

Hindered rotation in an “exploded” biphenyl†

Ognjen Š. Miljanić, Sangdon Han,‡ Daniel Holmes, Gaston R. Schaller and K. Peter C. Vollhardt*

Received (in Bloomington, IN, USA) 3rd March 2005, Accepted 21st March 2005

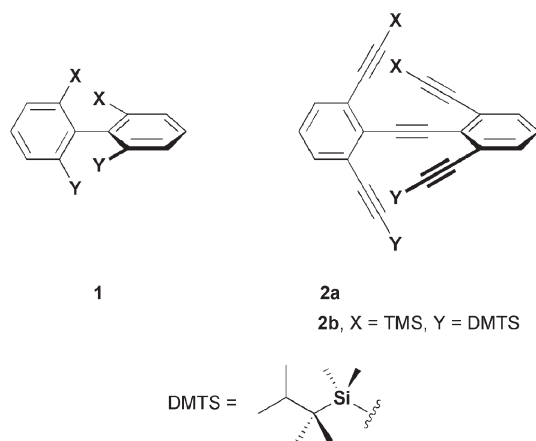
First published as an Advance Article on the web 6th April 2005

DOI: 10.1039/b503173g

The first cases of hindered rotation around the triple bond in simple diphenylacetylenes were observed, including that in chiral 2,2'-bis(trimethylsilyl)-6,6'-bis(dimethylthexylsilyl)-diphenylacetylene.

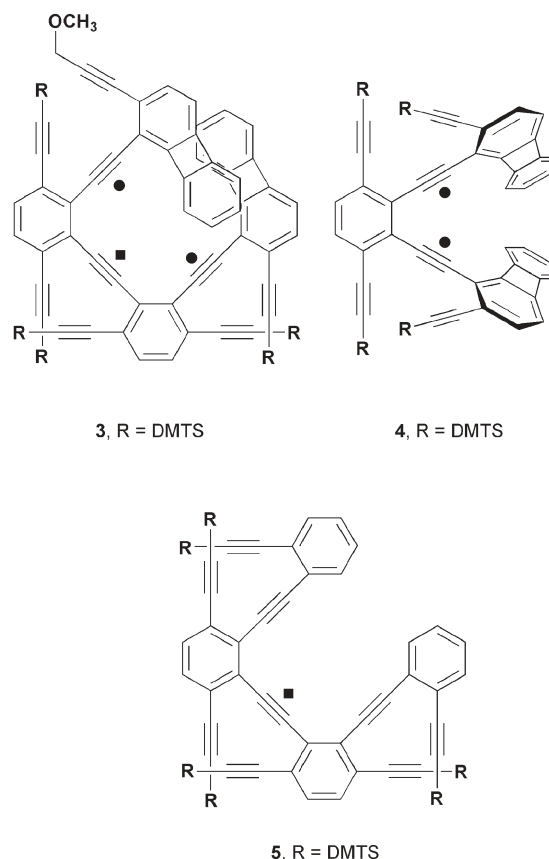
Tetrasubstituted biphenyls **1** ($X \neq Y \neq H$) constitute an intriguing class of chiral compounds that lack chirogenic centers.¹ Their atropisomerism arises from a) restricted rotation around the axis of the central single bond, which prevents molecules from equilibrating with their mirror images, and b) differential substitution, which makes those mirror images inequivalent. These two principles are general and can guide the construction of other chiral systems. A simple case is diphenylacetylene: while the parent molecule rotates essentially freely around its ~ 4.0 Å long $-C\equiv C-$ unit ($\Delta G^\ddagger < 1$ kcal mol⁻¹),² appropriate substitution should hinder this motion.^{2b} Rotational isomerism in diaryl- and other alkynes is of interest fundamentally³ as well as in applications, for example the design and construction of novel devices⁴ and polymers.⁵ Despite these efforts, observable hindered rotation in a simple diphenylacetylene has remained elusive. Notably, a 2,2',6,6'-tetra-*p*-tolyl derivative remained conformationally mobile on the NMR time scale at temperatures as low as -100 °C.^{3a}

This communication reports on the NMR-detection of hindered rotation around the $-C\equiv C-$ unit in alkynylated diphenylacetylenes, notably core **2b**, the simplest member of the class of chiral 2,2',6,6'-tetrakis(alkynyl)diphenylacetylenes **2a**.⁶ These compounds relate to chiral biphenyls by the simple insertion of a $C\equiv C$ fragment into all five of the single bonds that bring about the chirality of **1** and are thus, in Houk–Scott terminology,⁷ “exploded” biphenyls.



