Synthesis and Regioselective Hydrolysis of 2-Imidazol-1-ylsuccinic Esters

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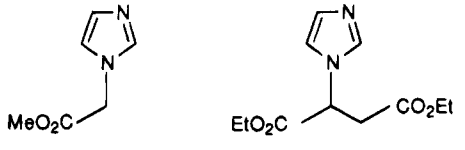
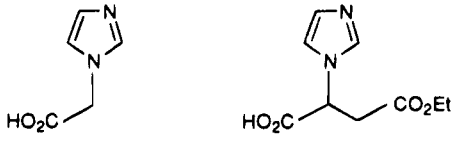
Received March 15, 1994®

(±)-2-Imidazol-1-ylsuccinic esters were synthesized by thermal addition of imidazole to either fumaric or maleic esters. Acceleration of the reaction was achieved, in some cases, using microwave heating. These esters underwent an easy regioselective hydrolysis, under neutral conditions, to give the corresponding half-esters: (±)-3-(alkoxycarbonyl)-2-imidazol-1-ylpropionic acids, through either BAC[3] or BAL[1] mechanisms. Kinetic studies in H_2O and D_2O as well as ^{18}O and ^{17}O labeling experiments supported the proposed mechanism. The results of these hydrolyses, which depended on the nature of the alcohol moiety, were compared with those obtained with some imidazol-1-ylacetate analogues or with (±)-2-pyrazol-1-yl- and benzimidazol-1-ylsuccinic esters. In general, imidazolylsuccinic esters hydrolyzed faster than the homologous derivatives from pyrazole or benzimidazole.

We have recently proposed that methyl imidazol-1-ylacetate (**1**) and diethyl 2-imidazol-1-ylsuccinate (**2**) can be used as novel extrinsic ^1H NMR probes for the measurement of intracellular pH in erythrocytes.[1] Even though these compounds were administered as their ester forms, they underwent an easy hydrolysis to their corresponding acids **3** and **4** in the biological medium. However, the behavior of esters **1** and **2** was not exactly the same. While compounds **1** and **3** were both permeable through the erythrocyte membrane, compound **2** was only moderately permeable, requiring an incubation period at 37 °C to penetrate the erythrocyte interior and to be hydrolyzed inside the cell. When compound **2** was hydrolyzed outside the cell, the corresponding acid **4** was not able to penetrate to the cellular interior. Therefore, the stability of the ester linkage toward hydrolysis plays an important role in the delivery of extracellular probes to the cellular interior.



1 **2**



3 **4**

We described also that both esters underwent neutral hydrolysis by heating in water, and that compound **2** hydrolyzed to **4** even by standing in a moist atmosphere. These hydrolyses represented clear examples of neutral or spontaneous hydrolysis found in esters with electron-withdrawing substituents.[2]

Few imidazol-1-ylacetates have been described in the literature and no details about their neutral hydrolysis have been communicated. Furthermore, no information is currently available on the regioselective hydrolysis of 2-imidazol-1-ylsuccinic esters. In this work we contribute the preparation of several 2-imidazol-1-ylsuccinates and imidazol-1-ylacetates and provide a comparative study on their behavior toward hydrolysis. The results obtained are compared with those from other 2-azol-1-ylsuccinates.

Results and Discussion

Synthesis. Although extensive studies on the addition of imidazole to acetylenedicarboxylate esters have been described in the literature,[3] only the addition of imidazole to fumaric or maleic acids, either in absence of solvent[4a] or in DMF,[4b] has been previously reported. According to our previous results,[1] imidazole efficiently added to diethyl fumarate and maleate to yield the racemic diethyl 2-imidazol-1-ylsuccinate (**2**). In this study we extend this reaction to the preparation of the new 2-imidazol-1-ylsuccinates **5a–d** (See Table 1) and diethyl 2-benzimidazol-1-ylsuccinate (**6**). The pyrazole derivative **7** was previously prepared in a similar manner.[5] No solvent was required except in the reaction with dimethyl fumarate in which acetonitrile was used, to avoid undesired polymerization side reactions. Due to the long reaction

® Abstract published in *Advance ACS Abstracts,* August 15, 1994.

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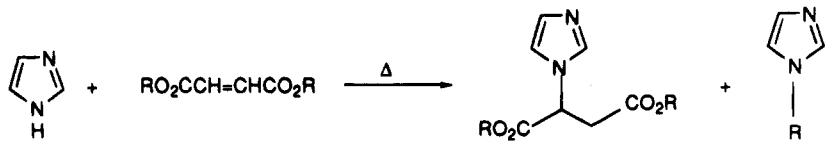
Table 1. Results Obtained in the Synthesis of 2-Imidazol-1-ylsuccinates by Thermal Reaction and Microwave Heating



2; 5 a-d

ester	R	temp (°C)	power (W)	time	succinate	yield, %[a]	*N*-alkylimidazole, % yield[a]
fumaric	Me[b]	reflux	–	72 h	**5a**	50 (40)	0
fumaric	Me	–	200	3 min	**5a**	0	0
fumaric	Me	–	400	2 min	**5a**	0	0
fumaric	Et	100	–	25 h	**2**	94 (76)	traces
fumaric	Et	–	200	2 min	**2**	59	6
fumaric	Et	–	200	3 min	**2**	64	4
fumaric	Et	–	200	4 min	**2**	50	14[b]
fumaric	Et	–	200	5 min	**2**	35	24[b]
fumaric	Et	–	400	2 min	**2**	0	100
maleic	Et	100	–	24 h	**2**	80 (65)	not detected
maleic	Et	–	200	3 min	**2**	64	0
maleic	Et	–	400	2 min	**2**	0	100
maleic	*n*-Bu	100	–	4 h	**5b**	90 (50)	traces
maleic	*n*-Bu	–	200	3 min	**5b**	60	0
maleic	*n*-Bu	–	400	2 min	**5b**	0	0
fumaric	c-hexyl	100	–	10 h	**5c**	87 (52)	0
fumaric	Bn	100	–	3 h	**5d**	83[c]	0

[a] Yields are given from the ^{1}H NMR spectrum in $CDCl_3$ of the reaction crude. Isolated yields are in parentheses. The remaining nonindicated percentages correspond to the starting materials. [b] Reaction performed in acetonitrile. [c] 7% of compound **4** was detected in the 4 min reaction and 12% in the 5 min reaction. [d] Isolated yield was not calculated due to this ester rapidly hydrolyzed to the half-ester form.

times required in most cases, microwave heating was applied to shorten the reaction times.

