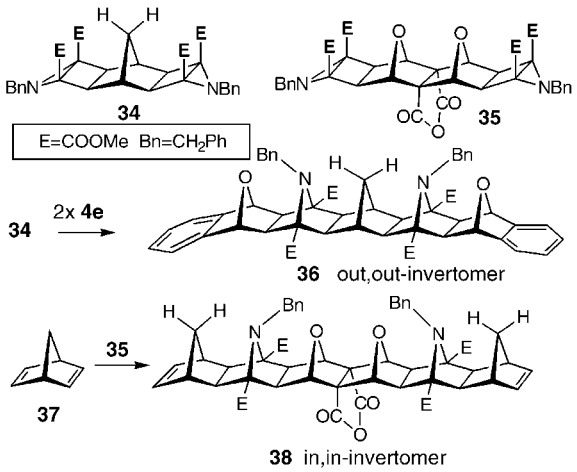
Sentinel Dominance Control. Since the sentinel groups are different in XNY systems, the invertomers are not isoenergetic and one invertomer is strongly favored in these systems[17] except for CNΔ, **25** which is dynamic (see accompanying Letter[13]). A priority order can be established in which the dominant sentinel group ($CH_2 \approx \Delta > \pi >$ NZ $\approx$ O) repels the central *N*-substituent, thereby providing a method for controling the invertomer geometry by varying the sentinel bridges.

The *N*-invertomer preference in solution for the XNY systems was established using NOE measurements involving the benzylic methylene protons and only one of the bridgehead protons (interaction with Hc on the proximate norbornane subunit shown in Figure 3, but not Hd on the remote bridgehead). These preferences correspond to those found in the solid state by X-ray crystallographic analysis of compounds **13**, **15**, **16**, **19**, and **24** and are reinforced by AM1 modeling studies. ^{1}H NMR, X-ray, and AM1 measurements are in concert and fully validate the order of sentinel effects.

Aza−ACE coupling of bis-aziridine **34**[18] with 7-oxabenzonorbornadiene **5e** yields the "windscreen wiper" **36**[15] in which the *N*-substituents are outward-facing (out,out-invertomer), so positioned by the dominance of the central methylene bridge (Scheme 2). Coupling of norbornadiene **37** with bis-aziridine **35** yields the "windscreen wiper" **38**,[15] where the dominance of the methylene bridge again exerts itself, this time forcing the *N*-substituent to adopt the in,in-invertomer geometry.

Compounds such as **11a**−**11e** which lack the second sentinel bridge exhibit decisive invertomer preferences and always direct the *N*-substituent away from the sentinel bridge. This effect provides an additional way to obtain predictable invertomer geometry.

Scheme 2



The advent of the aza−ACE cycloaddition reaction has allowed entry to aza[*n*]polynorbornanes, a new class of heteroalicycles not hitherto available by any other route. The substantial array of bridged polynorbornanes reported herein has allowed us to study proximity-based (sentinel) effects on the geometry of the *N*-substituents in fused 7-azanorbornanes and determine how to control invertomer geometry. These outcomes have direct bearing on the fundamental question of nitrogen inversion and hybridization in a confined environment and should allow these findings to be taken into the field of molecular architecture and drug design (bis-intercalators are currently under study in our laboratories).

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(16) Warrener, R. N.; Hammond, M. L. A.; Butler, D. N. 1999, unpublished results.

(17) Not only do the sentinels control the invertomer preference, they also cause flattening of the nitrogen pyramid and a concomitant change in hybridization of the *N*-bridge. These changes have been examined in more detail using ^{15}N NMR spectroscopy, and this aspect will be discussed elsewhere.

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