Published in final edited form as:

J Org Chem. 2009 May 1; 74(9): 3551–3553. doi:10.1021/jo900286f.

Cyclohexanecarbonitriles: Assigning Configurations at Quaternary Centers From ^{13}C NMR CN Chemical Shifts.¹

Fraser F. Fleming and Guoqing Wei

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh PA, 15282-1530, USA. flemingf@duq.edu

Abstract

^{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 intermediates² that are readily transformed into an array of bioactive targets.³ Cyclohexanecarbonitriles in particular have a long and distinguished history as versatile synthetic intermediates,^{2,4} partly because of the prevalence of 6-membered rings in nature⁵ 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 alkylations⁷ 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 cyanations¹² or alkylations¹³ 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

During the synthesis of several diastereomeric cyclohexanecarbonitriles, the ^{13}C chemical shift of the nitrile carbon was 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 126.8-124.4, whereas the axially oriented counterparts resonate further upfield, between δ 124.6-118.6. 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 database¹⁵ was performed using the cyclohexanecarbonitrile¹⁶ 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 onwards the reporting of ^{13}C NMR data was relatively routine. These search criteria returned 1008 references.

Nitriles without secure configurational assignments¹⁸ 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. 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 nuclei²³ through π -electron deshielding²⁴ 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* geometry 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 solution²⁷ 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 anisotropy³² and create a complex interplay between the adjacent σ - and π -electrons³³ 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 axially oriented nitriles (red), reflecting their facile formation by hydrocyanation of enones⁸ 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).

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 **8e** and **8a** 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 substituents. Carbonyl groups two, or more, carbons removed are tolerated but their strong anisotropy overrides the chemical shift correlation when adjacent to the nitrile-bearing carbon.³²

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 (**9e** Figure 4, black) and axial with respect to the other (**9e** Figure 4, magenta). In contrast, the angular nitrile of the *trans*-decalin counterpart is axial with respect to *two* rings (compare **9e** with **9a** 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.

Conclusion

An extensive literature search located more than 200 examples of 1-alkylcyclohexanecarbonitriles with assignable ¹³C NMR chemical shifts for the nitrile carbon. Equatorially oriented cyclohexanecarbonitriles, in which the nitrile-bearing carbon is fully substituted, typically resonate between δ 126.8–124.4 whereas the corresponding axial diastereomers resonate further upfield, between δ 124.6–118.6. 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 ¹³C NMR chemical shift of the nitrile carbon provides a rapid method of assigning the configuration of quaternary nitrile-bearing carbons in diverse cyclohexanecarbonitriles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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