Constructs of the type **2a** function as building blocks in the assembly of carbon rich materials, such as planar metalacycles,⁶ the phenylenes,⁸ substructures of graphyne and its relatives,⁹ and nanotubes.¹⁰ The findings of this paper suggest that they might also be viable as new scaffolds for chiral atropisomeric ligand construction.¹¹

The occurrence of atropisomerism in **2a** first became apparent during the course of the synthesis of the [N]heliphenes, $N = 7-9$, by triple cobalt-catalyzed cycloisomerization of the corresponding nonaynes.¹² In particular, the 500 MHz ¹H-NMR spectrum of the advanced intermediate **3** on route to methoxymethyl [9]heliphene revealed two doublets ($\delta = 4.08, 4.15$ ppm; AB, $J = 15$ Hz) for the methylene hydrogens at room temperature (500 MHz, CDCl₃), clearly signalling the presence of a configurationally stable chiral conformation. Furthermore, gradual cooling of the sample to -53 °C in toluene-*d*₈, caused further decoalescence and the appearance of several broad signals for these hydrogens. At this temperature, the corresponding methoxy singlet separated into two distinct peaks ($\Delta\nu = 36$ Hz), the combined data indicating the rotational restriction of a second (and perhaps third) stereogenic axis in the molecule giving rise to two, perhaps three diastereomers.



† Electronic supplementary information (ESI) available: experimental, spectroscopic, and analytical data for all new compounds. See <http://www.rsc.org/suppdata/cc/b5/b503173g/>

‡ Present address: Arena Pharmaceuticals, 6166 Nancy Ridge Dr., San Diego, California 92121, USA.

*kpcv@berkeley.edu

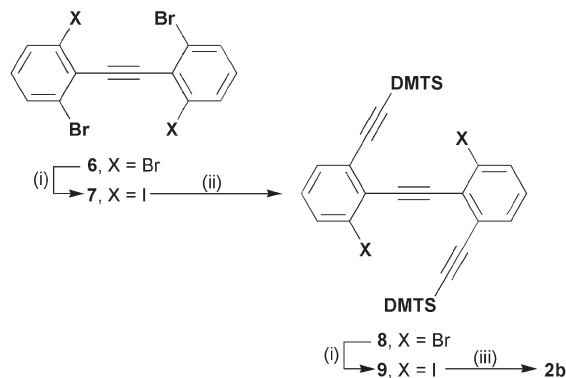
Because of the complexity of the NMR signals of unsymmetrical **3** and to elucidate the nature of these dynamic processes, we turned to the symmetrical **4**¹³ and **5**,¹² the former as a model for probing the hindered rotation of the “outside” diphenylacetylene axes (●), the latter for doing so with respect to their inside counterpart (■). In these molecules, the signals for the potentially diastereotopic pairs of methyls of the DMTS group, especially the distinct silylmethyl absorptions, were sufficiently well resolved to allow for variable temperature NMR studies.

In **4**, a precursor to [7]heliophene by double cyclization,¹³ restricted rotation may give rise to only two diastereomers: the *syn* form, in which the biphenylenyl substituents face each other (as shown), and the *anti* rotamer, in which they point in opposite directions. Molecular mechanics calculations favor the former energetically by ~ 1 kcal mol⁻¹. At room temperature, the ¹H-NMR spectrum of **4** displayed two sets of resonances for the two inequivalent DMTS groups, without any indication of hindered rotation. Specifically, only two silylmethyl singlets were visible at $\delta = 0.12$ and 0.16 ppm (400 MHz, CD₂Cl₂). Upon cooling to -54 °C, the latter decoalesced into two singlets, while the former started to broaden. The aromatic region of the spectrum remained unchanged. Similarly, at this temperature, the ¹³C signals for the three types of methyl carbons appeared as four lines each, while the remaining carbons gave rise to single resonances. These observations are consistent with the occurrence of hindered rotation around the biphenylenyl–phenyl alkyne bond and the presence of only one of the two possible diastereomers of **4**, presumably the *syn* isomer. Simple peak coalescence analysis provided a barrier of 11.5 kcal mol⁻¹ for this process,¹⁴ its facility suggesting that it is also responsible for the lower energy restricted movement(s) taking place in **3** (● axes).

