Cyclohexanecarbonitriles: Assigning Configurations at Quaternary Centers from ^{13}C NMR CN Chemical Shifts[1]

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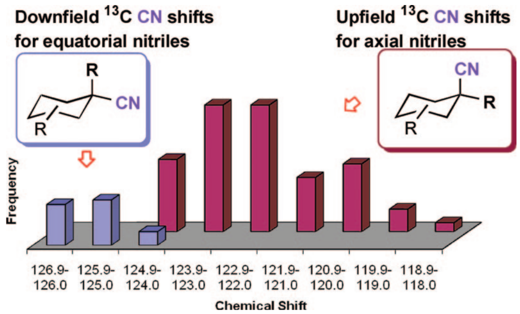
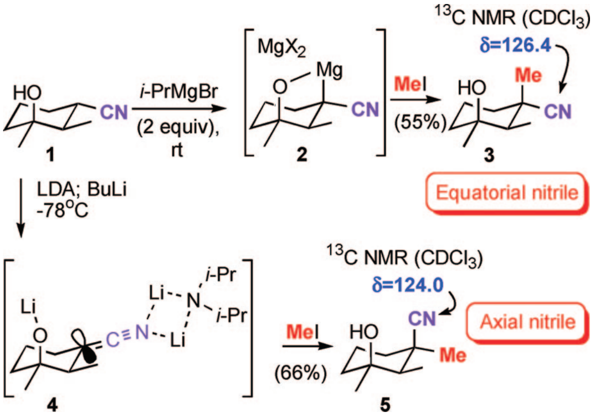


^{13}C NMR chemical shifts of the nitrile carbon in cyclohexanecarbonitriles directly correlate with the configuration of the quaternary, nitrile-bearing stereocenter. Comparing ^{13}C NMR chemical shifts for over 200 cyclohexanecarbonitriles reveals that equatorially oriented nitriles resonate 3.3 ppm downfield, on average, from their axial counterparts. Pairs of axial/equatorial diastereomers varying only at the nitrile-bearing carbon consistently exhibit downfield shifts of δ 0.4−7.2 for the equatorial nitrile carbon, even in angularly substituted decalins and hydrindanes.

Cyclic nitriles are versatile synthetic intermediates[2] that are readily transformed into an array of bioactive targets.[3] Cylcohexanecarbonitriles in particular have a long and distinguished history as versatile synthetic intermediates,[2,4] partly because of the prevalence of 6-membered rings in nature[5] and partly because of the nitrile's small steric demand.[6] The miniscule steric demand of the nitrile group, a mere 0.2 kcal mol^{-1},[6] allows efficient installation of hindered quaternary carbons through alkylations[7] and conjugate cyanations,[8] even in cases where other methods fail.[9]

Assigning the configuration of nitrile-bearing, quaternary centers is challenging.[10] X-ray crystallography provides an excellent method for *crystalline* nitriles whereas axial and equatorial orientations of liquid cyclohexanecarbonitrile diastereomers can be differentiated by their infrared CN bond intensity.[11] In contrast, using mechanistic arguments to assign the configuration of cyclic nitriles resulting from conjugate cyanations[12] or alkylations[13] is not always reliable. An illustrative case is the alkylation of **1** in which deprotonations with *i*-PrMgBr or LDA/BuLi and methylation leads to different nitrile diastereomers (Scheme 1, **1** → **2** → **3** and **1** → **4** → **5**). The divergent stereoselectivity is consistent with alkylations via *C*- or *N*-metalated cyclohexanecarbonitriles **2** and **4**, respectively.[14]

SCHEME 1. Stereodivergent Alkylations of Metalated Nitriles



During the synthesis of several diastereomeric cyclohexanecarbonitriles, the ^{13}C chemical shift of the nitrile carbon was

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(1) Taken in part from the Ph.D. Thesis of G. Wei, Duquesne University, 2007.

(2) (a) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747. (b) North, M. Nitriles: General Methods and Aliphatic Nitriles. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, pp 611−640.

(3) (a) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597. (b) Fatiadi, A. J. Preparation and Synthetic Applications of Cyano Compounds. In *The Chemistry of Functional Groups. Supplement C*; Patai, S., Ed.: Wiley: New York, 1983; pp 1157−1190.

(4) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. In *Organic Reactions: Addition and Substitution Reactions of Nitrile-stabilized Carbanions*; Wiley: New York, 1984.

