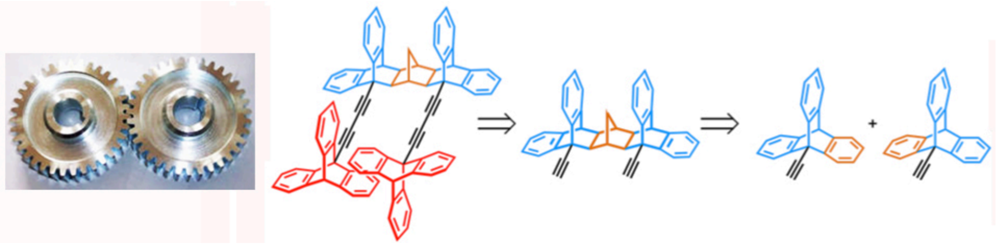
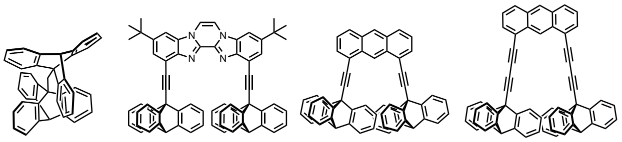
Molecular Spur Gears with Triptycene Rotators and a Norbornane-Based Stator

Xing Jiang, Song Yang, Marcus J. Jellen, K. N. Houk,* and Miguel Garcia-Garibay*
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States



ABSTRACT: We report here our efforts to prepare a molecular spur gear by taking advantage of a convenient synthesis of an iptycene-like norbornane stator that positions two di-yne-linked triptycene in parallel alignment and with inter-digitated blades. A one pot Diels-Alder reaction between two equivalents of 9-anthracenylcarbaldehyde and norbornadiene gives 38% of the desired double syn-adduct, which can be further functionalized to attach the two triptycene rotators with a center-to-center distance of ca. 5.4 Å. Evidence for gearing was not observed by ^{19}F NMR for a -CF_3 labeled analog at temperatures that are as low as 213 K. We used, for the first time, molecular dynamics simulation and 2D metadynamics calculation to understand the energetic profile of the gearing/slippage in the molecular gears, and to guide future designs of molecular spur gears. We determined that slippage in this system and Toyota's spur gear **4** is preferred over gearing by 3.4 and 3.9 kcal mol^{-1}, whereas gearing is favored in Siegel's gear **2** by 1.1 kcal/mol, suggesting that gearing is possible with further optimization of **2**.

The study of molecular gears dates back to the 1980s[1] when Mislow and Iwamura studied the gearing dynamic of molecular bevel gears, which are built with two triptycenes linked at their bridgehead carbons by single atom (i.e., C, O and N), such that they are meshed at an angle of *ca*. 109° (**1**, Figure 1).[1,2] It was shown that concerted disrotatory motion of the two-triptycene groups occurs with a very low energy barrier of 1-2 kcal/mol, whereas the activation energy for conrotatory gear slippage is very high, in the range of 32−45 kcal/mol.[3] As a result of the large difference in activation energies, triptycene bevel gears display a very high gearing fidelity (F_{gear}), which is defined as the number of geared rotations that occur in the average time course of one gear slippage ($F_{gear} = k_{gear}/k_{slippage} \approx 10^{30}$).[4] While there is essentially no slippage in the sterically congested triptycene bevel gears, there has been no examples of high-fidelity molecular analogs of spur gears where the two triptycenes are meshed in a parallel arrangement. Notable literature examples of molecular spur gears are illustrated in Figure 1.[5,6] These include structure **2** with two 9-triptycyl acetylenes attached to bis(benzimidazole), which was reported by Siegel,[5] and structures **3** and **4** with 9-triptycyl-acetylene and 9- triptycyl-butadyine, respectively, attached the 1,8-carbons of an anthracene stator, as reported Toyota.[6] Based on computational models and guided by the gearing and slippage activation energies, Siegel and coworkers suggested that the ideal distance between the points of attachment on the two rotators should be ca. 8.0 Å.[4,5] As shown in Figure 2, a single crystal X-ray structure revealed that spur gear **2** features anchoring points separated by 8.12 Å. It was also noticed that the bis(benzimidazole) stator shows a slight deviation from planarity such that the two alkynes are not parallel to each other. The proximal bridgehead carbons of the triptycene rotators, C9 and C9', are separated from each other by 8.42 Å and the two alkynes tend to bend inwards, suggesting that the distance between the two rotators may be longer than ideal, which might be responsible for the absence of dominant gearing.



