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LETTERS

Solid-state NMR and X-ray diffractional analysis of conformational effects in σ-symmetric bicyclo[2.2.1]hept-2-ene diester and monoesters

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Abstract

Solid state NMR and X-ray crystallographic analysis have proven that dissymmetrization by enzymatic asymmetric hydrolysis of *meso* bicyclo[2.2.1]hept-2-ene(norbornene) diesters does not induce significant electron distortion of the olefinic bond. © 1999 Elsevier Science Ltd. All rights reserved.

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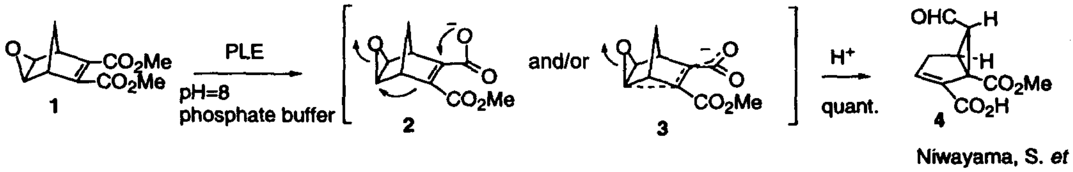
The introduction of chiral centers in *meso* compounds has been a versatile concept in organic synthesis. In theory, this dissymmetrization potentially affords only one enantiomer. Enzymatic hydrolysis of *meso* diesters in particular has been known as one of the most powerful tools for the production of chiral synthons on a large scale.[1] Further chemospecific conversions after the dissymmetrization usually arise entirely from the differences in the reactivity of the two functional groups themselves: in comparing carboalkoxy and carboxyl groups, the difference is merely that carboxyl groups possess acidic protons. One of the most illustrative examples is shown in Scheme 1.[2]



Scheme 1.

Norbornene derivatives are known for their characteristic reactivities. Their π-orbitals have intrinsic nonsymmetrical features which interact with surrounding nonequivalent environments around the sp^2 trigonal centers. The π-orbital tilting and pyramidalization are also well-known explanations for their

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various reactivities.[3] Combined with their strained and rigid structures, these properties have been under close scrutiny.

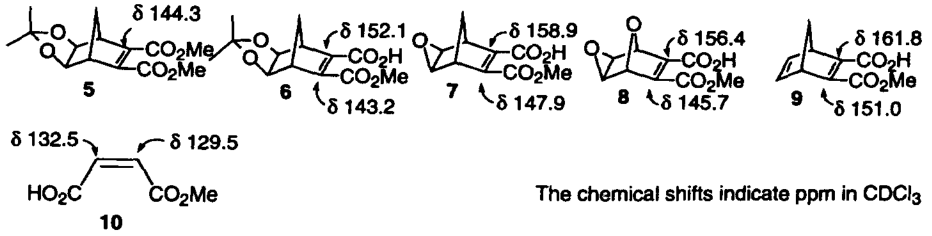
When this enzymatic enantioselective differentiation is applied to the norbornene systems, some distortions in the electron distribution may be observed, which can result in site-selective differences in reactivities. The ^{13}C NMR chemical shift can be an indicator of these distortions in the electron distribution. We observed that the two olefinic carbons of the bicyclo[2.2.1]heptane systems, **6**,[1b] **7**,[2] **8**[1c] and **9**[1d] obtained by enzymatic monohydrolysis, show significantly large differences of about 10 ppm in their ^{13}C chemical shifts (Table 1), in both solid-state and solution-state ^{13}C NMR spectra, despite the similar electron-withdrawing character of the carbomethoxy and carboxyl groups (Taft $\sigma_R°$; COOH=0.11, COOMe=0.11).[4] The assignments of the two sp^2 carbons in $CDCl_3$ were made by C-H COSY and 2D-INADEQUATE as shown in **5**–**9** in Scheme 2. For monoesters **6** and **9**, the chemical shifts in the solution state and solid state are quite similar. On the other hand, while diester **5** shows only one olefinic carbon signal in the solution state, solid-state NMR revealed two pairs of signals with similar chemical shift differences. Since the difference in ^{13}C NMR chemical shifts for the two olefinic carbons for monomethyl maleate, **10**, is only ~3 ppm, we questioned whether these large differences may be characteristic of norbornene derivatives.

