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Conformational stability of atropisomeric 1-naphthylcarbinols and 1-(1-naphthyl)ethylamines

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Abstract—The stereodynamics of atropisomeric 1-naphthylcarbinols and 1-(1-naphthyl)ethylamines exhibiting two stereogenic elements, i.e. a chiral center and a chiral axis, were investigated. PM3 calculations suggest that these atropisomers populate two major conformations bearing the most sterically demanding group perpendicular to the naphthalene moiety. Due to its high conformational stability, the atropisomers of 1-(1-naphthyl)-2,2-dimethyl-1-propanol can be separated by HPLC at room temperature. Kinetic studies revealed a free energy of activation for rotation about the chiral axis of 158 kJ/mol. Incorporation of less bulky substituents into the stereogenic center of this class of atropisomers results in significantly reduced steric hindrance to isomerization. The conformational stability of *N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine was determined as 75.9 kJ/mol by variable-temperature NMR spectroscopy.

The stereomutation and chromatographic separation of atropisomeric 1-naphthyl derivatives have recently received considerable attention.[1–12] In particular, variable-temperature NMR spectroscopy and dynamic chromatography have been used to investigate the isomerization process of constrained 1-substituted naphthalenes.[13] Following literature procedures, we prepared 1-naphthylcarbinols **1**–**3** and structurally similar 1-(1-naphthyl)ethylamines **4**–**7** to study the conformational stability of these atropisomers (Fig. 1).[14–22]

1-Naphthyl-derived carbinols and amines **1**–**7** exist as a pair of diastereoisomeric racemates since they afford a stereogenic center in addition to a chiral axis. Semiempirical quantum mechanical calculations suggest that these atropisomers populate two major conformations bearing the most sterically demanding group perpendicular to the naphthalene moiety. For instance, (*S*)-1-(1-naphthyl)-2,2-dimethyl-1-propanol, (*S*)-**3**, affords two diastereoisomeric conformers exhibiting (*M*) and (*P*) helicity, respectively (Fig. 2). Similarly, (*R*)-**3** exists as a mixture of two isomers possessing (*M*) or (*P*) helicity.

In addition to minimization of steric repulsion between the bulky *tert*-butyl group and the naphthyl moiety, the two favored conformations may be further stabilized by intramolecular CH/π interactions of C–H bonds of the *tert*-butyl group and the adjacent aromatic π-system (Fig. 3). Notably, all 9 hydrogens of the *tert*-butyl moiety are available to participate in CH/π interactions with C_{ipso} and C_{ortho} of the naphthalene ring, respectively.[23]

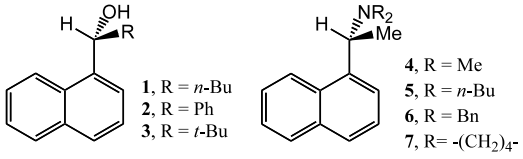

Figure 1. Structure of atropisomeric 1-naphthylcarbinols **1**–**3** and 1-(1-naphthyl)ethylamines **4**–**7**.

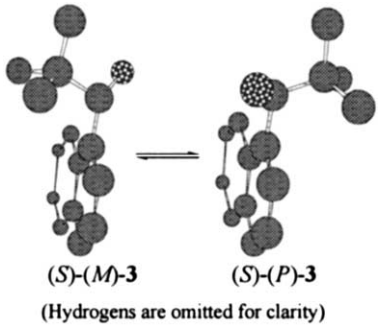

Figure 2. Favored ground states of (*S*)-1-(1-naphthyl)-2,2-dimethyl-1-propanol, **3**, optimized by PM3 calculations.

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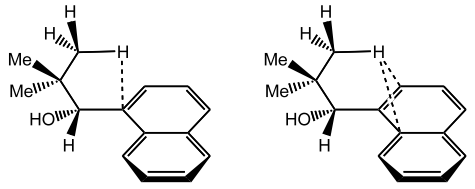


Figure 3. Intramolecular CH/π interactions (dotted lines) between $C(CH_3)_3$ and C_{ipso} (left) and C_{ortho} (right) of (*R*)-1-(1-naphthyl)-2,2-dimethyl-1-propanol, **3**.

Rotation about the chiral axis results in interconversion of the diastereoisomers. To limit steric repulsion in the transition state the bulky *tert*-butyl group is likely to pass the 2- rather than the 8-position of the naphthalene ring.