(5) Banthorpe, D. V. Terpenoids. In *Natural Products: Their Chemistry and Biological Significance*; Mann, J., Davidson, R. S., Hobbs, J. B., Banthorpe, D. V., Harborne, J. B., Eds.; Addison Wesley Longman Ltd.: Reading, MA, 1994; Chapter 5.

(6) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−697.

(7) For a recent example see: Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 7098. For a review of cyclic nitrile alkylations see: Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

(8) Podlech, J. (a) Introduction of the Cyano Group by Conjugate Addition. In *Science of Synthesis (Houben-Weyl)*; Murahashi, S.-i., Ed.; Georg Thieme: Stuttgart, Germany, 2004; Vol. 19, pp 311−324. (b) Nagata, W.; Yoshikoshi, M. *Org. React.* **1977**, *25*, 255.

(9) (a) Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Steroids* **2007**, *72*, 297. (b) Barton, D. H. R.; Bringmann, G.; Motherwell, W. B. *Synthesis* **1980**, 68.

(10) For an example where NMR was unable to resolve the stereochemistry of a nitrile-bearing carbon see: Smith, P. H.; Fine, S. M.; Del Paggio, A. A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *C41*, 581.

(11) (a) Takasuka, M.; Saito, T.; Yamakawa, M. *J. Chem. Soc., Perkin Trans. 2* **1984**, 419. (b) Nagata, W.; Yoshioka, M.; Narisada, M.; Watanabe, H. *Tetrahedron Lett.* **1964**, 3133. No citations of these references were located using SciFinder Scholar (02/06/09). Whereas an empirical correlation exists between the band intensity and configuration, the stretching frequency, at least for cyclohexanecarbonitrile, is the same for both diastereomers: Horntvedt, H. T.; Klæboe, P. *Acta Chem. Scand.* **1975**, *29*, 528.

(12) Kinetic hydrocyanation of decalones installs axial nitriles whereas both isomers can form under thermodynamic conditions: Agami, C.; Fadlallah, M.; Levisalles, J. *Tetrahedron* **1981**, *37*, 903.

(13) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008**, 5365.

(14) (a) Fleming, F. F.; Wei, G.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2007**, *72*, 5270. (b) Fleming, F. F.; Zhiyu, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430.

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found to correlate with the orientation of the nitrile group (Scheme 1, compare **3** and **5**). The attraction of using a simple NMR method to assign the stereochemistry of quaternary nitrile-bearing carbons stimulated an extensive examination of ^{13}C NMR shifts in a diverse population of substituted cyclohexanecarbonitriles. Comparison of the chemical shifts revealed distinct regions depending on the configuration at the quaternary center. Equatorially oriented nitriles on fully substituted carbons typically resonate downfield, between δ 126.8 and 124.4, whereas the axially oriented counterparts resonate further upfield, between δ 124.6 and 118.6. Equatorial cyclohexanecarbonitrile diastereomers consistently resonate downfield from their axial counterparts, even for angular nitriles embedded within *cis*- and *trans*-decalins. The ^{13}C NMR chemical shift provides a rapid, useful method for assigning the configuration of quaternary, nitrile-bearing centers in cyclohexanecarbonitriles.

Searching the Chemical Abstracts Service database[15] was performed with the cyclohexanecarbonitrile[16] substructure **6** (Figure 1).[17] The search results were refined by specifying that the structures were single components, with reported stereochemistry, and with one or more references to articles in English. The references were limited to “journals” or “letters” appearing after 1985 from which time onward the reporting of ^{13}C NMR data was relatively routine. These search criteria returned 1008 references.

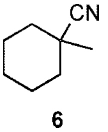

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FIGURE 1. Cyclohexanecarbonitrile search fragment.

Nitriles without secure configurational assignments[18] in the chair conformation were removed and duplications noted. *cis*-fused cyclohexanecarbonitriles with nitrile substitution in the angular position were removed unless a matching *trans*-diastereomer was present. By using these criteria, comparative ^{13}C NMR chemical shifts of the nitrile carbon, acquired in $CDCl_3$, were obtained for 211 structures.[19] Structures were categorized into three structural types: equatorially oriented nitriles other than angularly substituted nitriles in *cis*-fused polycycles, axially oriented nitriles including angularly substituted nitriles in *trans*-fused polycycles, and pairs of nitrile diastereomers differing solely in the configuration of the angularly substituted nitrile (Tables 1, 2, and 3 respectively in the Supporting Information).