Table 1 shows the combined results obtained in the reaction of imidazole with either fumarates or maleates using conventional or microwave heating. In the reaction between imidazole and diethyl fumarate, microwave heating at 200 W drastically reduced the reaction time from 25 h to 3 min. The same effect was obtained in the reaction with diethyl and di-*n*-butyl maleates. However, microwave heating failed to accelerate the reaction rates with dimethyl fumarate and when pyrazole was used instead of imidazole. In both cases the untransformed starting materials were obtained. Longer reaction times with irradiation produced a pyrolytic breakdown of the ester as a side reaction, to yield 1-ethylimidazole or 1-*n*-butylimidazole, identified as single products in the ^{1}H NMR spectra of the reaction crudes. The pyrolytic process, which was also detected as traces in the conventional thermal reaction with diethyl fumarate and di-*n*-butyl maleate, was converted in the major reaction at 400 W. This cleavage could be explained as a consequence of the attack of imidazole either to the fumarate or the succinate, as it is suggested by the presence of monoacid **4** in the reaction crude.

The structures of the new diesters were unambiguously assigned by ^{1}H and ^{13}C NMR spectroscopy. Substitution on the nitrogen atom N_1 of the imidazole ring was evidenced by the presence of the three resonances corresponding to the protons H_2, H_4, and H_5 of the imidazole nucleus. In compound **6**, N-substitution was also confirmed by the presence H_2 and H_{4-7} aromatic protons of the benzimidazole nucleus. The alkane chain was readily identified in all azol-1-ylsuccinates by the presence of an ABX system at $\delta \sim 5.2-5.5$ ppm (X part, CH) and $\delta \sim 3.1-3.2$ ppm (AB part, diastereotopic CH_2).

Hydrolysis. Some of the new 2-imidazol-1-ylsuccinates (mainly R = Me, Et, Bn) underwent neutral or spontanous hydrolysis on standing to yield their half-ester form, 3-(alkoxycarbonyl)-2-imidazol-1-ylpropionic acids. This regioselective hydrolysis was accelerated when the succinates were heated in water. The presence of diester, monoacid, and diacid in the reaction crude was easily identified in the ^{1}H NMR spectrum in D_2O, considering the well-resolved quartets (X part) of the CH proton from the succinic chain moiety. In all cases, this proton in monoacid and diacid resonated at an upper field from that of the corresponding diesters.

According to the results shown in Table 2, the presence of imidazole ring in the α position favored the hydrolytic process, being the acetate-type ester more easily hydrolyzed to yield the corresponding half-ester with a high regioselectivity. This hydrolysis is strongly related with that observed in α-halo esters or esters with electron-withdrawing substituents.[6] However, the low regioselectivity obtained with diethyl 2-pyrazol-1-ylsuccinate (**7**) and with diethyl 2-benzimidazol-1-ylsuccinate **6** suggested that the imidazole ring was implied in the hydrolysis in a similar manner as 1-methylimidazole was involved in the hydrolysis of esters.[7] On the other hand, steric hindrance was also an important factor in the regioselective process. With short chains such as methyl and ethyl, the hydrolysis of the acetate-type ester was faster than the propionate-type ester; however, with larger or bulky chains such as *n*-butyl or cyclohexyl the hydrolysis of acetate-type ester required longer reaction times. In consequence, the propionate-type ester is hydrolyzed as well to yield the diacid. However, further hydrolysis of monoacid **4** yielded only 37% of diacid **11** after being heated in water at 100 °C for 74 h. The decrease of regioselectivity was also observed in the pyrazole and benzimidazole derivatives. In the latter case, isolation of the monoester only without diacid was possible by stopping the reaction at the first stages.

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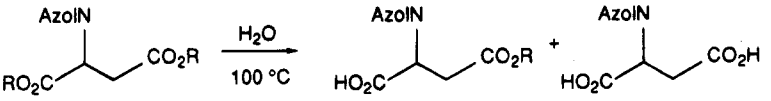
Table 2. Results of Neutral Hydrolysis of Azol-1-ylsuccinic Esters. Yields are Given from the ^{1}H NMR Spectra of the Reaction Crudes

