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Accelerating influence of the *gem*-difluoromethylene group in a ring-closing olefin metathesis reaction. A Thorpe–Ingold effect?†

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The *gem*-difluoromethylene (CF_2) group significantly accelerates ring-closing metathesis of 1,8-nonadienes relative to the methylene (CH_2) group demonstrating similar rate accelerations to that observed for the classic Thorpe–Ingold substituents, diester malonates and ketals.

Ring-closing reactions, in small to medium rings, involving substrates bearing *geminal* R groups (C–CR_2–C) often exhibit rate accelerations when compared to reactions of their methylene (CH_2) analogues.[1] To a first approximation, the presence of larger R groups at this position leads to faster reactions. Beesley, Ingold and Thorpe rationalised this as a consequence of C–C(R_2)–C angle compression arising from the steric impact of the R-groups, orientating the peripheral groups towards each other.[2] This is more generally known as the "Thorpe–Ingold effect" (Fig. 1). Bruice and Pandit refined the argument introducing the concept of the 'reactive rotamer effect'[3] whereby the steric impact of the *geminal* substituents increases *gauche* conformer populations in the acyclic substrate to promote chain termini proximity for cyclisation. The *gem*-disubstituent effect is consistently reproduced in organic transformations including metal-catalysed cyclisations[4,5] and ring-closing metathesis (RCM) reactions.[6–9] In the context of a general interest in increasing the efficiency of olefin metathesis reactions and to understand the mechanisms that govern such reactions,[10–19] we now report the influence of the CF_2 group on a classical RCM reaction to generate cycloheptenes. Recently we reported on the structures of CF_2 containing cyclododecane rings and noted a geometric perturbation at carbon with C–CF_2–C angle widening.[20]

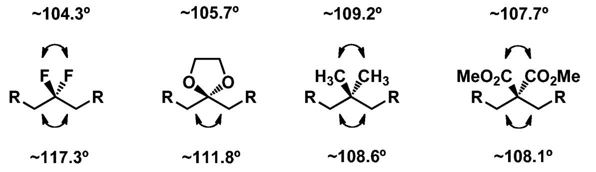

Fig. 1 Perturbations to hybridisation found for *gem*-disubstituted groups at carbon. Top angles = X–C–X, lower angles = C–C(X_2)–C. Data represent averages from surveys of the CSD.[21]

A more extensive analysis of relevant structures in the CSD revealed a significant and consistent CH_2–CF_2–CH_2 angle widening (~117.3°) relative to hydrocarbon chains. Conversely the F–C–F angle (~104.3°) is consistently narrower than tetrahedral (T_d), (Fig. 1). *gem*-Dimethyl (108.6° and 109.2°) and *gem*-diesters (108.1° and 107.7°) do indeed display angle compression, but significantly less so[21] for ketal structures in the Cambridge Structural Database (CSD) where the CH_2–C(OR_2)–CH_2 angle of ketals is wider than T_d (~111.8°) and the O–C–O angle narrower (~105.7°) on average. Thus *geminal* electronegative functional groups have the opposite hybridisation characteristics (wider C–CR_2–C angle) to other substituents required to promote a classical Thorpe–Ingold effect (narrower C–CR_2–C angle).

The high electronegativity and low steric impact of fluorine[22] provides a unique contrast and it was not obvious how the CF_2 group would behave as a *gem*-disubstituent. 1,8-Nonadienes (**1a**–**1e**) featuring a range of substituents at C-5 and including **1c** containing the CF_2 group, were subjected to ring-closing metathesis to generate the corresponding cycloheptenes (**2a**–**2e**). The reactions used $\mathbf{M_{20}}$ recently reported as an efficient metathesis catalyst (Scheme 1).[23,24] Malonate esters (R = CO_2Me) such as **1d** are well known to efficiently undergo RCM reactions when compared to **1a** (R = H) representing a prototypical example of a Thorpe–Ingold substituent.

The reactions were carried out at a preparative concentration (250 mM) and the profiles of the substrates studied (Fig. 2) fell into two categories; those that predominantly oligomerise (**1a**, **1b**) to form **3a**/**3b** and those that efficiently cyclise (**1c**–**1e**) to the corresponding cycloheptene (**2c**–**2e**). It is clear that the CF_2 substrate **1c** undergoes a much more efficient RCM reaction than **1a** and **1b**. Despite the low steric influence of fluorine the CF_2 group behaves much more similarly to the

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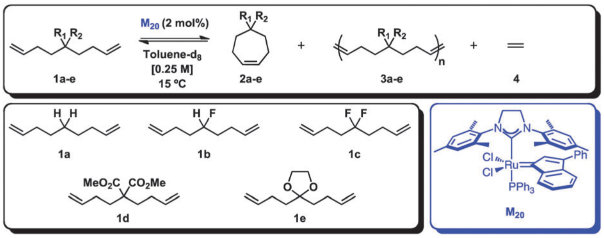


Scheme 1 Reaction conditions and substrates for $\mathbf{M_{20}}$ mediated RCM reactions.