Using the ^{13}C NMR nitrile chemical shift to assign configurations in cyclohexanecarbonitriles is attractive because the nitrile carbon resonates in a narrow chemical shift range,[20] has a diagnostic signal intensity,[21] and occupies a spectral window with minimal overlap by other functionalities.[22] Nitriles influence the chemical shifts of adjacent nucleii[23] through π-electron deshielding[24] and through a polar inductive effect.[25] The reverse anisotropic influence on the *nitrile* carbon chemical shift appears to only have been used in assigning the *E*/*Z* geomertry in a series of alkenenitriles.[26] The consistent downfield shift of the ^{13}C nitrile resonance in *E*-alkenenitriles provides a valuable assignment method that hints at a greater role for the nitrile ^{13}C NMR resonance in reporting the local stereochemistry.

Cyclohexanecarbonitriles preferentially adopt slightly flattened chair conformations in solution[27] and the solid state.[14,28] The ^{13}C NMR shifts of axial and equatorial substituents on regular chair conformations depend on the complex interplay between steric effects,[29] electron motion, and hyperconjugation.[30] Analyzing the cyclohexanecarbonitrile ^{13}C chemical shifts for the nitrile carbon reveals two distinct populations: equatorial nitrile carbons resonate downfield (δ 126.8−124.4 ppm) and axial nitrile carbons resonate further upfield (δ 124.6−118.6 ppm). A third group of cyclohexanecarbonitriles bearing adjacent heteroatoms or carbonyls exhibit no clear correlation of chemical shift with stereochemistry (Table 4, Supporting Information).[31] These electron-withdrawing groups induce their own anisotropy[32] and create a complex interplay between the adjacent σ- and π-electrons[33] that overrides the local magnetic field.

The two populations of equatorially and axially oriented nitriles have a region of chemical shift overlap for the nitrile carbon resonances of only 0.2 ppm! Only 9 out of 129 axial or equatorial cyclohexanecarbonitrile resonances lie in the same chemical shift region (Tables 1 and 2, Supporting Information). The graphical representation of this distribution shows the different chemical shift regions for these two populations and the small region where the two populations overlap (Figure 2). The visual picture also highlights the greater population of

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(15) Searches conducted on December 17, 2008 using SciFinder Scholar.

(16) Insufficient data prevented the analysis from being extended to 5- and 7-membered cyclic nitriles. Exploratory comparisons of the ^{13}C NMR chemical shifts for 2-cyanopiperidines show minimal differences for the nitrile carbon in axial and equatorial diastereomers: Wolckenhauser, S. A.; Rychnovsky, S. D. *Tetrahedron* **2005**, *61*, 3371.

(17) Heteroatom substituents on the nitrile-bearing carbon induce different anisotropy effects. From the limited available chemical shifts of cyclohexanone cyanohydrins, equatorially oriented nitriles resonate further downfield than their axial counterparts in the ^{13}C NMR: Kobler, C.; Bohrer, A.; Effenberger, F. *Tetrahedron* **2004**, *60*, 10397.

(18) Many of the configurational assignments were based on crystallographic analyses or made by chemical correlation. Configurational assignments were often evident from diagnostic coupling constants at other ring positions and in other cases were made by assuming that the small nitrile adopts the more sterically demanding axial orientation.

(19) The structures, the ^{13}C NMR shifts, and the references are collated in tables provided in the Supporting Information.

(20) Long chain nitriles resonate from δ 119−122 (refs 20a and 20b) while alkylsubstituted benzonitriles resonate from δ 117−121 (ref 20c). (a) Gunstone, F. D. *Chem. Phys. Lipids* **1993**, *66*, 189. (b) Terent’ev, A. B.; Dostovalova, V. I.; Freidlina, R. K. *Org. Magn. Reson.* **1977**, *9*, 301. (c) Haupt, E. T. K.; Leibfritz, D. *Spectrochim. Acta, Part A* **1989**, *45A*, 119.

(21) Aromatic methine signals occasionally extend into the nitrile region but are readily differentiated from the quaternary nitrile signals by DEPT NMR.

(22) Bailey, W. F.; Cioffi, A. *Magn. Reson. Chem.* **1987**, *25*, 181.

(23) (a) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866. (b) Schneider, H.-J.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579.

