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Short Report

Differentiation Between the *like* and *unlike* Isomers of Dimethyl 3,4-di(*p*-anisyl)adipate Using ^{1}H NMR Spectroscopy

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Apresenta-se aqui a diferenciação entre os isômeros *like* (igual) e *unlike* (diferente) do 3,4-di (*p*-anisil)adipato de dimetila, que foi efetuada pelo uso combinado de espectroscopia de RMN de ^{1}H, simulação espectral e Mecânica Molecular, correlacionados pelo uso da Equação de Altona, uma versão generalizada da Equação de Karplus.

The differentiation between the *like* and *unlike* isomers of the title compound, achieved by combined use of ^{1}H NMR spectroscopy, spectral simulation and Molecular Mechanics, correlated by means of the Altona Equation (a generalized version of the Karplus Equation), is reported herein.

Keywords: *like* and *unlike* diastereomers, Altona Equation, stereochemical analysis by NMR, stereochemical analysis.

Introduction

The electrohydrodimerization[1] of olefin derivatives is a versatile reaction, which has attracted considerable interest in recent years.

In the course of an investigation[2] on the electrochemical reduction of substituted cinnamic esters, we have prepared and isolated both diastereomers of dimethyl 3,4-di(*p*-anisyl)adipate (**dAA**, Figure 1). At that point, however, we still had the problem of discerning the *unlike*[3] (*meso*) compound from the *like*[3] isomer racemate. As outlined below, we have accomplished this objective by employing well-established procedures but, to our knowledge, this approach has never been applied to the stereochemical analysis of open-chain molecules, such as substituted adipic acid derivatives.

Results and Discussion

After acquisition of the 300 MHz ^{1}H NMR spectrum from each sample (in $CDCl_3$, at room temperature), we noticed that although both presented the expected[4] AA'BB'XX' second-order sub-spectra (Figures 1, 2a and 3), besides the methoxy singlets and the signals due to the aromatic protons, only one of them (henceforward denoted as Sample I) presented this AA'BB'XX' sub-spectrum sufficiently well resolved for further analysis (Figure 2a).

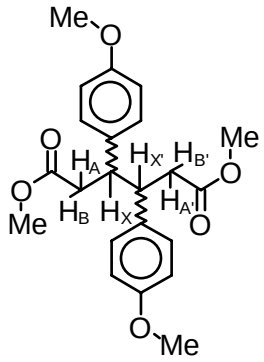

Figure 1. Representation of **dAA**, highlighting the protons of the AA'BB'XX' sub-system.

Hence, after having measured J(AX) = J(A'X') = 8.55 Hz, J(BX) = J(B'X') = 6.20 Hz and δ(X) = 3.411, by assuming that J(A'X) ≈ J(AX') ≈ J(B'X) ≈ J(BX') » J(AA') ≈ J(AB') ≈ J(A'B) ≈ J(BB') ≈ 0 Hz (see Figure 2a), the AA'BB' part of the AA'BB'XX' sub-spectrum is amenable to direct solution[5], on taking the centers of the doublets (due to coupling to either the X or the X' nuclei) as the four lines of an AB system, this procedure yielding: δ(A) = 2.548, δ(B) = 2.688 and J(AB) = J(A'B') = 15.43 Hz.

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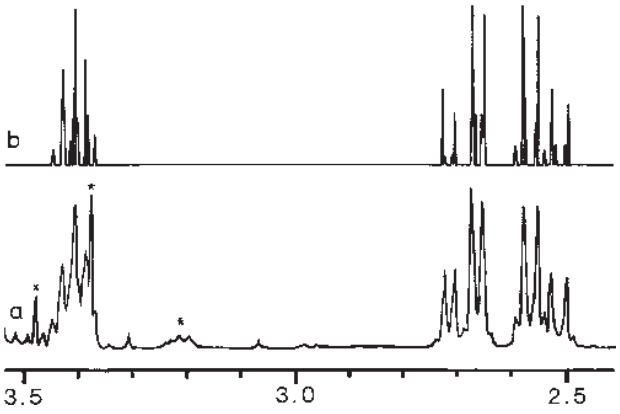


Figure 2. The experimental (a) and simulated (b) AA'BB'XX' sub-spectra (at 300.13 MHz) of *l*-**dAA** (the signals marked with * are due to *ca.* 10% of *u*-**dAA** present in the sample, while that marked with x is due to an unidentified inpurity).