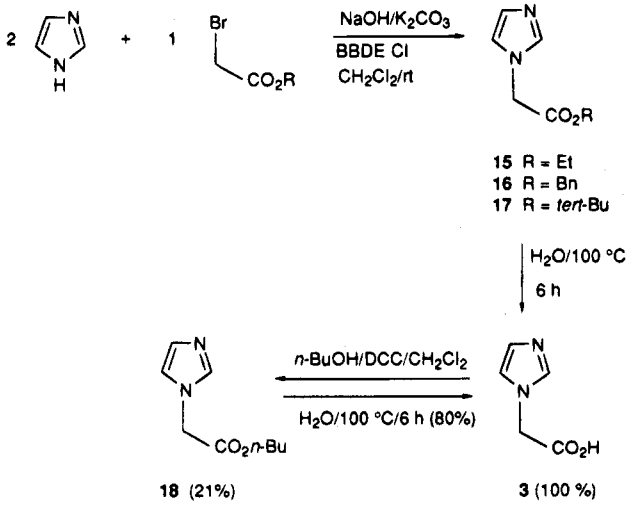


2; 5 a-d; 6; 7 4; 8 a-d; 9; 10 11; 12; 13

azole	R	mM	time, h	diester	% yield	monoacid	% yield	diacid	% yield	imidazole, % yield	unsaturated ester, % yield
imidazole	Me	156	6	**5a**	0	**8a**	100	**11**	0		
imidazole	Et	42	18	**2**	8	**4**	82	**11**	10[a]		
		83	18	**2**	8	**4**	82	**11**	10		
		370	20	**2**	6	**4**	83	**11**	11		
		1000	18	**2**	2	**4**	90	**11**	8		
imidazole	*n*-Bu	112[b] (0.1 g/3 mL)	48	**5b**	0	**8b**	54	**11**	11	17.5	17.5
imidazole	c-hexyl	29[b] (0.5 g/50 mL)	79	**5c**	48	**8c**	38	**11**	0	7	7
		1000[b] (0.4 g/1.2 mL)	72	**5c**	traces	**8c**	60	**11**	40	traces	traces
imidazole	Bn[c]			**5d**	0	**8d**	100	**11**	0		
benzimidazole	Et	172[b] (1 g/20 mL)	78	**6**	1	**9**	66	**12**	33		
		206[b] (1.2 g/20 mL)	21	**6**	42	**9**	58	**12**	0		
pyrazole	Et	42	18	**7**	100	**10**	0	**13**	0		
		100	76[d]								

[a] Formation of diacid **11** was avoided when the hydrolysis was performed at 50 °C, but only 77% of the monoacid was obtained after 58 h. [b] Low solubility in water. Very similar results were obtained even after adding dioxane to generate a homogeneous mixture of **5b**. [c] From spontaneous hydrolysis on standing of the crude **5d**. [d] ^{13}C NMR spectrum of the reaction crude suggested a mixture of the starting diester **7** (δ CO = 168.6 and 169.6 ppm), both monoacids **10** (δ CO = 169.8 and 170.2 ppm), and **14** (δ CO = 168.7 and 171.2 ppm), and the diacid **13** (δ CO = 170.3 and 171.4 ppm). The relative amount of them was very difficult to calculate by ^{1}H NMR. ^{13}C NMR spectrum of the reaction crude suggested that unhydrolyzed diester **7** and diacid **13** were the major compounds.

Scheme 1



To confirm that steric hindrance is a factor to be considered in this type of regioselective hydrolysis, some imidazol-1-ylacetic esters were prepared and hydrolyzed in water. Imidazol-1-ylacetic esters **15-17** were synthesized by alkylation of imidazole with the corresponding bromoacetate using PTC[1] and 1,5-bis[(*N*-benzyl-*N*,*N*-diethylammonio)ethyl] ether dichloride (BBDE Cl)[8] as catalyst. The *n*-butyl ester **18** was prepared by reaction of **3** with *n*-butanol and DCC.

Esters **15-17** were completely hydrolyzed to imidazol-1-ylacetic acid after being heated in water for 6 h. However, as it would be expected, the *n*-butyl ester **18** required longer time and only 80% underwent hydrolysis (Scheme 1).

The kinetics of hydrolysis of compound **5a** were followed by ^{1}H NMR spectroscopy. Hydrolyses were performed at 80 °C in H_2O and D_2O at two different concentrations. The results were compared with those obtained with compound **1**. Data from the hydrolysis of **5a** were taken from the relative intensities of the well-resolved singlets from the methyl groups of the starting ester and the resulting monoacid. Data on the hydrolysis of **1** were obtained considering the relative areas of the singlets of the methyl group of the starting ester and that of the methanol produced. Most of the remaining proton resonances could not be used for this purpose, since they underwent deuterium exchange during the hydrolytic process in D_2O. The first-order kinetics followed in all cases are illustrated in Figure 1 and in Table 3.

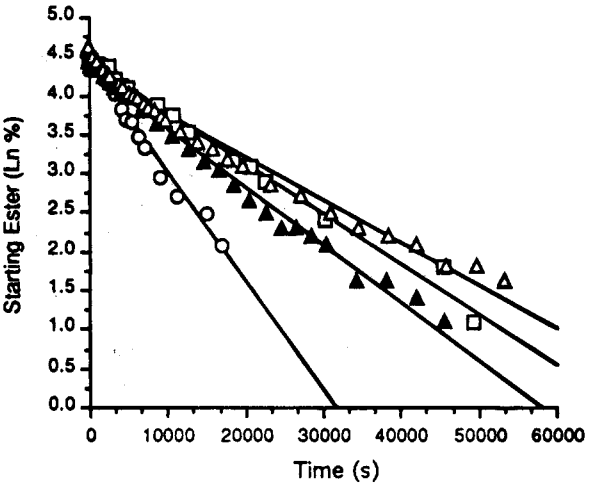


Figure 1. First-order kinetics of hydrolysis of esters **5a** and **1**. (□) 94 mM solution of **5a** in D_2O; (▲) 284 mM solution of **5a** in D_2O; (○) 284 mM solution of **5a** in H_2O; (△) 143 mM solution of **1** in D_2O.

Figure 2 depicts the time course of changes observed in the hydrolysis of diester **6.** The kinetics of this process are more complex than those presented in Figure 1 and Table 3. In general, the time course of decay in diester **6** concentration (k = 11.0 × 10^{-6} s^{-1}) seemed complementary with the time course of the appearance of the

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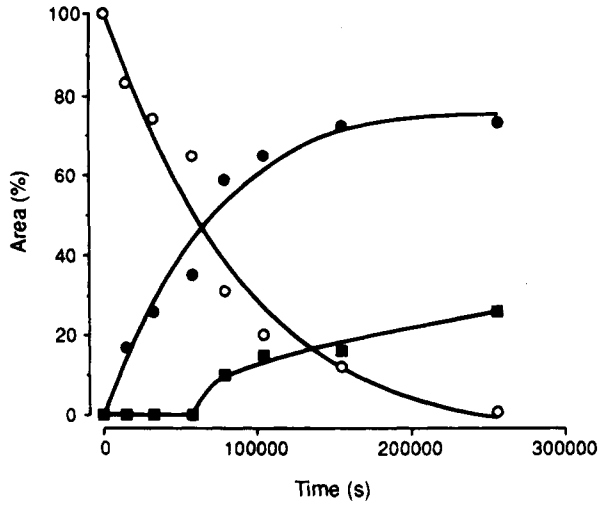

Figure 2. Kinetics of hydrolysis of diester **6**. Relative areas (%) of diester **6** (○), monoacid **9** (●), and diacid **12** (■) were determined from the ^{1}H NMR spectra of reaction mixtures of the hydrolysis of **6** performed as indicated in Experimental Section (method b). The continuous lines represent the best fit of the data points to a single exponential determined by nonlinear least squares minimization. Values for the rate constants were (○) $k = 11.0 \times 10^{-6}$ s^{-1}, (●) $k = 14.0 \times 10^{-6}$ s^{-1}, and (■) $k = 3.1 \times 10^{-6}$ s^{-1}.

