for the reaction of 1 and alanine.[32] The second-order rate constants were obtained from the slope of the linear plots of the observed pseudo-first-order rate constants (measured at 10, 20, 25, and 30 °C) vs the concentration of the anionic form of the amino acid. Buffer solutions were prepared by adding NaOH to solutions of alanine, in the amount required to have equal concentrations of the anionic and zwitterionic forms of the amino acid.

In order to determine the effect of β- or γ-cyclodextrin, a series of solutions containing the same amount of amino acid and variable concentrations of β- or γ-cyclodextrin were prepared. The pH values were adjusted to that of the solution without cyclodextrin by adding a drop of diluted acid or base.

The observed rate constants (k_{obsd}) were determined by following the appearance of the aminolysis product. The change in optical density at the maximum absorption of the product was recorded during a kinetic run on a Beckman 24 spectrophotometer or on a Shimadzu 260 recording spectrophotometer, both with a thermostated cell compartment. All the reactions were run under pseudo-first-order conditions and were followed up to 80–90% conversion.

The yield of the aminolysis (f_A) and hydrolysis (f_H) products were determined as indicated before.[33] The yield of (2,4-dinitrophenyl)cycloheptaamylose (f_{CD}) was calculated as $f_{CD} = 1 - (f_A + f_H)$. In the reactions with tyrosine, the fraction $f = 1 - (f_A + f_H)$ corresponds to the sum of the yield of (2,4-dinitrophenyl)cycloheptaamylose and that of 4. The yield of the former was independently determined through a series of reactions carried out under the same experimental conditions but in the absence of tyrosine. Thus, the yield of *O*-(2,4-dinitrophenyl)tyrosine (f_O) was calculated as $f_O = 1 - (f_H + f_A + f_{CD})$.

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Registry No. β-CD, 7585-39-9; γ-CD, 17465-86-0; D-Ala, 338-69-2; L-Ala, 56-41-7; D-Met, 348-67-4; L-Met, 63-68-3; D-Val, 640-68-6; L-Val, 72-18-4; D-Leu, 328-38-1; L-Leu, 61-90-5; D-Tyr, 556-02-5; L-Tyr, 60-18-4; D-Phe, 673-06-3; L-Phe, 63-91-2; D-Trp, 153-94-6; L-Trp, 73-22-3; *N*-2,4-DNP-L-Trp, 1655-51-2; *N*-2,4-DNP-L-Tyr, 10457-30-4; *O*-2,4-DNP-L-Tyr, 10567-73-4; 1-fluoro-2,4-dinitrobenzene, 70-34-8.

Supplementary Material Available: Table II containing the observed rate constants for the reactions of 1 with 2 at different β-cyclodextrin concentrations (6 pages). Ordering information is given on any current masthead page.

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Experimental and Theoretical Study on the Reactivity of Imidazo-1,2,6-thiadiazine 2,2-Dioxide Derivatives toward Electrophiles

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The differences found in the reactivity toward electrophiles of two dimethyl isomers, **1a** and **2a**, derived from 4-amino-1*H*,5*H*-imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-dioxide (**1e**) are reported. While 1,7-dimethyl isomer **2a** reacts with electrophiles, giving 6-substituted derivatives, 1,5-dimethyl isomer **1a** does not react. In order to find whether there are some geometrical or thermodynamic reasons for this behavior, experimental studies, including X-ray analysis and dipole moment measurements, as well as STO-3G* theoretical calculations have been carried out. Theoretical and experimental findings are in good agreement. No thermodynamic aspects seem to be responsible for the different behaviors, and so the difference must be due to kinetic factors.

In the course of the preparation of several imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-dioxides, we observed noticeable differences in the reactivity of dimethyl isomers **1a** and **2a** toward electrophiles. Nitration, which could be achieved by using HNO_3/H_2O mixtures, was the first reaction studied. In these conditions, the existence of nitryl cation (NO_2^+) is very unfavorable; because of this, and because of the complexity of nitration equilibria involving water,[1] a more simple aromatic electrophilic substitution, using an aromatic diazonium ion, was studied. In both cases, the behavior of **1a** and **2a** was similar: nitration and diazonium coupling reactions of 1,7-dimethyl derivative **2a** yielded the corresponding 6-substituted derivatives **2b** and **2c**, respectively, while the 1,5-dimethyl isomer **1a** did not react.

Due to these interesting features and in order to complete former studies[2] of these derivatives, the X-ray analysis of **1a** was carried out and measurements of dipole moments were made.