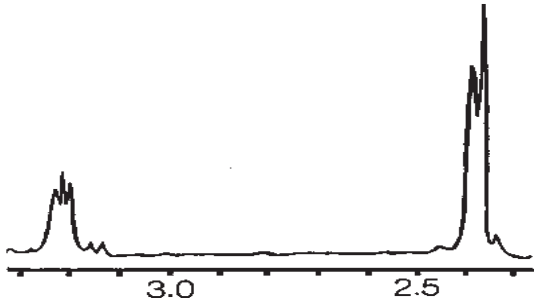


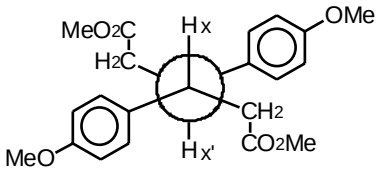
Figure 3. The experimental AA'BB'XX' sub-spectrum (at 300.13 MHz) of *u*-**dAA**.

Using the above data, together with the measured positions of the 15 observed lines, as input for the program LAOCOON 3[6], we have obtained a very good fit (Figure 2b, RMS Error = 0.0012 Hz) for the 208 calculated lines, together with the calculated value for J(XX') = 5.06 Hz. This value was, then, converted to a 46° dihedral angle (Hx–C–C–Hx') for Sample I, by using the Altona Equation[7] (a generalized version of the Karplus Equation).

Now, to be able to distinguish between the diastereomers of **dAA**, an acyclic compound, two conditions must be met: each isomer must have only one strongly preferred rotamer, and these two rotamers must present different H_x–C–C–$H_{x'}$ dihedral angles.

Thus, we have performed Molecular Mechanics calculations (MM+, Hyperchem 3) and found that both above conditions are met, each diastereomer strongly favoring the rotamer with distal *p*-anisyl groups, represented in Figure 4, below.

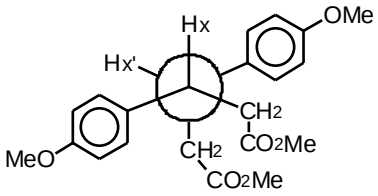
Hence we concluded that Sample I is the *l*-**dAA**. It should be pointed out that this assignment was only possible because these compounds present second-order sub-spectra: were it otherwise, it would be impossible to obtain the values of the coupling constants between the protons on each side of the relevant symmetry element.



unlike or S*/R*

∃ σ => protons are enantiotopic

∢(Hx-C-C-Hx')=171.5º



like or S*/S*

∃ C_2 => protons are homotopic

∢ (Hx-C-C-Hx')=45.0º

Figure 4. The two diastereomers of **dAA**, as calculated by MM+.

It should be added that X-ray Diffraction analysis results[8] on a crystal obtained from Sample II shows it to be the *unlike* isomer, thus confirming our conclusion regarding Sample I. Furthermore, the X-ray data show a dihedral angle (CH_2-C-C-CH_2) of 177.51° for the *u*-**dAA** (in a monocrystal), which is near enough the 171.50° value our MM+ calculations yielded for the same angle (for one molecule alone in the vacuum) and thus confirms both the accuracy of our calculations and the very strong preference presented by **dAA** isomers for the rotamers with distal *p*-anisyl groups.

Experimental

Materials

Deuterochloroform and methyl *p*-methoxycinnamate were used as received from Aldrich, after being checked for purity. Both isomers of dimethyl 3,4-di(*p*-anisyl) adipate (**dAA**) were simultaneously formed by cathodic reduction of methyl *p*-methoxycinnamate in methanol, using either platinum or mercury cathodes and TEAB as support electrolyte, as described elsewhere[2,9,10]. The isomers of **dAA** were subsequently resolved and purified by column chromatography on silica-gel 60. The complete assigned ^{1}H and ^{13}C NMR dataset for these compounds is presented in Table 1, below. The HETCOR (^{1}H-^{13}C) experiments were performed in order to assure the internal consistency of the assignments here presented.