Table 3. Results Obtained in the Kinetics of Hydrolysis of 5a and 1

compound	concentration (mM)	solvent	$k \times 10^5$ (s^{-1})	R^2	k_{H_2O}/k_{D_2O}
5a	94	D_2O	6.49	0.990	
5a	284	D_2O	7.40	0.991	
5a	284	H_2O	13.97	0.980	
					1.81
1	143	D_2O	5.50	0.979	

monoacid **9** ($k = 14.0 \times 10^{-6}$ s^{-1}). Formation of diacid **12** required an induction period of approximately 20 h before it became detectable ($k = 3.1 \times 10^{-6}$ s^{-1}). Similar values of induction period and rate constant ($k = 6.3 \times 10^{-6}$ s^{-1}) were obtained in the hydrolysis of **4** to **11**.

Hydrolyses of compounds **1** and **17** were also conducted in water simultaneously enriched in ^{17}O (28%) and ^{18}O (32%). ^{17}O NMR spectra showed unambiguously that only in the case of **1**, the carboxylic group presented ^{17}O labeling as revealed by the presence of the C^{17}OOH resonance at 271.1 ppm.[9] This value was in agreement with the ^{17}O chemical shift of other carboxylic groups described for amino acids in zwitterionic form.[10] Furthermore a clear ^{18}O isotope effect (−31.2 ppb)[11] was observed on the ^{13}C resonance (δ = 172.5 ppm) of C^{18}OOH. However, in the case of compound **17**, no ^{17}O labeling on the carboxylic group was observed but a clear ^{17}O resonance of *t*-Bu^{17}OH appeared at δ = 64.7 ppm. This value is consistent with that previously described for *tert*-butyl alcohol (δ = 62.3 ppm).[12] Similarly, a clear ^{18}O isotope effect (−36.2 ppb)[11] was observed on the ^{13}C resonance (δ = 69.8 ppm) of the quaternary carbon of the *tert*-butyl group.

Influence of the imidazole nucleus in these hydrolyses has been established by comparison with the results obtained with other azol-1-ylalkanoate esters. Probably, and taking into account the H_2O/D_2O isotope effect[13] (k_{H_2O}/k_{D_2O} = 1.8) observed on the rate constant of the hydrolysis of **5a**, imidazole would probably accelerate the hydrolytic process favoring the proton transfer involved in a BAC[3] mechanism. This feature would be less effective in the case of a bulky susbtituent and when pyrazole or benzimidazole replaced the imidazole ring.

In summary, our results have shown that 2-imidazol-1-ylsuccinic esters, easily prepared by addition of imidazole to fumaric or maleic esters, undergo neutral hydrolysis to give regioselectively half-esters: 2-imidazol-1-yl-3-(alkoxycarbonyl)-propionic acids. The regioselectivity is strongly dependent on the nature of the alcohol. Esters from simple alcohols undergo a fast hydrolysis of the acetate-type ester. However, in esters from alcohols with bulky chains the rate of hydrolysis of acetate-type ester is slower. In these latter cases, hydrolysis of propionate-type esters becomes competitive, giving 2-imidazol-1-ylsuccinic acid. These similarities between rates of hydrolysis were also observed when pyrazole and benzimidazole derivatives were used. Considering the alcohol moiety, the regioselective hydrolysis proceeds in the following decreasing order: Bn > *t*-Bu > Me > Et ≫ *n*-Bu > c-hexyl. With consideration of the acyl moiety, the decreasing order is the following: imidazole ≫ benzimidazole ≫ pyrazole. Therefore, the mechanism is in accordance with that suggested for other esters activated by electron-withdrawing sustituents through either a BAC[3] [14] for primary or secondary groups or BAL[1] for benzyl or *tert*-butyl groups.[15]

Experimental Section

General. Melting points were obtained on a microscope hot stage and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 240 apparatus. NMR spectra were recorded with a Bruker AC-200 (200.13 MHz for ^{1}H, and 50.33 MHz for ^{13}C) and a Bruker AM-360 (360.13 MHz for ^{1}H, 90.55 MHz for ^{13}C, and 42.82 MHz for ^{17}O). ^{1}H and ^{13}C chemical shifts (δ) in $CDCl_3$ are given from internal tetramethylsilane, ^{1}H δ in D_2O are given from internal 3-(trimethylsilyl)tetradeuteropropionic acid sodium salt, and ^{13}C δ in D_2O are given from external DMSO-d_6, with an accuracy of ±0.01 for ^{1}H and ±0.1 ppm for ^{13}C. The residual water signal in ^{1}H NMR spectra in D_2O solutions was supressed using a 1 s (low power, 0.5 watts) presaturating pulse applied with the decoupler. ^{1}H−^{1}H coupling constants (J) are accurate to ±0.2 Hz for ^{1}H NMR spectra. TLC chromatography was performed on DC-Alufolien/Kieselgel 60 F_{254} (Merck, 0.2 mm) and column chromatography through silica gel Merck 60 (70−230 mesh). Products were purchased from commercial sources. Water enriched with ^{17}O (28%) and ^{18}O (32%) was purchased from Isotec Inc., Ohio. The following compounds were prepared according to literature procedures: dibenzyl fumarate;[16] dicyclohexyl fumarate;[17] (±)-diethyl 2-imidazol-1-ylsuccinate (**2**);[1] methyl imidazol-1-ylacetate (**1**);[1] (±)-diethyl 2-pyrazol-1-ylsuccinate (**7**).[4] The 2-azol-1-ylsuccinic esters **2**, **5a−d**, **6** and the imidazol-1-ylacetic esters **1**, **15-18** were stored under argon in a desiccator to prevent spontaneous hydrolysis. Microwave

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experiments were carried out with a Panasonic kitchen oven Model NN-5352.