Casarini and co-workers investigated the stereodynamics of sterically hindered 1-naphthyldialkylmethanols.[7] To minimize steric interactions between bulky alkyl substituents of the tertiary alcohol moiety and the aromatic ring, the C–O–H moiety is forced into the plane of the naphthalene and thus favors a *syn*-periplanar and an *anti*-periplanar conformation (Fig. 4). The periplanarity of aryl C–H bonds and the hydroxyl moiety is likely to result in destabilizing steric repulsion in the ground state that may partially be compensated by hydrogen bonding. Due to its high conformationally stability, the atropisomers of 1-naphthyl-di-*tert*-butyl carbinol, **8**, can be separated at room temperature. The free energy of activation for the interconversion of the *sp*- and *ap*-conformers of **8** was reported as 137.7 kJ/mol. Furthermore, a dramatic decrease in conformational stability was observed by replacing the *tert*-butyl moieties for isopropyl, ethyl, and methyl groups, respectively. For example, 1-naphthyl-diisopropyl carbinol, **9**, exhibits a rotational energy barrier of only 62.4 kJ/mol, i.e. interconversion proceeds fast and the two conformers cannot be separated at room temperature.

Compared to atropisomer **8** and **9**, the stereodynamics of unsymmetrically substituted, secondary alcohols **1**–**3** are somewhat different. The latter class of atropisomers prefers a staggered conformation exhibiting the most sterically demanding group perpendicular to the naphthalene ring. Accordingly, one would not expect strong destabilizing steric repulsion of periplanar C–O–H and aryl C–H bonds in the ground state.

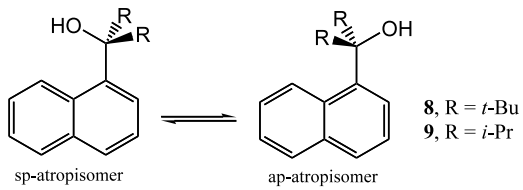
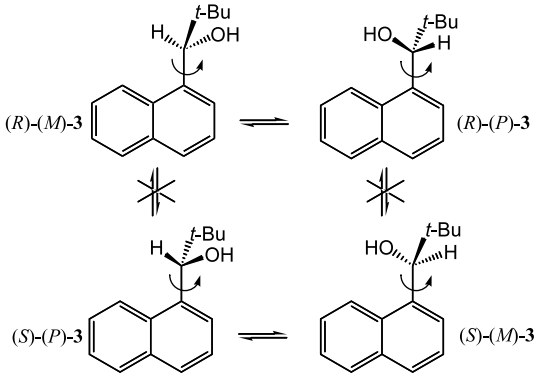


Figure 4. Isomerization of 1-naphthyldialkylcarbinols **8** and **9**.

As a consequence of sterically hindrance to rotation about the sp^2–sp^3 bond, the constrained diastereoisomeric conformers of 1-(1-naphthyl)-2,2-dimethylpropan-1-ol, **3**, are stable to isomerization at room temperature (Scheme 1). We were able to separate **3** into almost equimolar amounts of atropisomers by semipreparative HPLC.[24] Since **3** was prepared from 1-naphthylaldehyde using *tert*-butyllithium in absence of any chiral catalyst, one would expect a mixture of racemic diastereoisomers. In addition, the high conformational stability of **3** impedes equilibration of the two atropisomers under the reaction conditions used. The observed diastereomeric 1:1 ratio is thus a consequence of the low stereoselectivity of the alkylation reaction and does not correspond to the relative thermodynamic stability of the diastereoisomers. One isolated conformer was dissolved in ethanol and heated to 170°C in a closed reaction vessel to investigate the free energy barrier to rotation. The interconversion of the two diastereoisomers was monitored by HPLC using Whelk-O 1 as the stationary phase and naphthalene as the internal standard. The free energy barrier to rotation was determined as 158(±2) kJ/mol.[25] Thus, carbinol **3** exhibits a significantly higher conformational stability than **8**. This may be attributed to a more stable ground state of unsymmetrically substituted 1-naphthylcarbinols **1**–**3** that are expected to afford less periplanar repulsion than carbinols **8** and **9**. All attempts to investigate the rotation about the chiral axis of **1**–**3** by variable-temperature NMR spectroscopy were not fruitful. We did not observe anisochronous proton signals of the diastereomeric conformers of carbinols **1**–**3** using a variety of deuterated solvents including toluene, *ortho*-xylene, acetonitrile, DMSO, 1,1,2,2-tetrachloroethane, and chloroform. Furthermore, HPLC studies using a number of columns over a wide temperature range (−78 to +130°C) did not show any sign of competition between interconversion and separation of diastereoisomers for carbinols **1**–**3**. Thus, we were not able to employ dynamic HPLC to further study the stereodynamics of these atropisomers.[26]