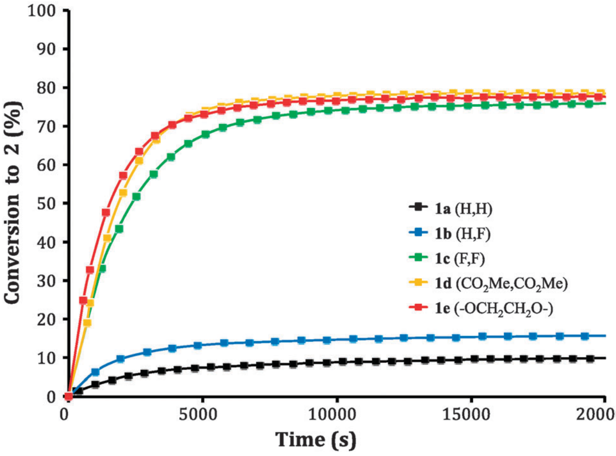


Fig. 2 Reaction conversion profiles for RCM reactions of **1a–1e** (250 mM) with $\mathbf{M_{20}}$ as a catalyst.

classical Thorpe–Ingold substrates. In order to help rationalise the experimental observations, conformational DFT analyses[25] with B3LYP functional[26] and the 6-3111+G(d,p) basis set[27] were carried out to evaluate the *anti*/*gauche* preference of the open-chain substrates. Rotational energy profiles for **1a–1e** are shown in Fig. 3. The diester malonate **1d** has a lower energy for its *gauche* over *anti* conformer, as expected. The ketal substrate **1e**, which has almost isoenergetic *gauche*/*anti* conformers, displays a comparable cyclisation efficiency to **1d**. Therefore the reactive rotamer effect which may contribute to the efficient cyclisation of **1d**, only partially explains the efficiency of **1e**. For substrates **1a**, **1b** and **1c**, the *anti* conformer is favoured over the *gauche* (Fig. 3), and thus the markedly improved performance of **1c** relative to **1a** and **1b** cannot be accounted for by the reactive rotamer effect.

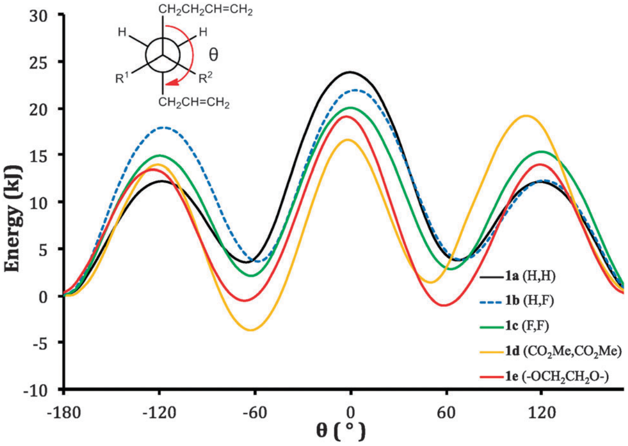
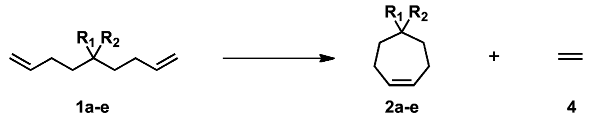


Fig. 3 Energy (B3LYP/6-311+G(d,p)) *vs.* angle φ for substrates **1a–1e**. All energies are relative to $E(\varphi = 180°)$ and given in kJ mol^{-1}.

Table 1 DFT (B3LYP/6-311+G(d,p)) calculated relative energies ($\Delta\Delta H$) from isodesmic reactions comparing substrates **1a–e** and products **2a–e** + ethene



	Substituents (R^1, R^2)	ΔH	$\Delta\Delta H$
a	–H, –H	19.7	0.0
b	–H, –F	16.4	−3.3
c	–F, –F	12.3	−7.5
d	–CO_2Me, –CO_2Me	4.5	−15.2
e	–OCH_2CH_2O–	10.2	−9.6