(±)-Dimethyl 2-Imidazol-1-ylsuccinate (5a). A solution of imidazole (7.22 g, 103 mmol) and dimethyl fumarate (5.06 g, 51.5 mmol) in CH_3CN (100 mL) was refluxed for 4.5 days. After cooling at room temperature, the solvent was evaporated *in vacuo* and the residue was purified through a silica gel column using CH_2Cl_2:methanol, 98:2, as eluent to obtain **5a** as a yellow oil (4.4 g, 40%): picrate mp 87–90 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 3.12 (AB part, 2 H, J_{AB} = 16.9, J_{AX} = 7.6, J_{BX} = 6.7 Hz), 3.69 (s, 3 H), 3.78 (s, 3 H), 5.25 (X part, 1 H), 6.99 (br s, 1 H, 7.08 (br s, 1 H), 7.58 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.1 (t), 52.2 (q), 53.0 (q), 55.4 (d), 117.7 (d), 129.6 (d), 136.9 (d), 168.7 (s), 169.5 (s); IR (film) ν 1730 (CO) cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_5O_{11}$ (picrate): C, 40.82; H, 3.43; N, 15.87. Found: C, 40.65; H, 3.34; N, 15.29.

(±)-Di-*n*-butyl 2-Imidazol-1-ylsuccinate (5b). A mixture of imidazole (3 g, 44.0 mmol) and di-*n*-butyl maleate (10 g, 44.0 mmol) was heated at 100 °C for 7 h. After cooling at room temperature, the reaction mixture was purified through a silica gel column using CH_2Cl_2:ethanol, 95:5 as eluent to yield **5b** as a yellow oil (6.5 g, 50%): picrate mp 90–92 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 0.91 (t, 3 H, J = 7.2 Hz), 1.20–1.42 (m, 4 H), 1.50–1.66 (m, 4 H), 3.14 (AB part, 2 H, J_{AB} = 17.0, J_{AX} = 7.6, J_{BX} = 6.2 Hz), 4.09 (t, 2 H, J = 6.6 Hz), 4.19 (t, 2 H, J = 6.6 Hz), 5.34 (X part, 1 H), 7.07 (br s, 1 H), 7.13 (br s, 1 H), 7.96 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.2 (q), 13.3 (q), 18.5 (t), 18.6 (t), 30.0 (t), 30.1 (t), 37.2 (t), 55.5 (d), 117.6 (d), 129.3 (d), 136.8 (d), 168.2 (s), 169.0 (s); IR (film) ν 1725 (CO) cm^{-1}. Anal. Calcd for $C_{21}H_{27}N_5O_{11}$ (picrate): C, 47.99; H, 5.18; N, 13.33. Found: C, 48.21; H, 4.96; N, 13.33.

(±)-Dicyclohexyl 2-Imidazol-1-ylsuccinate (5c). A mixture of imidazole (0.361 g, 5.30 mmol) and dicyclohexyl fumarate (1.484 g, 5.30 mmol) was heated at 100 °C for 10 h. After cooling at room temperature, the reaction mixture was purified through a silica gel column using hexane:ethyl acetate, 1:1, as eluent to yield **6c** as a yellow oil (0.917 g, 52%): picrate mp 120–121 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 20 H), 3.08 (AB part, 2 H, J_{AB} = 16.6, J_{AX} = 7.9, J_{BX} = 6.8 Hz), 4.65–4.90 (m, 2 H), 5.18 (X part, 1 H), 6.98 (br s, 1 H), 7.05 (br s, 1 H), 7.56 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.1 (t), 23.2 (t), 23.5 (t), 24.9 (t), 25.0 (t), 30.9 (t), 31.0 (t), 31.2 (t), 31.3 (t), 37.7 (t), 56.1 (d), 73.8 (d), 74.8 (d), 117.7 (d), 129.5 (d), 136.9 (d), 167.6 (s), 168.4 (s); IR (film) ν 1725 (CO) cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_5O_{11}$ (picrate): C, 51.89; H, 5.57; N, 12.11. Found: C, 52.08; H, 5.27; N, 12.21.

(±)-Dibenzyl 2-Imidazol-1-ylsuccinate (5d). A mixture of imidazole (0.230 g, 3.40 mmol) and dibenzyl fumarate (1.00 g, 3.40 mmol) under argon atmosphere was heated at 100 °C for 5 h. After cooling at room temperature, the crude compound **5d** (83% by ^1H NMR) rapidly hydrolyzed on standing to give (±)-3-(benzyloxycarbonyl)-2-imidazol-1-ylpropionic acid. ^1H NMR from the reaction crude ($CDCl_3$) δ 3.16 (AB part, 2 H, J_{AB} = 16.9, J_{AX} = 7.8, J_{BX} = 6.6 Hz), 5.07 (s, 2 H), 5.16 (s, 2 H), 5.30 (X part, 1 H), 6.97 (br s, 1 H), 7.07 (br s, 1 H), 7.20–7.40 (m, 10 H), 7.62 (br s, 1 H).