To support this hypothesis, a similar analysis was performed on **5**. Indeed, decoalescence of the three silylmethyl singlets ($\delta = 0.04$, 0.10 , 0.16 ppm, 40 °C) associated with the three distinct DMTS groups, to six singlets occurred already at 28.1 °C (400 MHz, CDCl₃). Analysis of the decoalescence of the low field signal furnished an approximate activation barrier of 15.6 kcal mol⁻¹.¹⁴ It therefore seems that the substructure **2a** is responsible for the higher energy conformational process observed in **3** (■ axis).

These observations provided the impetus for the synthesis of **2b**, devoid of all the unessential elements present in **3–5**. In this system, there is only one stereogenic axis, and a variable temperature NMR analysis would provide unambiguous data addressing the possibility of hindered rotation around a diphenylacetylene triple bond. The preparation of **2b** (Scheme 1) commenced with the previously described tetrabromodiphenylacetylene **6**,⁶ which was desymmetrized to 2,2'-dibromo-6,6'-diiododiphenylacetylene **7** by bromine–iodine exchange. The iodinated positions in **7** were alkynylated with DMTSA¹⁵ under standard Sonogashira coupling conditions¹⁶ to furnish triyne **8** in 52% yield. A second bromine–iodine exchange afforded the doubly iodinated **9**, the trimethylsilylethynylation of which proceeded with great difficulty to give only 15% of **2b**, after a laborious purification sequence that involved column chromatography, Kugelrohr distillation, and HPLC.

Remarkably, restricted rotation was evident already at room-temperature in both the ¹H- and ¹³C-NMR spectra. The former featured a doubling of all the signals due to the diastereotopic methyls of the DMTS group, observable in dioxane-*d*₈ (Fig. 1a),



Scheme 1 Synthesis of **2b**. Reagents and conditions: (i) BuLi, Et₂O, -45 °C, 1 h, then I₂, Et₂O, -45 °C to rt, 2 h, 75% (for **7**), 92% (for **9**); (ii) DMTSA, PdCl₂(PPh₃)₂, CuI, NEt₃, rt, 20 h, 52%; (iii) TMSA, PdCl₂(PPh₃)₂, CuI, NEt₃, 100 °C, 72 h, 15%.

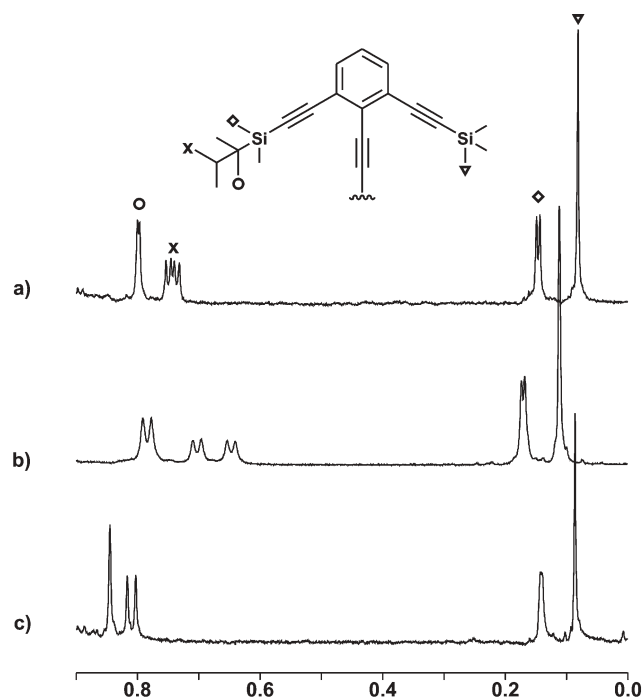


Fig. 1 ¹H-NMR (500 MHz) spectra of **2b** (methyl group region). Conditions: a) dioxane-*d*₈, 22 °C; b) THF-*d*₈, -82 °C; c) dioxane-*d*₈, 109 °C, sealed tube.