In an attempt to find if some thermodynamic aspects could explain the different reactivities, a theoretical study using ab initio calculations, at the STO-3G* level,[3] of six closely related structures (**1a**, **1d**, **1e**, **2a**, **2d**, and **2e**) was performed by using our VM/CMS version of the Gaussian

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80 series of programs.[4] Unfortunately, the size of the systems under study and our computational capability prevent a kinetic study using reaction surfaces. Moreover, no SCF convergence was achieved for 6-nitro-6*H*-arenium ion and 6-nitro derivative systems. Besides, our study had to be restricted to employ a STO-3G* basis set because a more elaborated basis was beyond our computational capabilities. However, this basis set has proved its correct behavior for cyclic[5] and sulfur hypervalent compounds.[6] Although there are other ab initio calculations of heterocyclic compounds with the SO_2 moiety,[7] to our knowledge, this is the first theoretical geometry optimization for compounds of such a size bearing an SO_2 moiety.

Experimental Section

Syntheses. Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh ASTM). DC-Alufolien silica gel 60 F254 (Merck, layer thickness 0.2 mm) was used for analytical TLC. 4-Amino-1*H*,5*H*-imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-dioxide (**1e**)[8] and its dimethyl derivatives **1a** and **2a**[9] have already been described.

Nitration Reaction. 4-Amino-1,7-dimethyl-6-nitroimidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (2b). Compound **2a** (0.6 g, 2.8 mmol) was refluxed for 45 min in a solution of concentrated nitric acid (15 mL) and water (15 mL). The mixture was allowed to stand at room temperature and then extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with saturated sodium bicarbonate, until the pH of the solution became neutral. Evaporation of the dried ($MgSO_4$) organic layer gave 0.27 g (37%) of a white product, which crystallized from water into prismatic needles: mp 303 °C; ^1H NMR δ 8.67 (br s, 1 H, NH, exch), 8.48 (br s, 1 H, NH, exch) 3.83 (s, 3 H, N7-CH_3), 3.20 (s, 3 H, N1-CH_3); UV, λ_{max} (log ϵ) (H_2O) 190 (4.2), 210 (4.1), 262 (3.99), 336 nm (3.88); IR (KBr) ν 3295, 3160 (NH_2), 1660 (C=N), 1550, 1350 (NO_2), 1295, 1170–1100 cm^{-1} (SO_2).

Anal. Calcd for $C_6H_8N_6O_4S$: C, 27.69; H, 3.10; N, 32.29; S, 12.32. Found: C, 27.62; H, 3.11; N, 32.31; S, 12.25.

Diazo Coupling Reactions. General Procedure. *p*-Chloroaniline (2 g, 16 mmol) was diazotized by described procedures.[10] Then 11 mmol of the corresponding imidazothiadiazine derivative was treated with the diazo solution as previously reported for xanthine.[10] The red solution obtained was stirred for 4 h at room temperature, and the solid that appeared was filtered.

4-Amino-1,7-dimethyl-6-[(4′-chlorophenyl)azo]imidazo-[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (2c). From **2a** (2.4 g), 0.96 g (25%) of **2c** was obtained as red needles (from ethanol–water): mp 260 °C dec; ^1H NMR δ 8.62 (br s, 1 H, NH, exch), 8.40 (br s, 1 H, NH, exch), 7.99 (d, 2 H, J = 8.7 Hz, H_o), 7.69 (d, 2 H, J = 8.7 Hz, H_m), 4.06 (s, 3 H, N7-CH_3), 3.40 (s, 3 H, N1-CH_3); UV λ_{max} (log ϵ) (methanol) 229 (4.04), 287 (3.85), 393 nm (4.17); IR (KBr) ν 3400, 3300 (NH_2), 1640 (C=N), 1330–1310, 1160 (SO_2).

Anal. Calcd for $C_{12}H_{12}N_7O_2SCl$: C, 40.74; H, 3.42; N, 27.71; S, 9.06; Cl, 10.02. Found: C, 40.82; H, 3.45; N, 27.52; S, 9.27; Cl, 9.98.