(±)-Diethyl 2-Benzimidazol-1-ylsuccinate (6). A mixture of benzimidazole (2 g, 17.0 mmol) and diethyl fumarate (2.91 g, 17.0 mmol) was heated at 120 °C for 14 h. After cooling at room temperature, the reaction mixture was purified through a silica gel column using CH_2Cl_2:ethanol, 95:5, as eluent to yield **6** as a yellow oil (3.76 g, 76.4%): picrate mp 158–160 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 7.1 Hz), 1.17 (t, 3 H, J = 7.1 Hz), 3.25 (AB part, 2 H, J_{AB} = 16.9, J_{AX} = 7.4, J_{BX} = 6.3 Hz), 4.09 (q, 2 H, J = 7.1 Hz), 4.20 (q, 2 H, J = 7.1 Hz), 5.52 (X part, 1 H), 7.27–7.42 (m, 3H), 7.77–7.84 (m, 3H), 8.04 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 36.1 (t), 54.4 (d), 61.4 (t), 62.5 (t), 109.7 (d), 120.5 (d), 122.5 (d), 123.5 (d), 132.7 (s), 142.5 (d), 143.4 (s), 168.2 (s), 169.4 (s); IR (film) ν 1730 (CO) cm^{-1}. Anal. Calcd for $C_{21}H_{21}N_5O_{11}$ (picrate): C, 48.55; H, 4.07; N, 13.48. Found: C, 48.41; H, 3.89; N, 13.10.

(±)-Diethyl 2-pyrazol-1-ylsuccinate (7): picrate mp 70 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 6.9 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 3.27 (AB part, 2 H, J_{AB} = 16.9, J_{AX} = 7.1, J_{BX} = 6.4 Hz), 4.13 (q, 2 H, J = 6.9 Hz), 4.21 (q, 2 H, J = 7.1 Hz), 5.39 (X part, 1 H), 6.28 (pseudo t, 1 H), 7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 13.9 (q), 36.3 (t), 60.0 (d), 61.1 (t), 62.0 (t), 105.8 (d), 130.0 (d), 140.0 (d), 168.4 (s), 169.9 (s); IR (film) ν 1730 (CO) cm^{-1}.

Reactions Performed with Microwave Heating. General Procedure. Azole (7.40 mmol) and the corresponding fumaric or maleic esters (7.40 mmol) were located in a 23 mL Parr bomb with a Teflon sample cup. The reaction mixture was heated in the microwave oven at 200 or 400 W for the time shown in Table 1. After cooling at room temperature, the bomb was placed into an ice bath and carefully opened. The crude reaction mixture was analyzed by ^1H NMR spectroscopy. Isolation of the reaction products could be easily performed by chromatography as it is mentioned above.

Hydrolysis of 2-Imidazol-1-ylsuccinic Esters. General Procedures: Method a. The corresponding dialkyl 2-imidazol-1-ylsuccinate was left in an open flask placed inside a closed bottle with water in the bottom. After several days (more than 30 days) the solid residue was treated with dry diethyl ether or CH_2Cl_2 to separate the monoester from the unhydrolyzed diester. **Method b.** A solution or a suspension of the corresponding 2-imidazol-1-ylsuccinic ester in distilled water was heated in an oil bath at 100 °C (concentrations and heating time are given in Table 2). Then, the reaction mixture was concentrated *in vacuo* and the residue analyzed by ^1H NMR in D_2O. When the reaction finished, the water was evaporated *in vacuo*, and the hygroscopic residue was dried *in vacuo* and purified as it is described below.

(±)-3-(Methoxycarbonyl)-2-imidazol-1-ylpropionic acid (8a): obtained by the general procedure b. The hygroscopic residue was treated with hexane:ethanol to give a white solid mp = 175–177 °C (from ethanol 90%): ^1H NMR (D_2O) δ 3.39 (AB part, 2 H, J_{AB} = 17.3, J_{AX} = 8.4, J_{BX} = 5.3 Hz), 3.70 (s, 3 H), 5.38 (X part, 1 H), 7.46 (br s, 1 H), 7.56 (br s, 1 H), 8.79 (br s, 1 H); ^{13}C NMR (D_2O) δ 36.2 (t), 51,8 (q), 59.5 (d), 118.6 (d), 120.7 (d), 134.4 (d), 171.5 (s), 171.6 (s); IR (KBr) ν 2680–2310, 2100–1820 (NH^+), 1730 (CO), 1600 (CO) cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.36; H, 4.99; N, 14.04.

(±)-3-(Ethoxycarbonyl)-2-imidazol-1-ylpropionic acid (4): obtained by the general procedure a. Treatment with diethyl ether gave **4** as a white solid mp 141–143 °C (from ethanol) (lit.[1b] 141–143 °C). When it was obtained by the general procedure b, the crude residue was extracted with hot ethanol to separate **4** (83%) from the insoluble diacid **11**. Compound **4**: ^1H NMR (D_2O) δ 1.12 (t, 3 H, J = 7.2 Hz), 3.23 (AB part, 2 H, J_{AB} = 17.4, J_{AX} = 8.7, J_{BX} = 5.3 Hz), 4.07 (q, 2 H, J = 7.2 Hz), 5.32 (X part, 1 H), 7.41 (br s, 1 H), 7.51 (br s, 1 H), 8.79 (br s, 1 H); ^{13}C NMR (D_2O) δ 12.3 (q), 36.40 (t), 59.5 (d), 61.3 (t), 118.6 (d), 120.6 (d), 134.3 (d), 171.0 (s), 171.4 (s). Compound **11** ^1H NMR (D_2O) δ 3.41–3.20 (AB part, m, 2 H), 5.34 (X part, q, 1 H, J_{AX} = 9.7, J_{BX} = 4.8 Hz), 7.47 (br s, 1 H), 7.58 (br s, 1 H), 8.87 (br s, 1 H); ^{13}C NMR (D_2O) δ 36.6 (t), 59.6 (d), 118.4 (d), 120.6 (d), 134.3 (d), 171.7 (s), 173.2 (s).