Optimization of the ground state of 1-(1-naphthyl)ethylamines **4**–**7** by PM3 calculations suggests two



Scheme 1. Interconversion of atropisomers of 1-naphthylcarbinol **3**.

favored conformations bearing the amine moiety almost perpendicular to the naphthalene ring. Thus, (*S*)-*N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine, (*S*)-**5**, affords two diastereotopic isomers exhibiting either (*M*) or (*P*) helicity (Fig. 5). The dihedral angle ($N–C–C_{naphthalene\text{-}1}–C_{naphthalene\text{-}2}$) was calculated as +78 and −73° for the (*M*)- and (*P*)-isomer, respectively. As it was discussed for carbinols **1**–**3**, these conformations are also likely to be stabilized by intramolecular CH/π interactions between C–H bonds of the *N*-butyl groups and the aromatic π-system.

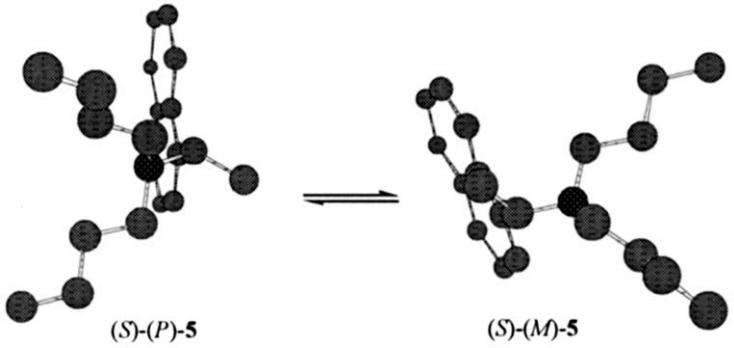


Figure 5. View along the chiral axis of the favored conformations of (*S*)-*N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine, (*S*)-**5**.