1 2 3 4

Figure 1. Triptycene pairs arranged as a molecular bevel (**1**) and spur (**2-4**) gears.

On the other hand, Toyota and coworkers examined the use planar 1,8-disubstituted anthracenes with a distance of only 4.99 Å between anchoring points.[6] As the two triptycenes are forced to such a short distance, repulsion becomes the dominant interactions between them and the acetylene (**3**) and butadiyne (**4**) linkers bent outwards to relieve strain, as illustrated by the single crystal X-ray diffraction structure of **3** in Figure 2. Variable temperature NMR measurements were attempted for an analog of compound **4** with methyl groups at the triptycenes C2 and C2' positions. However, the presence of two sets of signals corresponding to two different sets of rapidly interconverting conformers (see Figure 5 and its discussion for details) was not observed.

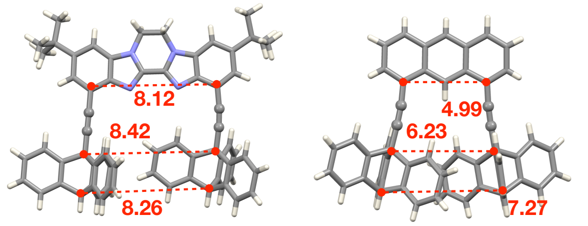


Figure 2. Crystal structures of **2** (left) and **3** (right) with the distances between the points of alkyne attachment and triptycene bridgehead carbons highlighted (from references X and Y, respectively).

While one may speculate that the lack of gearing is due to the fact that the triptycene gears in **4** are too close, it is also conceivable that steric congestion may actually favor a gearing processes (as it occurs in the case of molecular bevel gears), and that the lack of gearing may be the result of steric hindrance by the methyl groups pointing outwards at C2 and C2'.

We reasoned that a rigid pentiptycene group would be an interesting a stator for triptycene-based spur gears since it may be viewed as the fusion of two triptycene rotators (**A** in Figure 3) brought together with a distance of ca. 5.5 Å between the points of attachment (**B** in Figure 3). However, considering the synthetic challenge involved in the installation of two syn-alkyne linkers on a pentiptycenes core, we selected the structurally similar but the synthetically more accessible stator **C**, based on the use of a norbornadiene core (Figure 3).[7] The alkyne spacers in **C** are parallel to each other with the distance between them estimated to be 5.4 Å. The core structure of **C** (compound **5**, Scheme 1) was prepared in one step using a sealed tube at 200 ˚C by a two-fold Diels-Alder reaction between norbornadiene and 9-anthracene carboxaldehyde.

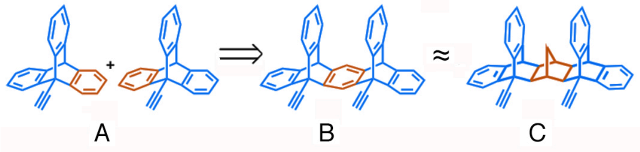
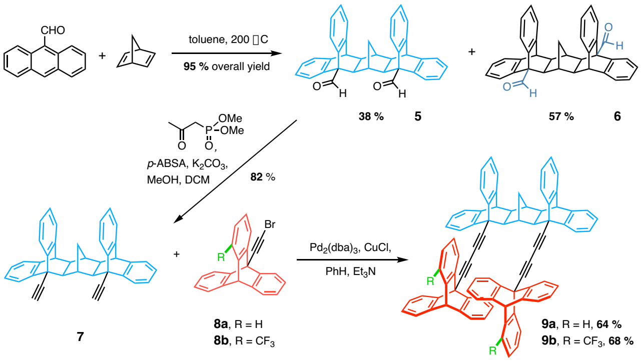


Figure 3. (A) The fusion of two triptycenes to generate, (B) a pentiptycene stator, and (C) the analogy between the latter and a stator formed by two norbornane-fused dibenzobarrelenes.