Table I. Experimental Data and Structure Refinement Procedures

Crystal Data	
formula	$C_6H_9N_5O_2S_1$
cryst habit	prismatic
cryst size (mm)	0.2 × 0.25 × 0.30
symmetry	triclinic, *p*-1
unit cell determination	least-squares fit from 56 reflctns ($\theta < 38°$)
unit cell dimens	9.050 (1), 6.752 (2), 14.961 (4) Å 90.0°, 106.51 (2)°, 90.0
packing: V (Å^3), Z	876.5 (4), 4
D_{calcd} (g cm^{-3}), M, F(000)	1.631, 215.229, 448
μ(Mo Kα) (cm^{-1})	3.354
Experimental Data	
technique	four-circle diffractometer, Enraf-Nonius CAD-4, bisecting geometry; graphite-oriented monochromator, Mo Kα, w/2θ scans; detector apertures 1 × 1, up θ_{max}, 30°, 1.5 min/reflctn
number of reflctns	
measd	2548
independent	2058
obsd	1568 [2σ(I) criterion]
range of *hkl*	12 to 0, 9 to 0, 21 to −21 [[(sin θ)/λ]$_{max}$ = 0.60]
value of R_{int}	0.010
abs correctn	1.318–0.674
Solution and Refinement	
solution	direct methods
refinement	least square on F_o with 1 block
parameters	
no. of variables	163
degrees of freedom	1405
ratio of freedom	9.6
H atoms	difference synthesis and refined
final shift/error	0.02
weight	1
final F peaks	0.31 e Å^{-3}
final R and Rw	0.046, 0.049

4-Amino-6-[(4′-chlorophenyl)azo]-1*H*,5*H*-imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (1f). From **1e** (2 g). The solid that appeared in the reaction corresponds to the potassium salt of **1f**, since the compound has two acid NH groups. The salt was filtered, washed with acetone, and dissolved in water. The acidification (pH = 1) of the solution gave **1f** as a yellow product (1.25 g, 35%). The precipitate was recrystallized from DMF/H_2O to give a complex (**1f·DMF**) as amber prismatic crystals (this behavior had been observed in other imidazothiadiazine derivatives, which crystallized also with DMF[11]): mp 308–310 °C; ^1H NMR δ 13.5–9.0 (br, 3 H, NH, NH_2, exch), 8.13 (br s, 1 H, NH, exch) 7.95 (s, 1 H, HCO), 7.87 (d, 2 H, J = 8.7 Hz, H_o), 7.67 (d, 2 H, J = 8.7, H_m) 2.88 [s, 3 H, NCH_3(DMF)], 2.73 [s, 3 H, NCH_3(DMF)]; UV λ_{max} (log ϵ) (methanol) 220 (sh) (4.04), 273 (sh) (3.82), 298 (3.95), 490 nm (4.46); IR (KBr) ν 3400, 3300, 3100 (NH_2, NH), 1655 (C=N), 1300, 1160–1120 cm^{-1} (SO_2).

Anal. Calcd for $C_{13}H_{15}N_8O_3SCl$: C, 39.15; H, 3.79; N, 28.09; S, 8.04; Cl, 8.82. Found: C, 38.91; H, 3.79; N, 27.89; S, 8.34; Cl, 8.82.

Methylation Reaction. General Procedure. A solution of methyl iodide (1 mL) in acetone (3 mL) was added to a solution of **1f** (0.3 g, 0.92 mmol) in acetone (30 mL) with sodium bicarbonate (0.19 g). The mixture was refluxed for 2 h, and then methyl iodide (1 mL) was added. After 2 h more under reflux, TLC (chloroform/ethanol, 7/1) indicated the formation of two new products (**2c**, R_f = 0.6; **1c**, R_f = 0.4), which were separated by column chromatography.

4-Amino-1,5-dimethyl-6-[(4′-chlorophenyl)azo]imidazo-[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (1c). Compound **1c** was eluted with chloroform/methanol (25/1) (0.082 g, 25%): orange crystals (from ethanol/water), mp >300 °C; ^1H NMR δ 8.06 (d,

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Table II. Selected Experimental and Calculated Bond Distances (Å)