References

1. Taken in part from Wei G. Ph.D. Thesis. 2007 Duquesne University
2. (a) Fleming FF, Zhang Z. *Tetrahedron* 2005;61:747. North, M. Nitriles: General Methods and Aliphatic Nitriles. In: Trost, BM.; Fleming, I., editors. *Comprehensive Organic Synthesis*. Vol. 3. Oxford: Pergamon; 1991. p. 611-640.
3. (a) Fleming FF. *Nat. Prod. Rep* 1999;16:597. Fatiadi, AJ. Preparation and Synthetic Applications of Cyano Compounds. In: Patai, S., editor. *The Chemistry of Functional Groups*. Supplement C. Wiley; 1983. p. 1157-1190.
4. Arseniyadis, S.; Kyler, KS.; Watt, DS. *Organic Reactions: Addition and Substitution Reactions of Nitrile-stabilized Carbanions*. New York: Wiley; 1984.
5. Banthorpe, DV. Ch 5. Terpenoids. In: Mann, J.; Davidson, RS.; Hobbs, JB.; Banthorpe, DV.; Harborne, JB., editors. *Natural Products: Their Chemistry and Biological Significance*. Addison Wesley Longman Ltd.; 1994.
6. Eliel, Ernest L.; Wilen, Samuel H.; Mander, Lewis N. *Stereochemistry of Organic Compounds*. Wiley, NY; 1994. p. 696-697.
7. For a recent example see: Fleming FF, Liu W, Ghosh S, Steward OW. *Angew. Chem., Int. Ed* 2007;46:7098. For a review of alkylations in cyclic nitriles Fleming FF, Shook BC. *Tetrahedron* 2002;58:1.
8. Podlech, J. Introduction of the Cyano Group by Conjugate Addition. In: Murahashi, S-i, editor. *Science of Synthesis (Houben-Weyl)*. Vol. 19. Georg Thieme: Stuttgart; 2004. p. 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. [PubMed: 17207507] (b) Barton DHR, Bringmann G, Motherwell WB. *Synthesis* 1980:68.
10. For an example where NMR was unable to resolve the stereochemistry of a nitrile-bearing carbon see: Smith PH, Fine SM, Del Paggio AA. *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 HT, 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 FF, Gudipati S. *Eur. J. Org. Chem* 2008:5365.
14. (a) Fleming FF, Wei G, Zhang Z, Steward OW. *J. Org. Chem* 2007;72:5270. [PubMed: 17567075] (b) Fleming FF, Zhiyu Z, Wei G, Steward OW. *J. Org. Chem* 2006;71:1430. [PubMed: 16468790]
15. Searches conducted on 17 December 2008 using SciFinder Scholar
16. Insufficient data prevented the analysis from being extended to 5- and 7-membered cyclic nitriles. Exploratory comparisons of the ¹³C NMR chemical shifts for 2-cyanopiperidines show minimal differences for the nitrile carbon in axial and equatorial diastereomers: Wolckenhauser SA, Rychnovsky SD. *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^{a,b} while alkylsubstituted benzonitriles resonate from δ 117–121.^c (a)Gunstone FD. *Chem. Phys. Lipids* 1993;66:189. (b)Terent'ev AB, Dostovalova VI, Freidlina RK. *Org. Magn. Reson* 1977;9:301. (c)Haupt ETK, 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 WF, 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. [PubMed: 15548087] (b) Wolff S, Smith AB III, Agosta WC. *J. Org. Chem* 1974;39:1607. (c) Madsen JØ, Lwesson S-O. *Tetrahedron* 1974;30:3481. (d) Weyler W Jr, Byrd LR, Caserio MC, Moore HW. *J. Am. Chem. Soc* 1972;94:1027. (e) Gardner DV, McGreer DE. *Can. J. Chem* 1970;48:2104. (f) Kurtz AN, Billups WE, Greenlee RB, Hamil HF, Pace WT. *J. Org. Chem* 1965;30:3141. (g) Cross AD, Harrison IT. *J. Am. Chem. Soc* 1963;85:3223. (h) Reddy GS, Goldstein JH, Mandell L. *J. Am. Chem. Soc* 1961;83:1300. (i) Cripps HN, Williams JK, Sharkey WH. *J. Am. Chem. Soc* 1959;81:2723.
25. Abraham RJ, Reid M. *Magn. Reson. Chem* 2000;38:570.
26. Tortajada J, Van Hemelryck B, Morizur J-P. *Bull. Chem. Soc. J* 1984:243.
27. (a) Lafrance R, Aycard J-P, Berger J, Bodot H. *Org. Magn. Resonance* 1976;8:95. (b) Aycard J-P, Bodot H. *Org. Magn. Resonance* 1975;7:35. (c) Hawkes GE, Utley JHP. *J. Chem. Soc., Chem. Commun* 1969:1033.
28. (a) Matsuya Y, Qin H, Nagaoka M, Nemoto H. *Heterocycles* 2004;62:207. (b) Ellis DD, Spek AL. *Acta Crystallogr* 2000;C56:1173. (c) Michel AG, Boulay G, Pothier N, Deslongchamps P. *Acta Crystallogr* 1989;C45:938. (d) Podlahová J, Podlaha J, Malý K, Petrčík V. *Acta Crystallogr* 1987;C43:2214. (e) Kametani T, Suzuki Y, Honda T. *Heterocycles* 1985;23:563.
29. Grant DM, Cheney BV. *J. Am. Chem. Soc* 1967;89:5315.
30. Klod S, Koch A, Kleinpeter E. *J. Chem. Soc., Perkin Trans. II* 2002:1506.
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 AD, Harrison IT. *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 tertiary nitriles resonate abnormally upfield. The assignment of the nitrile carbon resonances is made by analogy to the chemical shifts of similar β -oxonitriles^a which differs from the assignment in the original report.^b (a)Fleming FF, Shook BC, Jiang T, Steward OW. *Tetrahedron* 2003;59:737. (b) Rissafi B, Rachiqi N, El Louzi A, Loupy A, Petit A, Fkih-Tétouani S. *Tetrahedron* 2001;57:2761.
33. Yonemoto TJ. *Magn. Reson* 1973;12:93.
34. The conformational mobility of the *cis*-decalin (8'aS)-Methyl-6'-oxooctahydro-spiro[[1,3]dioxolane-2,2'-naphthalene]-(4'aR)-carbonitrile^a averages the anisotropy induced by the adjacent bonds: Johan Winne, personal communication Winne JM, Guang B, D'Herde J, De Clercq PJ. *Org. Lett* 2006;8:4815. [PubMed: 17020310]

Figure 1.
Cyclohexanecarbonitrile Search Fragment.

Figure 2.
Frequency vs ^{13}C NMR CN Chemical Shifts of Equatorial and Axial Quaternary Cyclohexanecarbonitriles.

Figure 3.
Typical Deshielding Trends in Nitrile Diastereomers

Figure 4.
Representative Deshielding in Angular Nitrile Diastereomers.

Scheme 1.
Stereodivergent Alkylations of Metalated Nitriles.