Regioisomers **5** and **6** were obtained in an isolated yield of 95% with a respective syn:anti regioselectivity of 38:57 in favor of anti-isomer **6**. Compound **5** was converted to syn-diyne **7** by a Bestmann-Ohira reaction.[8] A Pd(0)-catalyzed alkyne cross-coupling reaction between **7** and 9-bromoethynyltriptycene **8a** under conditions reported by Toyota and coworkers led to the desired molecular gear **9a**.[6] Analog **9b** with one of the three blades of each triptycenes substituted with a -CF_3 group was also prepared using the same coupling reaction with 4-trifluoromethyl-9-ethynyltriptycene **8b**. The substitution pattern of **8b** was established by Diels-Alder addition of 3-trifluoromethylbenzyne to 2-(anthracen-9-yl)-1,3-dioxolane similar to Siegel's report. Steric interactions between the cyclic acetal and the trifluoromethyl group gave complete preference for the desired regioisomer albeit in low yield (25%). Subsequent deprotection of the acetal yielded labeled 9-triptycynal, which then underwent an interrupted Corey-Fuchs homologation[9] to produce labeled 9-(2,2'-dibromoviynl)triptycene. Finally, the vinyltriptycene was treated with TBAF to afford **8b**.

Scheme 1



We were able to obtain single crystals of **9a** by slow evaporation from a toluene solution and solved the structure by X-Ray diffraction (XRD) at 100 K (Figure 4). Crystal with included toluene were solved in a space group $P2_1/n$ with a distance between anchoring points of 5.31 Å, which is slightly longer than that of Toyota's anthracene-based spur gears **3** and **4**. Steric repulsion between the triptycene rotators is quite apparent in **9a**. From a distance of 5.31 Å at the point of attachment, the distance between bridgehead carbons C9 and C9' increased to 6.67 Å and it was further extended to 7.46 Å for the distal bridgehead carbons C10 and C10' (Figure 4).

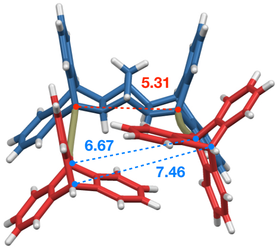


Figure 4. Crystal structure of molecular spur gear **9a**.

The stereochemical dynamics of molecular spur gear **9b** were analyzed by VT ^{1}H NMR and ^{19}F NMR in CD_2Cl_2 at temperatures that varied from 298 K to 213 K. As indicated in Figure 5a using projections of a bevel gear viewed along the parallel rotational axes with one of the blades labeled with a heavy dot, there are eighteen distinct conformers (a-i') in three different sets (I, II and III).[3] I and II correspond to *dl* isomers while set III is a *meso* phase. Rotational isomers of any individual set interconvert independently by a disrotatory gearing mechanism. Also indicated in Figure 5a, the conversion between different rotational isomers requires a conrotatory mechanism involving gear slippage. In the ideal scenario, it is expected that the NMR spectrum of a labeled bevel gear with fast, high fidelity gearing, will give rise to two sets of signals resulting from the time average chemical shifts of all the isomers within gearing each set. One set of signals for rapidly interconverting enantiomeric isomers a-f', and another set of signals for similarly equilibrating isomers g-i'. By contrast, it is expected that fast slippage will result in a single set of signals that represent the time average of all the rotational isomers, a-i'.

As shown Figure 5b, the 500 MHz ^{19}F NMR spectrum of **9b** in CD_2Cl_2 at 298 K referenced against Freon 113 consists of a single peak at -59.74 ppm, indicating that (1) all rotational isomers are able to interconvert within the time scale of the experiment, and/or (2) that the chemical shift of the CF_3 signal for the different isomers are not sufficiently distinct and cannot be resolved. Evidence for the first interpretation can be obtained by lowering the temperature down to 213 K in steps of ca. 10 K. One can see a gradual shift to lower chemical shift values, up to 59.77 ppm (i.e. $\Delta\delta \approx 15$ Hz), with significant broadening of the CF_3 signal. The results obtained by VT ^{1}H NMR were qualitatively similar with signals corresponding to the geared triptycene groups shifting and broadening while the signals corresponding to the stator remained unchanged. Taken together, these observations suggests that the dynamics of inter-conversion by gearing and slippage have slowed down, possibly entering a regime where signal splitting would occur if one could reach lower temperatures.