Table 1

^{13}C Spectrum data of olefinic carbons in the solid state and solution ($CDCl_3$)

Compound	δ (solid state) ppm	δ(solution, $CDCl_3$)
5	150.0, 146.2, 140.1, 137.0	144.3
6	153.3, 143.6	152.1, 143.2
7[a]		147.9, 158.9
8[a]		145.7, 156.4
9	161.8, 151.3	161.8, 151.0

a: Compounds 7 and 8 did not form a solid.



The chemical shifts indicate ppm in $CDCl_3$

Scheme 2.

These large chemical shift differences could be attributed to a potentially distorted electron distribution caused by the two functional groups due to the strained structure, or to some external conformational effect from the two functional groups. Since the olefinic bond of the norbornene derivatives tends to be particularly susceptible to orbital mixing with the surrounding bonds, and hence characteristic reactivities have been reported, we thought that solving the problem of this large ^{13}C chemical shift difference was important.

Initially, we conducted semi-empirical molecular orbital calculations (AM1)[5] for monoesters **7** and **8**, by changing the dihedral angles for the two carbonyl groups. However, no noticeable correlation was found between the electron density of the olefinic carbons and the orientation of the two carboalkoxy groups.

Therefore, in order to see the conformation of the two carboalkoxy groups, we conducted crystallographic structural analyses[6] using diester **5** and monoester **6**, which afforded the most suitable crystals among rigid compounds **5**–**9**. Because of the well-correlated chemical shift in the solid- and solution-state NMR, we rationalized that the conformational analysis in the solid state was applicable to the solution state as well.

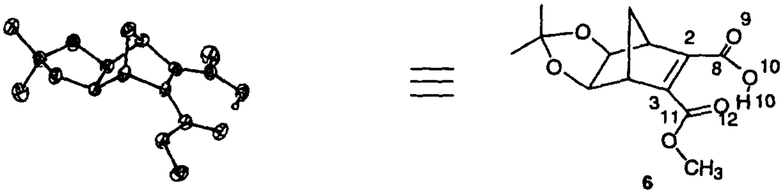


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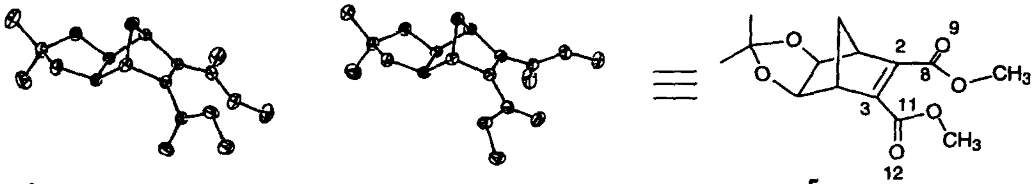
Figure 1. Molecular structure and numbering of **6**

The crystallographic data clearly demonstrates that the carboxyl and the methoxycarbonyl groups in **6** (Fig. 1) are fixed tightly by intramolecular H-bonding (O_{10}–H_{10}=0.86(7) Å, H_{10}–O_{12}=1.70(7) Å, O_{10}–O_{12}=2.565(8) Å, O_{10}–H_{10}–O_{12}=176(7)°). The dihedral angle (O_9–C_8–C_2–C_3) is 166.6(9)° and the carbonyl group (C_8=O_9) is in the *s-trans* conformation toward the olefinic bond (C_2=C_3). In this conformation, only the olefinic carbon C_2 lies in a region of deshielding by the carbonyl C_8=O_9, while this deshielding effect is obstructed for the other olefinic carbon, C_3. On the other hand, the dihedral angle (O_{12}–C_{11}–C_3–C_2) is 17.1(13)° and therefore this carbonyl group C_{11}=O_{12} is in the *s-cis* conformation toward the olefinic bond and deviates more than C_8=O_9 from the olefinic bond C_2=C_3. We speculate that the angle dependency for the deshielding effect is caused by the carbonyl group, and the two identifiable conformations have dihedral angles of 166–180° and 0–17°. This conformational analysis supports the large differences in the ^{13}C NMR chemical shifts in both the solid and solution state for this series of compounds, **6**–**9**, and helps to assign the two olefinic carbons in the solid state for **5**.[7]

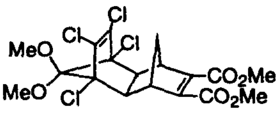
These conformational effects appeared to be more evident for the symmetric diester **5**. Although diester **5** shows only one olefinic carbon signal and one carbonyl carbon signal in the solution state, solid-state NMR revealed four olefinic carbons and four carbonyl carbon signals. In accordance with this observation, the X-ray crystallographic analysis of this diester **5** clarified the presence of two independent molecules (A and B) in a unit cell as shown in Fig. 2.