(±)-3-(*n*-Butoxycarbonyl)-2-imidazol-1-ylpropionic acid (8b): obtained by method a and isolated by treatment with CH_2Cl_2: mp 153–155 °C (from ethanol); ^1H NMR (D_2O) δ 0.86 (q, 3 H, J = 7.2 Hz), 1.20–1.32 (m, 2 H), 1.49–1.63 (m, 2 H), 3.31 (AB part, 2 H, J_{AB} = 17.3, J_{AX} = 9.1, J_{BX} = 5.2 Hz), 4.12 (t, 2 H, J = 6.4 Hz), 5.38 (X part, q, 1 H), 7.47 (br s, 1 H), 7.58 (br s, 1 H), 8.82 (br s, 1 H); ^{13}C NMR (D_2O) δ 11.9 (q), 17.5 (t), 28.8 (t), 36.4 (t), 59.5 (d), 65.0 (t), 119.0 (d), 120.5 (d), 134.4 (d), 171.2 (s), 171.6 (s); IR (KBr) ν 2750–2300, 2100–1850 (NH^+), 1720 (CO), 1660 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.08; H, 6.39; N, 11.55.

(±)-3-(Cyclohexyloxycarbonyl)-2-imidazol-1-ylpropionic acid (8c): obtained by the general procedure b. The residue was treated with hot ethanol and after cooling the white solid was filtered to remove diacid **12**. The ethanolic solution was evaporated *in vacuo* and the dry residue was dissolved in CH_2Cl_2. Hexane was added and a solid precipitated which was recrystallized from 2-propanol to give a white solid, mp 148 °C and 165–166 °C. This solid was identified as compound **8c** contaminated, possibly, with a trace of its regioisomer (±)-3-(cyclohexyloxycarbonyl)-3-imidazol-1-ylpropionic acid (**8e**), identified by ^{13}C NMR: ^1H NMR (D_2O) δ 1.20–

1.80 (m, 10 H), 3.29 (AB part, 2 H, J_{AB} = 17.1, J_{AX} = 9.3, J_{BX} = 5.2 Hz), 4.70 (masked by HDO, 1 H), 5.37 (X part, 1H) 7.45 (br s, 1 H), 7.57 (br s, 1 H), 8.78 (br s, 1 H); ^{13}C NMR (D_2O) δ 22.1 (t), 22.2 (t, **8e**), 23.7 (t), 29.7 (t), 36.4 (t, **8e**), 36.7 (t), 59.5 (d), 60.0 (d, **8e**), 74.3 (d), 118.0 (d, **8e**), 119.1 (d), 120.4 (d), 121.0 (d, **8e**), 134.2 (d, **8e**), 134.4 (d), 170.2 (s, **8e**), 170.4 (s), 171.0 (s, **8e**), 171.6 (s); IR (KBr) ν 2620–2320, 2050–1900 (NH^+), 1730 (CO), 1650 (CO), cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.20; H, 6.75; N, 10.44. Pure compound **8c** was obtained by method a and further precipitation with CH_2Cl_2, mp 167–169 °C.

(±)-3-(Benzyloxycarbonyl)-2-imidazol-1-ylpropionic acid (8d): obtained from spontaneous hydrolysis at room temperature of the reaction crude of the synthesis of compound **5d**. Recrystallization from 90% aqueous ethanol gave pure **8d:** mp 159–161 °C; ^{1}H NMR (D_2O/70 °C) δ 3.33 (AB part, 2 H, J_{AB} = 17.1, J_{AX} = 9.8, J_{BX} = 4.8 Hz), 5.13 (s, 2 H), 5.32 (X part, 1 H), 7.30–7.46 (m, 7 H), 8.68 (br s, 1 H); ^{13}C NMR (D_2O /70 °C) δ 36.1 (t), 59.4 (d), 66.0 (t), 118.2 (d), 120.0 (d), 127.0 (d), 127.3 (d), 127.4 (d), 133.6 (s), 134.0 (d), 170.1 (s), 170.4 (s); IR (film) ν 2680–2280, 2180–1820 (NH^+), 1720 (CO), 1660 (CO) cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_4 \cdot 1/4H_2O$: C, 60.30; H, 5.24; N, 10.05. Found: C, 60.15; H, 5.17; N, 10.14.

(±)-3-(Ethoxycarbonyl)-2-benzimidazol-1-ylpropionic acid (9): obtained by the general procedure b. The reaction crude was recrystallized from ethanol to give pure **9** (40%): mp 149–151 °C (from ethanol); ^{1}H NMR (D_2O) δ 1.0 (t, 3 H, J = 7.1 Hz), 3.29–3.38 (AB part, 2 H), 3.98 (q, 2 H, J = 7.1 Hz), 5.62 (X part, 1 H), 7.52-7.57 (m, 2 H), 7.69–7.74 (m, 2 H), 9.28 (br s, 1 H); ^{13}C NMR (D_2O) δ 12.1 (q), 35.6 (t), 57.4 (d), 61.3 (t), 111.8 (d), 113.8 (d), 125.6 (d), 125.9 (d), 129.4 (s), 129.6 (s), 139.7 (d), 170.8 (s), 170.9 (s); IR (film) ν 2700–2200 (NH^+), 1720 (CO), 1610 (CO) cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.09; H, 5.28; N, 10.65.

(±)-2-Benzimidazol-1-ylsuccinic acid (12): obtained by the general procedure b. The reaction crude was extracted with hot ethanol to remove the monoacid **9**, and the insoluble residue was recrystallized from water to yield pure **12** (25%): mp 200–202 °C (dec) (from water); ^{1}H NMR (D_2O) δ 3.29–3.47 (AB part, 2 H), 5.63 (X part, 1 H), 7.55–7.62 (m, 2 H), 7.69–7.79 (m, 2 H), 9.29 (br s, 1 H); IR (film) ν 2900–2400, 2000–1830 (COOH, NH^+), 1700 (CO), 1590 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.10; H, 4.45; N, 11.77.

(±)-2-Pyrazol-1-ylsuccinic acid (13): isolated, in part, from diester **7** and monoacids **10** and **14** by treatment of the reaction crude with ethanol; ^{1}H NMR (DMSO-d_6) δ 3.08 (AB part, 2 H, J_{AB} = 16.9, J_{AX} = 7.7, J_{BX} = 6.6 Hz), 5.34 (X part, 1 H), 6.23 (pseudo-t, 1 H), 7.44 (d, 1 H, J = 1.5 Hz), 7.80 (d, 1 H, J = 2.2 Hz); ^{13}C NMR (DMSO-d_6) δ 39.1 (t), 59.8 (d), 105.3 (d), 131.0 (d), 139.1 (d), 170.3 (s), 171.4 (s).