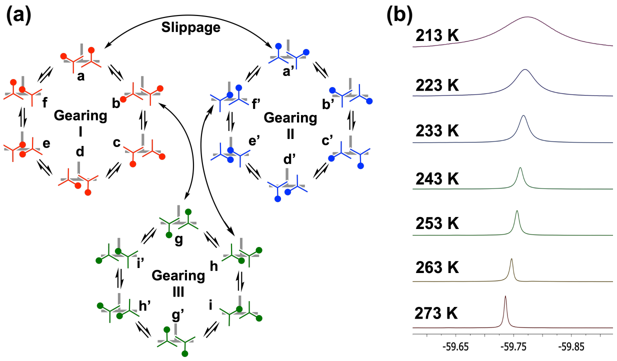


Figure 5: (a) Distinct sets of rotational isomers (I, II and III) of labeled triptycenes indicating the disrotatory interconversion of isomers by a gearing mechanism. Slippage requires conrotation and interconverts isomers from the three sets. Three possible slippage transitions are shown. Enantiomeric conformers are denoted with prime symbols. (b) VT ^{19}F NMR of trifluoromethyl-labeled molecular spur gear **9b** displaying line broadening at lower temperatures.

To better understand the results observed in Figure 5 in the context of previous literature results and to establish a robust method for future spur gear design, 2D metadynamics were carried out to depict the potential of mean force (PMF) for the rotational motions ditriptycyl methane bevel gear **1** (Figure 6a) and three spur gears **2**, **4**, and **9a** (Figure 6b-d). In the 2D PMF for rotations (Figure 6), the top-left to bottom-right diagonals represent the lowest energy trajectory for gearing, with dihedral angles changing in positive and negative direction, as required by a disrotatory motion. Conversely, low energy trajectories running bottom-left to top-right diagonals indicate rotation in the same (positive) direction as required by slippage. The energy barriers of slippage and gearing for each of the molecular spur gears are listed in Table 1.

In agreement with experimental results reported by Mislow and Iwamura, bevel gear **1** (Figure 6a) is the most efficient molecular gear, having an activation energy for slippage above 28 kcal mol^{-1} while the barrier for gearing is only on the order of 1 kcal mol^{-1}. Interestingly, metadynamics calculations for Siegel's spur gear **2** predict much lower slippage activation barrier (ca. 3.5 kcal mol^{-1}) and a smaller gap between slippage and gearing. The energy landscape of this molecule indicates that it should be capable of undergoing very rapid gearing and slippage at ambient conditions, explaining why phase isomers were not observed using VT NMR. For spur gear **4**, a slippage energy barrier of 1.1 kcal mol^{-1} is lower than that for gearing (5.4 kcal mol^{-1}), which is the reverse of what Toyota and coworkers observed for the anthracenyl gear **3** with a single alkyne as an axle. Finally, spur gear **9a** showed barriers for both slippage and gearing that are very similar to those of **4**. The wider spacing between the two axles for **9a** appears to have raised the slippage transition state energy from 1 to 2 kcal mol^{-1} while only having a marginal influence on the barrier to gearing.

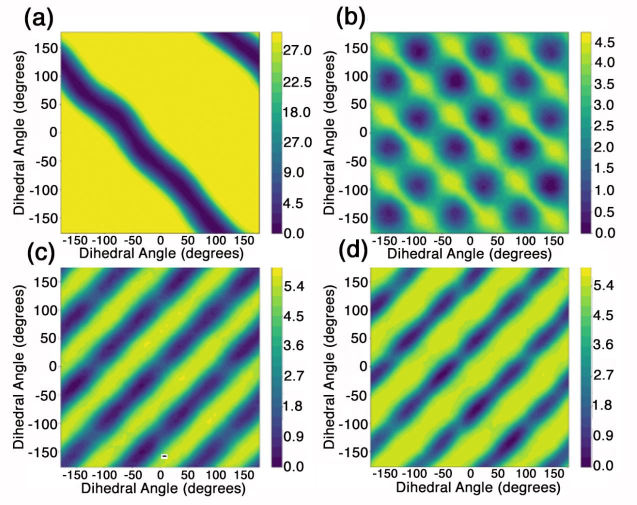


Figure 6: 2D Metadynamics for a) bevel gear **1**, b) spur gear **2**, c) spur gear **4** and d) spur gear **9a**. The energy scale in kcal/mol is defined on right side of each of the 2D plots.