	1a exptl	1a	1e	1d	2a exptl[2]	2a	2e	2d
S1–N2	1.582	1.699	1.699	1.721	1.609	1.698	1.677	1.704
S1–N7	1.662	1.708	1.711	1.702	1.667	1.743	1.752	1.720
S1–O10	1.420	1.444	1.444	1.444	1.428	1.444	1.444	1.444
S1–O11	1.434	1.453	1.453	1.451	1.426	1.451	1.453	1.451
N2–C3	1.336	1.303	1.306	1.295	1.332	1.315	1.320	1.299
C3–C9	1.424	1.462	1.462	1.453	1.444	1.474	1.465	1.452
C3–N12(H12)	1.331	1.444	1.425	1.094	1.321	1.399	1.394	1.094
N4–C5	1.338	1.376	1.376	1.375	1.314	1.314	1.309	1.306
N4–C9	1.389	1.410	1.404	1.402	1.391	1.410	1.416	1.418
N4–C13(H13)	1.466	1.474	1.021	1.022	1.462	1.474	1.022	1.021
C5–H5	0.949	1.085	1.086	1.086	0.990	1.084	1.083	1.083
C5–N6	1.325	1.328	1.327	1.328	1.369	1.399	1.406	1.410
N6–C8	1.355	1.399	1.403	1.402	1.359	1.386	1.379	1.378
N7–C8	1.375	1.411	1.420	1.409	1.391	1.433	1.409	1.393
N7–C14(H14)	1.470	1.479	1.026	1.025	1.471	1.496	1.031	1.023
C8–C9	1.377	1.365	1.360	1.361	1.369	1.359	1.363	1.366

2 H, J = 8.7 Hz, H_o), 7.69 (d, 2 H, J = 8.7 Hz, H_m), 4.27 (s, 3 H, N5-CH_3), 3.29 (s, 3 H, N1-CH_3); UV λ_{max} (log ϵ) (methanol) 225 (4.95), 287 (4.71), 329 (4.76), 418 nm (5.02); IR (Nujol) ν 3400, 3300 (NH_2), 1640 (C=N), 1310, 1160–1120 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{12}N_7O_2SCl$: C, 40.74; H, 3.42; N, 27.71; S, 9.06; Cl, 10.02. Found: C, 40.68; H, 3.51; N, 27.66; S, 9.23; Cl, 10.12.

4-Amino-1,7-dimethyl-6-[(4′-chlorophenyl)azo]imidazo-[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (2c). Compound **2c** was eluted with chloroform/methanol (50/1), before **1c** was eluted (0.032 g, 10%), and was shown to be identical with the product isolated by the method described above.

Crystal Structure Determination. Suitable single crystals of **1a** were obtained from methanol/water. Crystal data are reported in Table I. Calculations used the MULTAN[12] and X-ray[13] systems and the PLUTO package.[14] The scattering factors were taken from ref 15. All computing was done on a Vax 11/750.

Dipole Moment Determination. Dielectric measurements were carried out on a WTW Model DK 06 multidekameter at a frequency of 2.0 MHz. The cell used was made of silvered Pyrex glass, and the measured solutions acted as the dielectric of a capacitor. The cell was calibrated at the working temperature, 25.0 ± 0.05 °C, using solvents with well-known dielectric constants[16,17] (i.e., benzene, toluene, and cyclohexane). The specific volumes were measured in an Anton Paar DMA 55 digital densimeter, using water and air as calibrating substances. The differences between the refractive indices of the solution and the pure solvent 1,4-dioxane, Δn, were obtained at 546.1 nm in a Brice Phoenix Model 2000V differential refractometer, calibrated with aqueous KCl. The solvents used for calibrating the dielectric cell and for all the measurements, dielectric constant (e), specific volume (v), and refractive index (n), were Carlo Erba RPE and were dried over Merck 4-Å molecular sieves before use.

The concentration range of the measured solutions was $1.10^{-4} < \omega_2 < 6.10^{-4}$ (ω_2, weight fraction of solute).

Other Measurements. ^1H and ^{13}C NMR spectra were recorded on Varian XL-300 and Bruker AM-200 spectrometers, operating at 300, 200, 75, and 50 MHz, respectively. Chemical shifts are reported (in δ) referred to Me_4Si; DMSO-d_6 was used as solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. IR and UV spectra were obtained on Perkin-Elmer 257 and 550 SE spectrophotometers, respectively.