Preparation of Imidazol-1-ylacetic Esters by PTC. General Procedure. To a stirred suspension of powdered potassium hydroxide (1.65 g, 29.4 mmol) and potassium carbonate (4.06 g, 29.4 mmol) in CH_2Cl_2 (50 mL) were added imidazole (2 g, 29.4 mmol) and 1,5-bis[(*N*-benzyl-*N*,*N*-diethylammonio)ethyl] ether dichloride (BBDE Cl) (0.342 g, 0.73 mmol). To the vigorously stirred mixture was added the corresponding bromoacetate (14.7 mmol) and stirred at room temperature for the time shown below for each compound. After filtering, the residue was washed with methylene chloride (2 × 20 mL), and the organic solutions were dried over anhydrous sodium sulfate. The CH_2Cl_2 was evaporated *in vacuo* and the residue purified over a silica gel column using the eluents described for each compound.

Ethyl imidazol-1-ylacetate (15): reaction time 18 h; chromatographic eluent CH_2Cl_2:ethanol, 9:1; Kugelrohr distillation $ot_{0.1}$ 99–100 °C (66%); picrate mp 121–123 °C (from ethanol), lit.[18] 124 °C. Spectroscopic data are in agreement with those previously reported.[19]

Benzyl imidazol-1-ylacetate (16): reaction time 6 h; chromatographic eluent ethyl acetate (51%); picrate mp 151–153 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 2 H), 5.18 (s, 2 H), 6.92 (br s, 1 H), 7.07 (br s, 1 H), 7.31–7.36 (m, 5 H), 7.47 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.4 (t), 67.1 (t) 119.6 (d), 128.0 (d), 128.2 (d), 129.0 (d), 134.4 (s), 137.5 (d), 167.0 (s). Anal. Calcd for $C_{18}H_{15}N_5O_9$ (picrate): C, 48.54; H, 3.40; N, 15.73. Found: C, 48.49; H, 3.55; N, 15.57.

***tert*-Butyl imidazol-1-ylacetate (17):** reaction time 23 h; chromatographic eluent CH_2Cl_2:ethanol, 8:2 mp 111–113 °C (sublim) (50%). Subsequent sublimation gave analytically pure **17**: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 4.61 (s, 2 H), 6.96 (br s, 1 H), 7.10 (br s, 1 H), 7.61 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.6 (q), 48.4 (t), 82.7 (s), 119.6 (d), 129.1 (d), 137.6 (d), 166.2 (s); IR (KBr) ν 1730 (CO), cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.38. Found: C, 59.59; H, 7.60; N, 15.54.

***n*-Butyl Imidazol-1-ylacetate (18).** To a suspension of imidazol-1-ylacetic acid **3** (0.365 g, 3.15 mmol), DCC (0.724 g, 3.46 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.038 g, 3.11 mmol) in CH_2Cl_2 was added *n*-butanol (0.256 g, 3.45 mmol). The mixture was stirred at room temperature for 48 h and refluxed for 1 h more. The white powder of *N*,*N*'-dicyclohexylurea was filtered off and the organic solution concentrated *in vacuo*. The residue was purified by column chromatography over a silica gel column using CH_2Cl_2:ethanol, 98:2, to obtain compound **18** as a yellow oil (0.114 g, 21%). Hydrolysis of **18** was performed without additional purification: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.2 Hz), 1.26–1.40 (m, 2 H), 1.55–1.66 (m, 2 H), 4.18 (t, 2 H, J = 6.6 Hz), 4.68 (s, 2 H), 6.95 (br s, 1 H), 7.10 (br s, 1 H), 7.50 (br s, 1 H).

Kinetic Experiments. Dimethyl 2-imidazol-1-ylsuccinate (**5a**) was dissolved in D_2O (99.8%) at 94 and 284 mM and in H_2O (90% + 10% D_2O) at 284 mM. Methyl imidazol-1-acetate (**1**) was dissolved in D_2O (99.8%) at 129 mM. Each solution, placed in a 5 mm tube, was heated inside the magnet of a Bruker AC200 (200 MHz) at 80 °C. Spectra were taken automatically every 10 min during the first hour, every 30 min during the following 7 hours, and every 60 min during the final 4 h (total reaction time 12 h). Data were obtained from the relative areas of the well-resolved singlets of the $COOCH_3$ groups.

Hydrolysis with H_2O Enriched with ^{17}O and ^{18}O. A solution of methyl imidazol-1-ylacetate (**1**) (0.114 g, 0.814 mmol) or a suspension of *tert*-butyl imidazol-1-ylacetate (**17**) (0.146 g, 0.802 mmol) in enriched ^{17}O, ^{18}O water (0.4 mL) was placed in a coaxial NMR tube and heated at 80 °C for 4 h. ^{17}O NMR spectra were taken at 42.82 MHz on a Bruker AM-360, before and after the heating period, with the coaxial tube placed inside a 10 mm NMR tube containing D_2O (2 mL) used to helping the shimming. No field/frequency-locking system was used during the ^{17}O NMR acquisition. The probe temperature was kept constant at 22 ± 1 °C. Acquisition conditions were the following: 90° pulses, 800 ppm sweep width, 32K words data table (0.557 s acquisition time), and 1024 scans. Chemical shifts (ppm) are reported with respect to the internal $H_2{}^{17}O$ at 0 ppm. ^{18}O isotopic effects were detected in the proton-decoupled ^{13}C NMR spectra at 90.55 MHz. Dioxane or DMSO were used as external ^{13}C NMR references.

Acknowledgment. This work was supported by grants from the Community of Madrid (C015/91) and D.G.I.C.Y.T. (PM-92-011 and PB-93-0037). M.S.G. received a postdoctoral fellowship from the Community of Madrid and P.Z. a F.P.U. fellowship from the Spanish Ministry of Education and Science.

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