The S_N2 Reaction in the Solid State. An Unusual, $B_{Al}2$ Aminolysis of an Ester Group in Crystalline (±)-2-Amino-2′-hydroxy-3′-(methoxycarbonyl)-1,1′-binaphthyl Elucidated by X-ray Diffraction and Isotopic Labeling. New Experimental Evidence for Linearity in S_N2 Substitution

Martin Smrčina,[*,†] Štěpán Vyskočil,[†] Vladimír Hanuš,[‡]
Miroslav Polášek,[‡] Vratislav Langer,[§]
Benjamin G. M. Chew,[||] David B. Zax,[||] Hugh Verrier,[⊥]
Kevin Harper,[#] Thomas A. Claxton,[▽] and Pavel Kočovský[*,▽]

Department of Organic Chemistry, Charles University
128 40 Prague 2, Czech Republic
The J. Heyrovský Institute of Physical Chemistry
AVČR, 182 23 Prague 8, Czech Republic
Department of Inorganic Chemistry
Chalmers University of Technology and
University of Göteborg, S-412 96 Göteborg, Sweden
Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, New York 14853
Merck Sharp & Dohme Research Laboratories
Neuroscience Research Center, Harlow CM20 2QR, U.K.
Hickson Fine Chemicals
Castleford, West Yorkshire, WF10 2JT, U.K.
Department of Chemistry, University of Leicester
Leicester, LE1 7RH, U.K.

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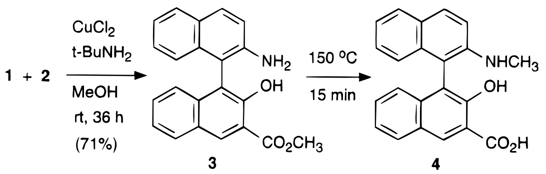
The fascinating molecular architecture of axially chiral 1,1′-binaphthyls creates an ideal environment for coordinated metals, thus enabling a variety of metal-catalyzed reactions to be performed with the degree of enantioselection previously known only for enzymes.[1] Furthermore, certain complexes of this kind have been shown to be capable of a stereoselective pairing in solution, which results in a nonlinear relationship between the enantiomeric purity of the catalyst and the product.[2] Herein, we report on another unique feature of the binaphthyl skeleton, namely, the way of stacking in the solid state, which facilitates an intermolecular S_N2 reaction[3,4] of the title compound (**3**).

Recently, we have reported on the highly selective, Cu(II)-mediated cross coupling of 2-aminonaphthalene (**1**) with methyl 3-hydroxy-2-naphthoate (**2**) that produced the racemic 1,1′-binaphthyl derivative **3**.[5,6] Although the IR and ^{1}H NMR spectra corroborated the product structure,[5] the fragmentation pattern in the EI MS suggested the alternative **4**.[7] We reasoned that this discrepancy could be attributed to a thermal lability of the original compound, giving rise to a rearrangement **3** → **4** in the direct inlet of the mass spectrometer.[8]



We endeavored to obtain an authentic sample of **4** for comparison. However, refluxing **3** in xylene for 3 h proved fruitless, leaving **3** unchanged,[9] which indicates that the reaction **3** → **4** is associated with the orienting of the molecules in the crystal. Indeed, heating the crystalline ester **3** at 150 °C for 15 min led to its almost quantitative conversion (93−95%) into the carboxylic acid **4**.[10] Monitoring the reaction by solid-state ^{13}C NMR confirmed the gradual change $OCH_3 \rightarrow NCH_3$.[11] The reaction is exothermic, with 4.44 kcal·mol^{-1} liberated between 95 and 145 °C, as revealed by differential scanning calorimetry.[12]

This solid-state transformation raised the question as to the actual mechanism. Since the S_N1 process (i.e., $B_{Al}1$ or $A_{Al}1$ ester cleavage) is extremely unlikely for a *methyl* ester, it can be assumed that the reaction occurs via the S_N2 pathway (i.e., $B_{Al}2$ aminolysis).[13] Furthermore, the distance between the reacting groups should be favorable and the angle of approach ($N-CH_3-O$) close to 180°.[14] As this is not possible within one molecule, the reaction must occur as a bimolecular process.

The single-crystal X-ray analysis[15,16] demonstrated the existence of a centrosymmetric (*R*)−(*S*) pair in the unit cell. However, the CH_3O group had a "wrong" orientation, being

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[†] Charles University.
[‡] The J. Heyrovský Institute.
[§] Chalmers University of Technology and University of Göteborg.
[||] Cornell University.
[⊥] Merck Sharp & Dohme.
[#] Hickson Fine Chemicals.
[▽] University of Leicester.