In order to explore the influence of inherent ring strain on the reaction rates, the relative energies from isodesmic reactions were calculated ΔH (kJ mol^{-1}) by direct comparison of the energy difference between the minimum energy structures of the acyclic substrates **1** and their cyclic products **2** plus ethane **4**. The data is presented in Table 1. As expected there is an energy increase (positive ΔH) for all of the cyclisations, although the reactions are entropically favourable due to ethene **4** release. The smallest energy change from substrates to products (4.5 kJ mol^{-1}) occurs for diester **1d**/**2d** indicating that the sterically bulky ester groups have raised the energy of the substrate close to that of the product consistent with Thorpe–Ingold angle compression. The CF_2 system **1c**/**2c** has a ΔH value (12.3 kJ mol^{-1}) close to ketal **1e**/**2e** (10.2 kJ mol^{-1}). The less efficient cyclisation systems **1a**/**2a** and **1b**/**2b** have significantly higher enthalpy changes, and clearly oligomerisation out competes cyclisation at this concentration (250 mM). 1,8-Nonadiene **1a** requires high dilution for efficient RCM. Oligomerisation occurs at concentrations higher than 0.5 mM.[5]

Given that substrate **1c** does not have an obviously lower energy *gauche* conformer, DFT structures were calculated to determine if there were any obvious favourable thermodynamic properties of product **2c**, relative to the other products. DFT derived structural analysis of cycloheptene **2a** reveals a CH_2–$CH_2(5)$–CH_2 angle at 116.0°, significantly wider than T_d, and indicative of inherent angle strain at the sp^3 C5 carbon within the parent cycloheptene (Fig. 4). This angle widening at C5 is consistent with previous structure calculations.[28] For **2c** however the CH_2–CF_2–CH_2 angle is calculated at 119°, significantly wider than T_d. Ring strain is therefore reduced in **2c** relative to **2a** as the CF_2 group can absorb this angle widening. Additionally two hyperconjugative stabilising interactions ($\sigma_{CH}/\sigma_{CF}{}^*$) are stereoelectronically accommodated between the axial C–H bonds antiperiplanar to the axial C–F bond.[29,30] A similar combination of effects occurs in ketal **2e** which has a calculated CH_2–$C(OR)_2$–CH_2 angle of 115.8° and a geometry to accommodate $\sigma_{CH}/\sigma_{CO}{}^*$ hyperconjugative stabilisation. The classical Thorpe–Ingold angle compression is not valid for ketal substrates **1e** as there is no obvious angle compression in ketals (Fig. 1), although the steric impact of the ring has a

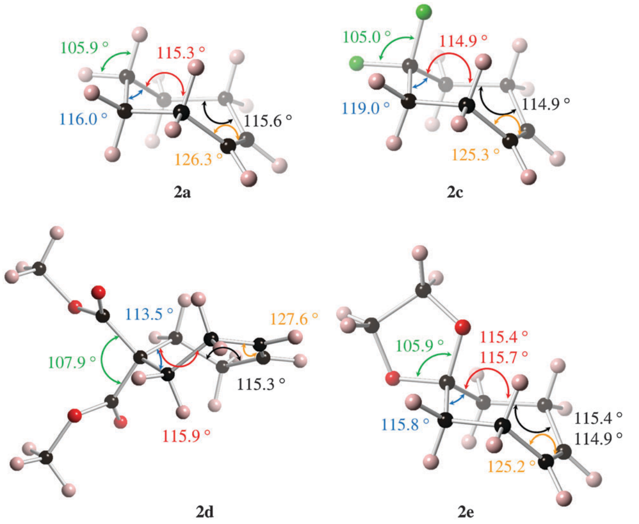


Fig. 4 Selected DFT structures (angles in degrees). Structures **2a**, **2c** and **2e** have C–C(5)–C angles wider than T_d, whereas **2d** is narrower than T_d.

partial rotamer effect (Fig. 2). These geometries can be contrasted with diester **2d** which has a narrower C–C(CO_2Me)$_2$–C angle (113.5°). Although approaching a T_d geometry, this places strain on the cycloheptene which compensates by ring puckering.

In conclusion, it has been observed experimentally that C5 *gem*-difluorination in **1c** has a substantial influence on increasing the efficiency of RCM when compared with **1a** and **1b**. The origin of this effect appears to be thermodynamic and lies in the hybridisation of the CF_2 group (angle widening) which absorbs angle strain in the cycloheptene product, as well as accommodating a geometry to support *trans*-axial hyperconjugative $\sigma_{CH}/\sigma_{CF}{}^*$ stabilizing interactions. The stereoelectronic influences of F extend to some extent to O in the ketal **1e**/**2e**. It remains to be seen if this is a general effect for all ring sizes as angle widening may actually destabilise other cycloalkene rings. We continue to explore the unique and unexpected influence of the difluoromethylene group on molecular properties and reactivity in organic transformations.

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