Table 1. Results of 2D Potential of Mean Force (PMF) Calculations (Energies in kcal mol^{-1}).

Energy Barrier	***1***	***2***	***4***	***9a***
Slippage	> 28	3.5	1.1	2
Gearing	1	2.4	5	5.4

In conclusion, we have demonstrated the highly efficient synthesis of norbornane-type stator and its derivatives to mount axles and rotators, allowing them to function collectively as molecular gears. Unfortunately, **9a** showed a higher preference for slippage over gearing. However, using 2D metadynamics to establish the energy landscape for these compounds we discovered that the addition of the second alkyne in **4** seems to reversed the transition state energies of gearing and slippage as compared to spur gear **3**.These results suggest that the added flexibility might allow the molecules to explore conformations that simultaneously minimize steric interactions and lower the barriers to slippage. Based on this analysis, it is possible that an analog of **9a** with a shorter axle and a rotator with different geometry may be able to function as a successful molecular spur gear.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic characterization … (PDF) CIF, etc. The Supporting Information is available free of charge on the ACS Publications website.

ACKNOWLEDGMENTS

This work was supported by grants National Science Foundation grants DMR-1700471 and MRI-1532232.

REFERENCES

1 a) Hounshell, W. D.; Johnson, C. A.; Guenziw, A.; Cozzit, F.; Mislow, K. Bis(9-Triptycyl)Methanes. **1980**, *77*, 6961–6964. b) Kawada, Y.; Iwamura, H. Unconventional Synthesis and Conformational Flexibility of Bis(l-triptycyl) Ether *J. Org. Chem*. **1980**, *45*, 2547-2548.

2 For a comprehensive review of molecular rotors including various types of molecular gears please see: Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. Artificial Molecular Rotors. *Chem. Rev.* **2005**, *105*, 1281–1376.

3 a) Iwamura, H.; Mislow, K. Stereochemical Consequences of Dynamic Gearing. *Acc. Chem. Res.* **1988**, *21*, 175–182. b) Kawada, Y.; Iwamura, H. Phase Isomerism in Gear-Shaped Molecules. *Tetrahedron Lett.* **1981**, *22*, 1533–1536.

4 Frantz, D. K.; Baldridge, K. K.; Siegel, J. S. *Chimia*, **2009**, *63*, 201-204.

5 Frantz, D. K.; Linden, A.; Baldridge, K. K.; Siegel, J. S. Molecular Spur Gears Comprising Triptycene Rotators and Bibenzimidazole-Based Stators. *J. Am. Chem. Soc.* **2012**, *134*, 1528–1535.

6 a) Toyota, S.; Shimizu, T.; Iwanaga, T.; Wakamatsu, K. Structures and Conformational Analysis of 1,8-Bis(9-Triptycylethynyl) Anthracene and Its Derivatives as Prototypes of Molecular Spur Gears. *Chem. Lett.* **2011**, *40*, 312–314. b) Huang, F.; Wang, G.; Ma, L.; Wang, Y.; Chen, X.; Che, Y.; Jiang, H. Molecular Spur Gears Based on a Switchable Quinquepyridine Foldamer Acting as a Stator. *J. Org. Chem.* **2017**, *82*, 12106–12111.

7 A previous examples of a double Diels-Alder reaction between anthracene and a norbornene derivative was previously reported in: Butler, D. N.; Gupta, I.; Ng, W. W.; Nyburg, S. C., An unusual bilaterally flanked olefin; X-ray crystal structure of 5,14;7,12-bis(o-benzeno)-6,13-ethenylidene-5,5a,6,6a,7,12,12a,13,13a,14-decahydropentacene. *J. Chem. Soc., Chem. Comm.* **1980**, 596-7.

8 S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, An Improved One-pot Procedure for the Synthesis of Alkynes from Aldehydes. *Synlett*, **1996**, *6*, 521-2.

9 E. J. Corey; P. L. Fuchs, A Synthetic Method for Formyl to Ethynyl Conversion. *Tetrahedron Lett.*, **1972**, *13*, 3769-72.