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(7) In the MS obtained at 150 °C, high abundances of the unexpected ions *m/z* 297 (43%, $M^{•+} - HCO_2H$) and 280 (34%, $C_{21}H_{14}N$) and the metastable transition 268 → 239 (loss of CH_3N) have been observed, which corresponds to the fragmentation of $\mathbf{4}^{•+}$ rather than $\mathbf{3}^{•+}$.

(8) This sample exhibited changes in the spectrum during the scanning (at 150 °C) so that the spectrum at the beginning of evaporation was not entirely identical to that obtained toward the end. This suggests a chemical reaction proceeding in the direct inlet. By contrast, the FAB spectrum was fully compatible with the structure **3**. The presence of the low-intensity satellite ions *m/z* 357 (M + 14) and 329 (M − 14) in the EIMS can be attributed to the contamination by homologues.

(9) Refluxing for 24 h led to a partial decomposition rather than to the formation of **4**.

(10) A slow **3** → **4** conversion occurs in the crystal at room temperature as revealed by the analysis of aged samples. For a similar observation, see ref 4c.

(11) The CH_3 signal in **3** and **4** appears at 51.7 and 30.8 ppm, respectively. Apparently, the zwitterionic intermediate is immediatley transformed into the neutral **4**, as evidenced by the comparison of the $N-CH_3$ signals in the solid state (30.8 ppm) and in the $CDCl_3$ solution (30.5 ppm).

(12) The reaction clearly occurs in the solid state since melting, an endothermic process (4.15 kcal·mol^{-1}), was observed at 230−245 °C.

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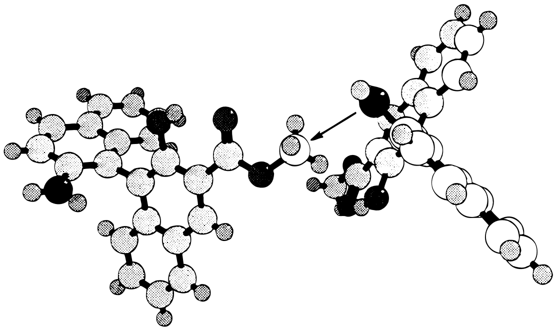

Figure 1. Bonding interaction between the NH_2 and CO_2Me groups of the two molecules of (*R*)-(+)-**3**, as revealed by X-ray data (3.20 Å; 173.2°).

too distant from NH_2 (3.79 Å) and having an unacceptable angle of approach (94.9°).[17] On the other hand, the X-ray structure also showed the NH_2 of one molecule to be only 3.20 Å away from the CH_3 of another homochiral molecule, related by a 2-fold screw axis (Figure 1),[18] the angle of approach (N−C−O) being 173.2°: only a 6.8° deviation from the ideally linear trajectory![20] Hence, the reaction should occur between the homochiral molecules, i.e., (*R*)−(*R*) and (*S*)−(*S*), but not between the (*R*) and the (*S*) molecules.[21]

Rigorous proof for the enantioselective course of the aminolysis was provided by double isotopic labeling, with CD_3 in one enantiomer and ^{18}O in the other.[22−24] The "racemate" obtained by cocrystallization of the CD_3 ester (*R*)-(+)-**3a** and the ^{18}O ester (*S*)-(−)-**3b** was then thermally converted into the "racemic" **4**. Mass spectrometric analysis confirmed the enantioselective process predicted by the X-ray data: the molecules of the product were labeled either by CD_3 (*m*/*z* 346 ions) or by ^{18}O (*m*/*z* 345 ions); no species containing both labels (i.e., *m*/*z* 348 ions) has been detected.

In summary, we have observed an unprecedented, solid-state interconversion $R-CO_2CH_3 + H_2N-R' \rightarrow R-CO_2H + CH_3-NH-R'$ (**3** → **4**), which occurs on heating of **3** at 150 °C for 15 min.[25] X-ray diffraction, in conjunction with double isotopic labeling and mass spectrometry, has demonstrated that the reaction occurs as an enantiodiscriminating, domino-like $B_{Al}2$ process between the homochiral molecules, i.e., within the (*R*)−(*R*)−(*R*)... and (*S*)−(*S*)−(*S*)... series of **3**.[26] To our knowledge, this is the first example of a $B_{Al}2$ mechanism in the solid state.[27] Moreover, our findings provide direct evidence for the linearity in the S_N2-type reactions (Figure 1).

Acknowledgment. We thank the reviewers for useful comments, Dr. G. Eaton for measuring the FAB spectrum of **3**, and Drs. M. Vorlíčková and I. Tejralová for recording the CD spectra of (+)-**3** and (−)-**3**. We also thank Charles University for Grant No. 86/95GAUK, the NSF for Award No. DMR-9121654, and Leicester and Göteborg Universities for financial support.