CDCl₃, and THF-*d*₈. The latter (CDCl₃) revealed such behavior only for the carbon-bound methyl groups, the silylmethyl carbons apparently being accidentally isochronous. In both cases, the remainder of the spectrum was as expected for a single species.

For the purpose of evaluating the barrier to rotation, the most diagnostic isopropyl doublets (marked with “x” in Fig. 1) were chosen. Unfortunately, a solvent covering the entire temperature range within which spectral changes were occurring could not be found. Thus, toluene did not provide clear peak separations and DMF did not dissolve **2b**. Therefore, low-temperature NMR measurements were undertaken in THF-*d*₈, whereas dioxane-*d*₈ was employed at high temperatures. An example of a clearly resolved low temperature spectrum is shown in Fig. 1b.

Coalescence of the isopropyl signals occurred at 96 °C, and increasing the temperature generated eventually a single set of DMTS peaks above 100 °C (Fig. 1c). The barrier to enantiomerization in **2b** was estimated at 18.7 kcal mol⁻¹.¹⁴

The rotational barrier in **2b** is remarkably high, in the high range of those reported for more complex diarylacetylene systems. For example, the ΔG^\ddagger values for Toyota's bis(1-phenyl-9-anthryl)acetylenes range between 10 and 18 kcal mol⁻¹,^{3b} while Moore's "molecular turnstiles" have corresponding values of 13–20 kcal mol⁻¹,^{4d} depending on the size of substituents on the aryl rings. On the other hand, the conformationally mobile 2,2',6,6'-tetrakis(aryl)diphenylacetylene frame exhibits barriers below 8 kcal mol⁻¹,^{3a} less than a half of that in **2b**.

In summary, the first cases of hindered rotation around the triple bond in simple diphenylacetylenes have been observed, including that in the simple chiral tetraethynyl system **2b**. The conformational barriers can be substantial, leading to the observation of restricted rotation by NMR at room temperature. Future work will aim to gain insight into the effect of substituent size on the flexibility of **2a** with the ultimate goal of achieving resolution of suitable derivatives. These investigations may lead to the development of **2a** as a viable new tool in chiral scaffold construction.

This work was supported by the National Science Foundation (CHE-0451241) and the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, of the U. S. Department of Energy, under Contract DE-AC03-76SF00098. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and Novartis as a Supporting Member.

Ognjen Š. Miljanić, Sangdon Han,† Daniel Holmes, Gaston R. Schaller and K. Peter C. Vollhardt*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California at Berkeley, and the Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720-1460, USA. E-mail: kpcv@berkeley.edu; Fax: +1 510 643 5208; Tel: +1 510 642 0286