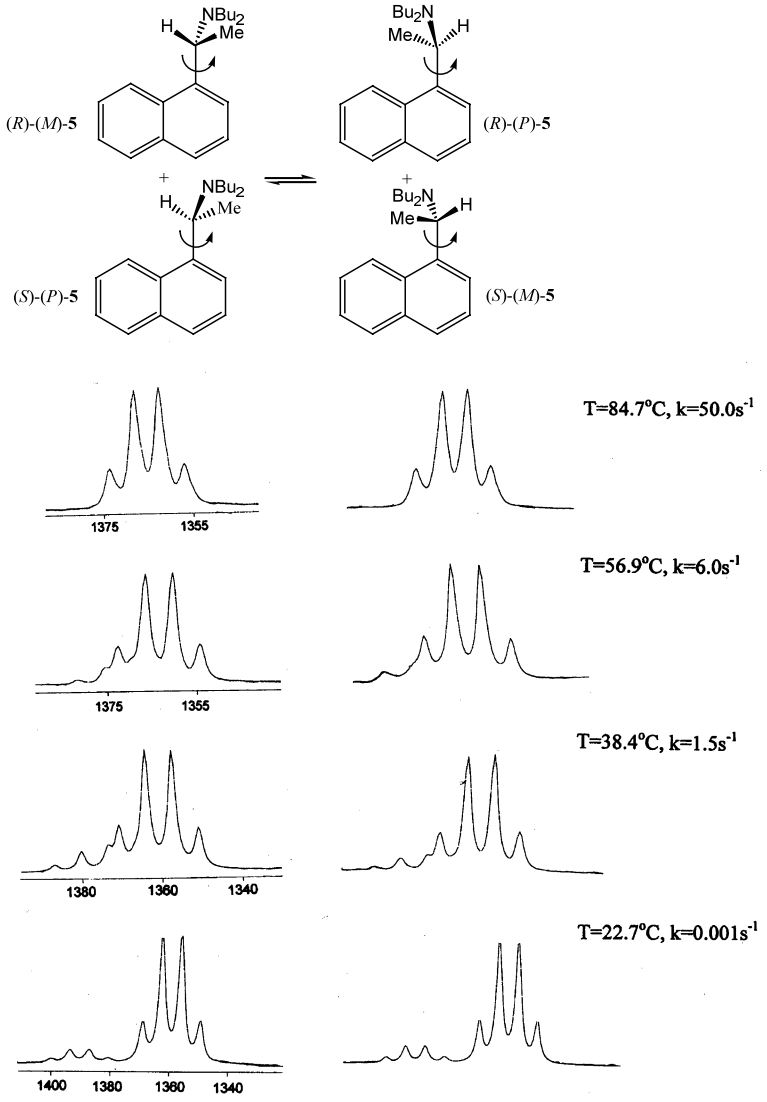


Figure 6. Experimental (left) ^1H NMR spectra of the methine proton of *N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine, **5**, in xylene-d_8 as a function of temperature. Computer simulations (right) obtained with the rate constants for the interconversion of the more stable to the less stable atropisomer.

As a consequence of some steric repulsion between the methyl group attached to the chiral center and the *peri* hydrogen in position 8 of the naphthalene ring, one would expect the (*S*)–(*M*)-isomer of **5** to be less stable than the (*S*)–(*P*)-isomer.[7] In order to investigate the conformational stability of 1-(1-naphthyl)ethylamines **4**–**7** we obtained NMR spectra in a variety of deuterated solvents. We observed diastereotopic signals for the methine protons attached to the chiral center of *N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine, **5**, using apolar solvents such as toluene-d_8 or *ortho*-xylene-d_{10} (Fig. 6). The ratio of the two isomers was determined as 6.5:1. This corresponds to a difference in the Gibbs free energy of 4.6 kJ/mol according to the Boltzmann equation (1).

$$n_1/n_2 = \exp(-\Delta G^0/RT) \quad (1)$$

Variable-temperature NMR spectroscopy showed two well-resolved quartets for the methine protons at room temperature that undergo coalescence at 84.7°C. Computer simulation of the experimentally obtained ^{1}H NMR spectra revealed a rotational energy barrier of 75.9(±0.2) kJ/mol for the isomerization of the more stable to the less stable rotamer (Fig. 6).[27–29]

The fast interconversion of the conformational isomers of 1-(1-naphthyl)ethylamine **5** is a consequence of the low steric hindrance to rotation about the atropisomeric axis. In addition, it seems possible that isomerization proceeds via two competing pathways exhibiting a similar energy barrier. Rotation about the chiral axis might occur through a clockwise or a counter-clockwise movement since the difference of steric repulsion between the amine moiety and the naphthyl C–H bond in the 8- and in the 2-position, respectively, might be small. Since amines **4**, **6**, and **7** exhibit similar steric constraints as **5**, one would assume that these atropisomers are also not stable to isomerization at room temperature. Unfortunately, we did not observe diastereotopic NMR signals and thus were not able to determine the rotational energy barrier of these amines.

In summary, we have investigated the favored ground state conformations and dynamic stereochemistry of a series of 1-(1-naphthyl)ethylamines and secondary 1-naphthylcarbinols experimentally and by PM3 computations. In contrast to tertiary 1-naphthylcarbinols, which favor periplanar ground state conformations,[7] secondary 1-naphthylcarbinols **1**–**3** prefer staggered ground state conformations exhibiting the most sterically demanding group perpendicular to the naphthalene ring. Thus, less steric repulsion and stabilizing intramolecular CH/π interactions in the ground state result in significantly increased rotational energy barriers. Accordingly, the energy barrier to isomerization of 1-(1-naphthyl)-2,2-dimethyl-1-propanol, **3**, was determined as 158 kJ/mol, whereas 1-naphthyl-di-*tert*-butyl carbinol, **8**, exhibits an isomerization barrier of only 137.7 kJ/mol.[7] Variable-temperature NMR studies of *N*,*N*′-dibutyl-1-(1-naphthyl)ethylamine, **5**, revealed an energy barrier to isomerization of 75.9 kJ/mol, which was attributed to low steric repulsion between the dibutylamino moiety and the naphthalene ring in the coplanar transition state.