Table 1. Assigned NMR Data from the Isomers of Dimethyl 3,4-Di(*p*-Anisyl)Adipate

a) 300.13 MHz ^{1}H NMR δ (multiplicity) of **dAA** Isomers in $CDCl_3$ (TMS = 0)

isomer	H-*meta*[a]	H-*orto*[a]	MeO[b]	MeOC=O	$H_x/H_{x'}$,[c]	$H_B/H_{B'}$,[c]	$H_A/H_{A'}$,[c]
unlike	7.18 (d[d])	6.86 (d[d])	3.79 (s)	3.38 (s)	3.22 (m[e])	2.39 (m[e])	2.37 (m[e])
like	6.77 (d[f])	6.72 (d[f])	3.76 (s)	3.56 (s)	3.41 (m[g])	2.69 (m[g])	2.55 (m[g])

[a]Positions relative to the MeO group in the anisyl moiety; [b]Attached to the *p*-anisyl moiety; [c]See Figure 1; [d]J = 5.79 Hz; [e]The coupling constants of this AA'BB'XX' system were not determined due to insufficient resolution; [f]J = 5.94 Hz; [g]For the coupling constants of this AA'BB'XX' system see Table 2.

b) 75.47 MHz ^{13}C NMR δ of **dAA** Isomers in $CDCl_3$ (TMS = 0)

isomer	C-*ipso*[a]	C-*para*[a]	C-*orto*[a]	C-*meta*[a]	MeO[b]	MeOC=O	CH	CH_2	C=O
unlike	158.51	133.76	114.02	129.02	55.18	51.28	47.11	39.83	172.58
like	158.27	131.88	113.12	129.82	55.10	51.56	45.43	38.00	172.61

[a] Positions relative to the MeO group in the anisyl moiety; [b]Attached to the *p*-anisyl moiety.

Table 2. Values of the ^{1}H NMR Scalar Coupling Constants for *l*-**dAA**.

Coupling Constants	Values / Hz
J(X,A) = J(X',A') =	8.55[a]
J(X,B) = J(X',B') =	6.20[a]
J(A,B) = J(A',B') =	–15.43[b]
J(X,X') =	5.06[c]
J(A,A') =	0.03[c]
J(B,B') =	0.01[c]
J(X,A') = J(A,X') =	–0.60[c]
J(X,B') = J(B,X') =	–0.42[c]
J(A,B') = J(B,A') =	–0.01[c]

[a]Measured values (see text); [b]Also measured and assumed to be negative because this is a geminal coupling; [c]Values resulting from fit using LAOCOON 3.

Instruments and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 instrument. Standard microprograms from Bruker Software Library were employed. All measurements were performed in 5 mm o.d. tubes, using a deuterium lock, at 20°C. Samples were prepared by dissolving *ca.* 5% v/v of each compound in 0.5 mL of $CDCl_3$, containing 0.01 % v/v of TMS as internal standard.

^{1}H spectra (300.13 MHz) were acquired with a sweep width 2250 Hz, corresponding to a final digital resolution 0.137 Hz per data point. 32 scans were accumulated, using a pulse duration of *ca.* 15º, with an acquisition time ≥ 7.4 s and a 10.0 s relaxation delay.

Broadband ^{1}H decoupled ^{13}C spectra (75.47 MHz), were acquired with a sweep width ≥ 8000 Hz, corresponding to a final digital resolution ≥ 0.488 Hz per data point. 64 scans were accumulated, using a pulse duration of *ca.* 36º, with an acquisition time ≥ 1.0 s and no relaxation delay. Raw data were zero-filled and Fourier transformed under matched-filter conditions.

HETCOR (^{1}H-^{13}C) experiments[11] were performed at 7.05 T, using a low decoupler power in CW mode (1.5 W) and composite pulse decoupling (CPD) with polarization transfer from ^{1}H to ^{13}C. The following pulse sequence was employed:

^{1}H: D_0 - 90x° - D_0 - - D_0 - D_3 - 90y° - - CPD
^{13}C: D_1 - 180x° - - 90x° - D_4 - FID

where:
D1 = 2 s; D3 = 4 ms; D4 = 2 ms; D0 = (3 + 178.6 n) μs and $0 \leq n \leq 512$.

The FIDs for the 2D experiments were acquired with *ca.* 8000 Hz of sweep width in F2; 32 scans were accumulated, with an acquisition time of 1.5 s; 512 such experiments were performed with the evolution time incremented so as to provide an effective sweep width of *ca.* 2800 Hz in F1. The delays D3 and D4 were chosen to show correlations with peaks of all multiplicities by assuming a J(CH) of *ca.* 125 Hz. The final data matrix was 512 x 4 Kbytes. Raw data were zero-filled in F1 and a gaussian window function was applied in both F1 and F2 prior to Fourier transformation.

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