(24) (a) Takeuchi, Y.; Fujisawa, H.; Noyori, R. *Org. Lett.* **2004**, *6*, 4607. (b) Wolff, S.; Smith, A. B., III.; Agosta, W. C. *J. Org. Chem.* **1974**, *39*, 1607. (c) Madsen, J. Ø.; Lwesson, S.-O. *Tetrahedron* **1974**, *30*, 3481. (d) Weyler, W., Jr.; Byrd, L. R.; Caserio, M. C.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 1027. (e) Gardner, D. V.; McGreer, D. E. *Can. J. Chem.* **1970**, *48*, 2104. (f) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141. (g) Cross, A. D.; Harrison, I. T. *J. Am. Chem. Soc.* **1963**, *85*, 3223. (h) Reddy, G. S.; Goldstein, J. H.; Mandell, L. *J. Am. Chem. Soc.* **1961**, *83*, 1300. (i) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 2723.

(25) Abraham, R. J.; Reid, M. *Magn. Reson. Chem.* **2000**, *38*, 570.

(26) Tortajada, J.; Van Hemelryck, B.; Morizur, J.-P. *Bull. Chem. Soc. Jpn.* **1984**, 243.

(27) (a) Lafrance, R.; Aycard, J.-P.; Berger, J.; Bodot, H. *Org. Magn. Reson.* **1976**, *8*, 95. (b) Aycard, J.-P.; Bodot, H. *Org. Magn. Reson.* **1975**, *7*, 35. (c) Hawkes, G. E.; Utley, J. H. P. *J. Chem. Soc., Chem. Commun.* **1969**, 1033.

(28) (a) Matsuya, Y.; Qin, H.; Nagaoka, M.; Nemoto, H. *Heterocycles* **2004**, *62*, 207. (b) Ellis, D. D.; Spek, A. L. *Acta Crystallogr.* **2000**, *C56*, 1173. (c) Michel, A. G.; Boulay, G.; Pothier, N.; Deslongchamps, P. *Acta Crystallogr.* **1989**, *C45*, 938. (d) Podlahová, J.; Podlaha, J.; Malý, K.; Petrícik, V. *Acta Crystallogr.* **1987**, *C43*, 2214. (e) Kametani, T.; Suzuki, Y.; Honda, T. *Heterocycles* **1985**, *23*, 563.

(29) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

(30) Klod, S.; Koch, A.; Kleinpeter, E. *J. Chem. Soc., Perkin Trans. II* **2002**, 1506.

axially oriented nitriles (red), reflecting their facile formation by hydrocyanation of enones[8] and through alkylations of *N*-metalated nitriles.[2a] The average chemical shift of the equatorially oriented nitriles is 3.3 ppm further downfield than the axial counterparts (125.7 ppm, $\sigma = 0.7$ and 122.4 ppm, $\sigma = 1.5$, respectively).

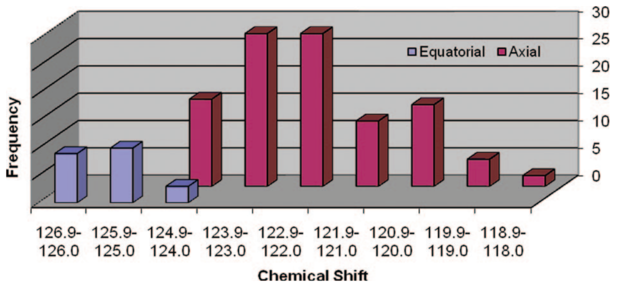

FIGURE 2. Frequency vs. ^{13}C NMR CN chemical shifts of equatorial and axial quaternary cyclcohexanecarbonitriles.

The correlation between the chemical shift and the configuration of the nitrile-bearing stereocenter is more pronounced in diastereomeric pairs of cyclohexanecarbonitriles (Table 3, Supporting Information). In 24 pairs of nitrile diastereomers, the equatorial nitriles consistently resonate downfield from their axial counterparts by 0.4−7.2 ppm. The diastereomeric nitriles **7e** and **7a** illustrate the general trends and the types of functionality present in the data set (Figure 3). Hydroxylation has a minimal effect on the nitrile chemical shift when present either within alkyl substituents or incorporated within the cyclohexane ring. Olefinic and aromatic substituents are tolerated as ring substitutents. Carbonyl groups two, or more, carbons removed are tolerated but their strong anisotropy overides the chemical shift correlation when adjacent to the nitrile-bearing carbon.[32]

FIGURE 3. Typical deshielding trends in nitrile diastereomers.