A B **5**

Figure 2. Molecular structure (A, B) and numbering of **5**

In both structures, one of the two carbomethoxy groups is nearly parallel to the olefinic bond C_2=C_3 within the range of angles described above, while the other carbomethoxy group is directed almost perpendicular to the olefinic bond. The dihedral angles are 173.8(2)°(O_9–C_8–C_2–C_3) and −94.3(3)°(O_{12}–C_{11}–C_3–C_2) for molecule A, and 102.5(3)°(O_9–C_8–C_2–C_3) and 13.3(4)°(O_{12}–C_{11}–C_3–C_2) for molecule B. As in the case of monoester **6**, only one of the two olefinic carbons lies in a region of deshielding by the carbonyl group, and therefore the two olefinic carbon chemical shifts are nonequivalent. Therefore, it is concluded that these conformational effects play a crucial role in the unusually large ^{13}C chemical shift difference. A similar destruction of molecular mirror symmetry has also been reported for the following σ-symmetric molecules, **11–13**, in their X-ray structures.[8]



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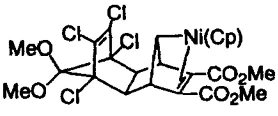

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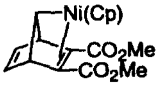

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In conclusion, we demonstrated that the large difference in the ^{13}C chemical shifts for the norbornene monoesters, **6–9**, in both the solution- and solid-state NMR are mostly attributable to the conformational effects of the carbonyls rather than to the electron distribution on the olefinic bond. It is safely assumed that electron distributions on the olefinic bond of the norbornene derivatives are not significantly distorted by this enzymatic dissymmetrization of *meso* diesters.

Acknowledgements

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6. X-Ray crystal analysis: The intensity data were collected on an Enraf–Nonius CAD4 diffractometer by using graphite monochromated Mo-Kα radiation at 293 K. The structure was solved by direct methods (SHELXS-86) and refined by SHELXL-93. Anisotropic thermal parameters were refined for all the non-hydrogen atoms. All the hydrogen atoms except the carboxyl hydrogen, which was found on the D-map, were geometrically fixed by the program. The positional and isotropic thermal parameters of the carboxyl hydrogen were refined. Atomic coordinates and bond distances have been deposited at the Cambridge Crystallographic Data Center. Crystal data for **5**, $C_{14}H_{18}O_6$; monoclinic, space group P21/n, a=21.921(4) Å, b=9.6620(10), c=13.865(3), β=104.136(9)°, V=2847.7(9) Å^3, Z=8, Dc=1.32 g cm^{-3}. The final refinement converged to R=0.042, wR=0.106 for 3448 [Fo>4σ(Fo)] reflections. Crystal data for **6**, $C_{13}H_{16}O_6$; orthorhombic, space group P212121, a=9.8594(9) Å, b=20.7582(19), c=6.5254(5), V=1336.8(4) Å^3, Z=4, Dc=1.33 g cm^{-3}. The final refinement converged to R=0.066, wR=0.223 for 1265 [Fo>4σ(Fo)] reflections.
7. In addition, the chemical shifts for the two olefinc carbons of **6** changed to δ 151.4 and 144.4 ppm in a weak H-bond accepting solvent, CD_3CN, and δ 147.9 and 144.5 ppm in a strong H-bond accepting solvent, CD_3OD. These decreased

chemical shift differences suggest that the intramolecular H-bonding in **6** was disrupted in these protic solvents, in which the carboxyl and carbomethoxy groups have free rotation, and indicate the extent of the intramolecular H-bonding. We are grateful for the reviewer's suggestion of conducting this experiment.

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