Supporting Information Available: Experimental procedures, calculation details with Cartesian coordinates of the dimer, CD, MS, and solid-state ^{13}C NMR spectra, differential scanning calorimetry curve, and details of the crystallographic analysis with a fully labeled ORTEP diagram,[28] atomic coordinates, selected bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[16] Crystal data for **4**: $C_{22}H_{17}NO_3$, $M = 343.38$. Crystals were obtained from methanol solution; they are orthorhombic, of space group *Pbca*, with $a = 11.319(2)$ Å, $b = 8.8990(10)$ Å, $c = 34.051(3)$ Å, $V = 3429.9(8)$ Å^3, $Z = 8$, $d_{calc} = 1.330$ g cm^{-3}, $\mu = 0.089$ mm^{-1}. Data were collected at 23 °C on an Enraf-Nonius CAD4 diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.710\ 69$ Å), a graphite monochromator, and the ω scan mode. A total of 1505 unique reflections were measured, with only 410 having $I > 2\sigma(I)$. All 1505 reflections were used in the structure refinement based on F^2 by full-matrix least-squares techniques with hydrogen atoms calculated in theoretical positions, riding during refinement on the respective pivot atom (239 parameters). Final, $R_F = 0.0424$, $R_w = 0.0973$ on F for observed data. The estimated error in bond lengths is 0.02 Å.

[17] Better alignment can be obtained via rotation about the $C(O)-OCH_3$ bond by 90°; in the resulting conformation, the calculated angle of approach N−C−O is 162° and the N−C distance 2.82 Å. However, *ab initio* calculation, using Gaussian 92 with a minimal basis set of orbitals (STO-3G), demonstrated the latter conformation to be 37 kcal·mol^{-1} higher in energy than the former.

[18] The sum of the van der Waals radii[19] for N and CH_3 is 3.55 Å.

[19] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

[20] The X-ray parameters reported for S_N2 reactions (two examples to date[4a,d]) are as follows: 3.42 Å/147° and 2.9 Å/164°, respectively.

[21] The reaction is presumably further boosted by the intramolecular hydrogen bonding between the phenolic OH and the C=O of the ester group.

[22] The resolution of (±)-**3** was carried out *via* aminolysis with (*S*)-(−)-$PhCH(NH_2)CH_3$. The resulting mixture of diastereoisomeric amides was separated by chromatography; each diastereoisomer was then hydrolyzed (KOH, ethylene glycol, 190 °C, 5 h), and each enantiomer of the free acid was methylated with CH_2N_2. On a small scale, (±)-**3** was resolved by chromatography on a Chiralpak AD column using a 1:1 hexane−ethanol mixture as a mobile phase. The faster moving enantiomer was identified as (*R*)-(+)-**3** (99.2% ee); (*S*)-(−)-**3** (98.8% ee) was slower moving.

[23] The absolute configuration of **3** was determined by CD *via* comparison with the spectra of 2,2′-dihydroxy-3-(methoxycarbonyl)-1,1′-binaphthyl and 2,2′-dihydroxy-3,3′-bis(methoxycarbonyl)-1,1′-binaphthyl.[6b]

[24] Labeling: the enantiomerically pure CH_3 ester (+)-**3** was converted into the CD_3 ester (+)-**3a** (99% d_3) on exchange reaction with CD_3ONa/CD_3OD. The (−)-**3** ester was hydrolyzed with $Na^{18}OH/H_2{}^{18}O$, generated from Na and $H_2{}^{18}O$ enriched with ^{18}O by ≥25%. The resulting ^{18}O-labeled acid was esterified with CH_2N_2 to afford (−)-**3b** containing 25% ^{18}O, according to MS.

[25] Two other examples of an intermolecular methyl transfer in the solid state have been reported to date, namely, the transformation of *p*-$Me_2NC_6H_4$-SO_3Me into *p*-$Me_3N^+C_6H_4SO_3^-$ and the rearrangement of an *O*-methyl imino ether into the corresponding *N*-methylamide.[4a,d]

[26] The observed level of conversion (up to 95%), unusually high for a solid-state reaction, suggests a fast, zip-fastening-type process occurring along the screw-axis chain throughout an entire crystalline block. The reaction is not terminated until the collapse of the majority (93−95%) of the original crystal lattice. An alternative explanation, which would require a single crystal to single crystal transformation, can be ruled out since **4** is not isostructural with **3**.

[27] Rigorously speaking, the $B_{Al}2$ mechanism refers to a bimolecular reaction.[13] In fact, the **3** → **4** transformation is likely to proceed as a multimolecular, chain reaction. By using the denomination $B_{Al}2$, we refer to the elementary process of interaction between two molecules of **3**.

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