Remarkably, the chemical shift trends are maintained in *cis*- and *trans*-decalins that differ only in the stereochemistry of an angular nitrile! In *cis*-decalins the angular nitrile is equatorial with respect to one cyclohexane ring (**8e** Figure 4, black) and axial with respect to the other (**8e** Figure 4, magenta). In contrast, the angular nitrile of the *trans*-decalin counterpart is axial with respect to *two* rings (compare **8e** with **8a** in Figure 4). Despite this seemingly small structural difference the "equatorial" nitrile carbon in *cis*-decalins resonates 0.4−4.6 ppm further downfield (Table 3, Supporting Information). The only instance in which the trend is not observed is with a conformationally mobile *cis*-decalin.[34] This underscores the requirement for the cyclohexanecarbonitrile to be in a "locked" chair conformation. The largest chemical shift differences were for angularly substituted *cis*- and *trans*-hydrindanes ($\Delta\delta = 4.2-7.6$ ppm) which show the same respective equatorial downfield and axial upfield chemical shift movements as the *cis*- and *trans*-decalins.

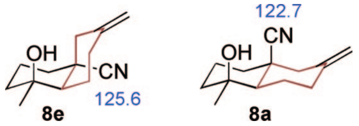

FIGURE 4. Representative deshielding in angular nitrile diastereomers.

In conclusion, an extensive literature search located more than 200 examples of 1-alkylcyclohexanecarbonitriles with assignable ^{13}C NMR chemical shifts for the nitrile carbon. Equatorially oriented cyclohexanecarbonitriles, in which the nitrile-bearing carbon is fully substituted, typically resonate between δ 126.8 and 124.4 whereas the corresponding axial diastereomers resonate further upfield, between δ 124.6 and 118.6. Only 9 out of 129 resonances lie in the same chemical shift region with the average equatorially oriented nitrile resonating 3.3 ppm downfield from the axial counterpart.

Diastereomeric pairs of cyclohexanecarbonitriles that vary only at the nitrile-bearing carbon exhibit consistent downfield shifts for the equatorial nitrile carbon provided that the chair conformation is not fluxional. The ^{13}C NMR chemical shift of the nitrile carbon provides a rapid method of assigning the configuration of quaternary nitrile-bearing carbons in diverse cyclohexanecarbonitriles.

Acknowledgement. Financial support of nitrile-based research from the NIH (2R15AI051352) and the NSF (CHE 0808996) is gratefully acknowledged.

Supporting Information Available: Tables of cyclohexanecarbonitrile ^{13}C NMR chemical shifts with the corresponding references. This material is available free of charge via the Internet at http://pubs.acs.org.

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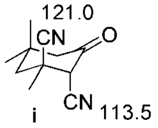
(31) For interaction of the carbonyl π-system with the nitrile see: (a) Agami, C.; Kazakos, A.; Levisalles, J.; Sevin, A. *Tetrahedron* **1980**, *36*, 2977. (b) Agami, C.; Fadlallah, M.; Kazakos, A.; Levisalles, J. *Tetrahedron* **1979**, *35*, 969.

(32) Cross, A. D.; Harrison, I. T. *J. Am. Chem. Soc.* **1963**, *85*, 3223. The effect of adjacent carbonyl groups is evident in nitriles **i** and **ii** where the quaternary nitriles resonate in the "normal" region while the tertirary nitriles resonate abnormally upfield. The assignment of the nitrile carbon resonances is made by analogy to the chemical shifts of similar β-oxonitiles (ref 32a) which differs from the assignment in the original report (ref 32b). (a) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Tetrahedron* **2003**, *59*, 737. (b) Rissafi, B.; Rachiqi, N.; El Louzi, A.; Loupy, A.; Petit, A.; Fkih-Tétouani, S. *Tetrahedron* **2001**, *57*, 2761.



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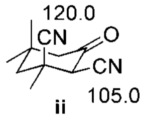

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(33) Yonemoto, T. *J. Magn. Reson.* **1973**, *12*, 93.

(34) The conformational mobility of the *cis*-decalin (8′a*S*)-methyl-6′-oxo-octahydro-spiro[[1,3]dioxolane-2,2′-naphthalene]-(4′a*R*)-carbonitrile (ref 34a) averages the anisotropy induced by the adjacent bonds: Johan Winne, personal communication. (a) Winne, J. M.; Guang, B.; D'Herde, J.; De Clercq, P. J. *Org. Lett.* **2006**, *8*, 4815.