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References

1. Casarini, D.; Lunazzi, L.; Macciantelli, D. *Tetrahedron Lett*. **1984**, *25*, 3641–3642.
2. Casarini, D.; Lunazzi, L. *J. Org. Chem*. **1988**, *53*, 182–185.
3. Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc*. **1988**, *110*, 4527–4532.
4. Casarini, D.; Davalli, S.; Lunazzi, L. *J. Org. Chem*. **1989**, *54*, 4616–4619.
5. Davalli, S.; Lunazzi, L. *J. Org. Chem*. **1991**, *56*, 1739–1747.
6. Villani, C.; Pirkle, W. H. *Tetrahedron: Asymmetry* **1995**, *6*, 27–30.
7. Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **1997**, *62*, 3315–3323.
8. Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **1998**, *63*, 4746–4754.
9. Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **1998**, *63*, 4991–4995.
10. Casarini, D.; Mazzanti, A.; Alvarez, A. M. *J. Org. Chem*. **2000**, *65*, 3200–3206.
11. Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem. Eur. J*. **2002**, *8*, 1279–1289.
12. Dell'Erba, C.; Gasparrini, F.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Novi, M.; Pierini, M.; Tavani, C.; Villani, C. *J. Org. Chem*. **2002**, *67*, 1663–1668.
13. For an excellent review on dynamic chromatography and computer simulation, see: Trapp, O.; Schoetz, G.; Schurig, V. *Chirality* **2001**, *13*, 403–414.
14. Harrold, G. C.; Hemphill, M. G. *J. Am. Chem. Soc*. **1936**, *58*, 747.
15. Ansell, M. F.; Berman, A. M. *J. Chem. Soc*. **1954**, 1792–1795.
16. Kice, J. L.; Hanson, G. C. *J. Org. Chem*. **1973**, *38*, 1410–1415.
17. Condon, F. E.; Mitchell, G. *J. Org. Chem*. **1980**, *45*, 2009–2010.
18. Tamioka, K.; Nakajima, M.; Koga, K. *Chem. Lett*. **1987**, 65–68.
19. Peyman, A.; Peters, K.; Von Schnering, H. G.; Ruchardt, C. *Chem. Ber*. **1990**, *123*, 1899–1904.
20. Heinz, T.; Wang, G. Z.; Pfaltz, A.; Minder, B.; Schurch, M.; Mallat, T.; Baiker, A. *J. Chem. Soc., Chem. Commun*. **1995**, 1421–1422.
21. Ebden, M. R.; Simpkins, N. S.; Fox, D. N. A. *Tetrahedron* **1998**, *54*, 12923–12952.
22. Pomares, M.; Grabuleda, X.; Jaime, C.; Virgili, A.; Alvarez-Larena, A.; Piniella, J. F. *Magn. Reson. Chem*. **1999**, *37*, 885–890.

23. Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201–7245.
24. Diastereoisomers of alcohol **3** were resolved on (*S*,*S*)-Whelk-O 1 or on phenylglycine using hexanes/EtOH (98:2) as the mobile phase at 25°C (diastereoselectivity $\alpha = 1.5$ and 1.2, respectively). Since the separation of conformational isomers of **3** was accomplished employing chiral stationary phases one could assume that indeed enantiomers were resolved. However, this can be ruled out due to different UV spectra observed for the separated isomers.
25. The rate constant and rotational energy barrier of isomerization were calculated according to the formalism of reversible first-order reactions. The accuracy of the free energy barrier to rotation of **3** determined in this study was limited to ±2 kJ/mol due to temperature fluctuations of ±5°C.
26. We observed coalescence of the two conformers of **3** at high temperatures. However, this is likely to be a consequence of decreasing selectivity of the stationary phase used. No unequivocal sign of diastereoisomerization on the HPLC column was observed.
27. The temperature was measured following a procedure reported by Merbach et al.: Ammann, C.; Meier, P.; Merbach, A. E. *J. Magn. Reson.* **1982**, *46*, 319–321.
28. Simulations were performed using mexico and mexicnonc (Alex D. Bain, McMaster University, Hamilton, Ont., Canada).
29. Dynamic HPLC studies on the free activation energy for rotation about the chiral axis were not feasible. No sign of competition between interconversion and separation of diastereoisomers of amines **4**–**7** were observed using a number of columns over a wide temperature range (−78 to +25°C).