Notes and references

- (a) E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 1142; (b) first observation: G. H. Christie and J. H. Kenner, *J. Chem. Soc. Trans.*, 1922, **121**, 614.
- (a) J. M. Seminario, A. G. Zacarias and J. M. Tour, *J. Am. Chem. Soc.*, 1998, **120**, 3970; (b) R. Stolevic and P. Bakken, *J. Mol. Struct.*, 1990, **239**, 205; (c) A. Grumadas and D. Poskus, *Zh. Fiz. Khim.*, 1987, **61**, 2838; (d) K. Okuyama, T. Hasegawa, M. Ito and N. Mikami, *J. Phys. Chem.*, 1984, **88**, 1711.
- See, *inter alia*: (a) S. Toyota, T. Iida, C. Kunizane, N. Tanifuji and Y. Yoshida, *Org. Biomol. Chem.*, 2003, **1**, 2298; (b) S. Toyota and T. Makino, *Tetrahedron Lett.*, 2003, **44**, 7775; (c) S. Toyota, T. Yamamori and T. Makino, *Tetrahedron*, 2001, **57**, 3521 (and cited references); (d) P. K. T. Mew and F. Vögtle, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 159.
- For examples, see: (a) "Chemosensors": J. Raker and T. E. Glass, *J. Org. Chem.*, 2001, **66**, 6505; T. E. Glass, *J. Am. Chem. Soc.*, 2000, **122**, 4522; S. Yagi, H. Kitayama and T. Takagishi, *J. Chem. Soc., Perkin Trans. 1*, 2000, 925; (b) "gyroscopes": C. E. Godinez, G. Zepeda, C. J. Mortko, H. Dang and M. A. Garcia-Garibay, *J. Org. Chem.*, 2004, **69**, 1652; Z. Dominguez, H. Dang, M. J. Strouse and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2002, **124**, 7719; Z. Dominguez, H. Dang, M. J. Strouse and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2002, **124**, 2398; (c) "barrow": C. Joachim, H. Tang, F. Moresco, G. Rapenne and G. Meyer, *Nanotechnology*, 2002, **13**, 330; (d) "turnstile": T. C. Bedard and J. S. Moore, *J. Am. Chem. Soc.*, 1995, **117**, 10662.
- For examples, see: (a) S. Toyota, M. Goichi and M. Kotani, *Angew. Chem. Int. Ed.*, 2004, **43**, 2248; (b) G. Brizius, K. Billingsley, M. D. Smith and U. H. F. Bunz, *Org. Lett.*, 2003, **5**, 3951; (c) M. Levitus, K. Schmieder, H. Ricks, K. D. Shimizu, U. H. F. Bunz and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2001, **123**, 4259; (d) T. Miteva, L. Palmer, L. Kloppenburg, D. Neher and U. H. F. Bunz, *Macromolecules*, 2000, **33**, 652.
- The parent 2,2',6,6'-tetrakis(ethynyl)diphenylacetylene (**2a**, X = Y = H) is known: J. D. Bradshaw, L. Guo, C. A. Tessier and W. J. Youngs, *Organometallics*, 1996, **15**, 2582.
- K. N. Houk, L. T. Scott, N. G. Rondan, D. C. Spellmeyer, G. Reinhardt, J. L. Hyun, G. J. DeCicco, R. Weiss, M. H. M. Chen, L. S. Bass, J. Clardy, F. S. Jørgensen, T. A. Eaton, V. Sarkozi, C. M. Petit, L. Ng and K. D. Jordan, *J. Am. Chem. Soc.*, 1985, **107**, 6556.
- (a) O. Š. Miljanić and K. P. C. Vollhardt, in *Carbon-Rich Compounds: Molecules to Materials*, ed. M. M. Haley and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005, in press; (b) K. P. C. Vollhardt and D. L. Mohler, in *Advances in Strain in Organic Chemistry*, ed. B. Halton, JAI, London, 1996, vol. 5, p. 121.
- (a) J. A. Marsden, M. J. O'Connor and M. M. Haley, *Org. Lett.*, 2004, **6**, 2385; (b) M. Sonoda, Y. Sakai, T. Yoshimura, Y. Tobe and K. Kamada, *Chem. Lett.*, 2004, **33**, 972; (c) J. M. Kehoe, J. H. Kiley, J. J. English, C. A. Johnson, R. C. Petersen and M. M. Haley, *Org. Lett.*, 2000, **2**, 969.
- (a) V. S. Iyer, K. P. C. Vollhardt and R. Wilhelm, *Angew. Chem. Int. Ed.*, 2003, **42**, 4379; (b) P. I. Dosa, C. Erben, V. S. Iyer, K. P. C. Vollhardt and I. M. Wasser, *J. Am. Chem. Soc.*, 1999, **121**, 10430; (c) R. Boese, A. J. Matzger and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1997, **119**, 2052.
- For reviews see: (a) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (b) K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry and M. Yamanaka, *Synlett*, 2002, 1561; (c) M. McCarthy and P. J. Guiry, *Tetrahedron*, 2001, **57**, 3809.
- S. Han, D. R. Anderson, A. D. Bond, H. V. Chu, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt and G. D. Whitener, *Angew. Chem. Int. Ed.*, 2002, **41**, 3227.
- S. Han, A. D. Bond, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt and G. D. Whitener, *Angew. Chem. Int. Ed.*, 2002, **41**, 3223.
- (a) M. Ōki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, Weinheim, 1985; (b) F. P. Gasparro and N. H. Kolodny, *J. Chem. Educ.*, 1977, **54**, 258.
- M. Müller, W.-R. Förster, A. Holst, A. J. Kingma, E. Schaumann and G. Adiwidjaja, *Chem. Eur. J.*, 1996, **2**, 949.
- K. Sonogashira, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, Wiley, New York, 2002, vol. 1, p. 493, (and cited references).