Results and Discussion

Synthesis. Nitration reactions of tautomeric mixtures of **1e** and **2e** were attempted using sulfuric/nitric acid mixtures at 0 °C and aqueous nitric acid at room and reflux temperatures, with no good results. Since, in analogous naturally occurring purines, electron-releasing groups are required to obtain 6-nitro derivatives,[18] methyl derivatives **1a** and **2a** were made to react in the above-mentioned conditions. Unaltered **1a** was recovered when a sulfuric/nitric acid mixture at 0 °C or HNO_3/H_2O and 6 h of reflux was used. At longer reflux time, the compound slowly decomposed. In contrast with this behavior, **2a** gave its 6-nitro derivative **2b** with 50% HNO_3/H_2O and 1 h of reflux. With longer reaction time, the starting material and **2b** decomposed. A weaker nucleophilic carbon is required in purines for coupling with diazonium salts than for nitration.[19] Thus, diazonium coupling reactions were obtained with the tautomeric mixture **1e** and **2e** as well as with 1,7-dimethyl derivative **2a**, affording the mixture of isomers **1f** and **2f** and dimethyl derivative **2c**, respectively. However, unchanged 1,5-dimethyl derivative **1a** was recovered from the diazonium coupling conditions, and **1c** could not be obtained in this way. Nevertheless, **1c** was synthesized together with **2c** by methylation of the mixture **1f** and **2f** (Scheme I).

X-ray Crystallography of 1a. The final atomic coordinates, equivalent isotropic thermal parameters, bond distances, angles, and a perspective view of the compound with the atomic numbering are given in the supplementary material. Selected bond distances and angles together with the calculated values are gathered in Tables II and III. Bond distances and angles for **1a** are in good agreement and comparable with those found in its isomer **2a**.[2] Except for the expected differences in the imidazole ring of both compounds, the more important ones in the thiadiazine ring are found in the SO_2–N7–C14 region (S1–N7–C8, O10–S1–N7–C14, O11–S1–N7–C14, and C14–N7–C8–C9 values). These differences are due to the steric hindrance between both NMe in compound **2a**, which compels C14 to go out of the plane. In **1a**, the imidazole ring is planar and coplanar with the rest of the molecule excluding the SO_2 group. Atoms O10, O11, S, and N12 are the most deviated from the molecular plane. The deviation of the

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Table III. Selected Angles and Dihedral Values (deg)

	1a exptl	1a	1e	1d	2a exptl[2]	2a	2e	2d
N2–S1–N7	105.7	102.6	102.2	102.8	106.9	106.6	103.2	103.4
O10–S1–O11	115.2	121.5	121.6	122.0	117.8	123.1	121.5	122.0
S1–N2–C3	122.2	119.6	119.1	120.2	118.3	115.3	118.0	120.9
N2–C3–C9	119.4	123.4	123.3	124.2	119.9	123.9	124.1	125.8
N2–C3–N12(H12)	117.4	116.8	117.7	117.0	118.8	118.7	118.3	116.4
C5–N4–C9	106.0	105.4	106.1	106.2	104.0	103.7	104.0	104.3
C5–N4–C13(H13)	126.2	125.4	126.0	126.0	–	–	–	–
N4–C5–N6	113.8	114.1	113.4	113.4	113.2	113.2	112.6	112.7
N4–C5–H5	121.7	121.1	121.6	121.6	128.0	128.0	126.5	126.6
C5–N6–C8	103.8	102.9	103.0	102.9	105.8	105.4	106.1	105.7
C5–N6–C13(H13)	–	–	–	–	126.6	127.1	126.9	127.1
S1–N7–C8	115.1	117.4	118.0	120.1	109.0	109.8	114.2	119.6
C8–N7–C14(H14)	121.3	119.4	117.5	118.6	118.8	115.2	115.3	120.9
N7–C8–C9	123.1	122.8	121.7	121.6	126.9	126.6	125.0	124.2
N6–C8–C9	111.6	112.4	112.4	112.6	107.0	106.4	106.2	106.7
C3–C9–C8	122.6	121.8	122.5	122.9	120.7	121.4	120.6	120.4
C3–C9–N4	132.5	133.1	132.2	132.3	129.9	127.2	128.2	129.0
H122–N12–H121	122.9	107.4	110.6	–	126.0	114.9	115.7	–
S1–N7–C8–C9	22.5	21.5	22.3	18.1	21.2	22.9	22.5	14.7
S1–N2–C3–C9	–14.9	–22.1	–22.7	–17.9	–11.8	–24.5	–24.4	–15.0
O10–S1–N7–C14	–73.1	–78.8	–73.8	–74.0	14.7	25.1	–72.6	–52.9
O11–S1–N7–C14	51.5	54.2	60.0	59.9	151.1	156.5	57.8	79.2
N12(H12)–C3–C9–C8	171.2	169.7	168.6	180.0	165.0	167.1	168.9	180.0
C13(H13)–N4–C5–N6	–179.2	–180.0	180.0	–180.0	–	–	–	–
C13(H13)–N4–C5–H5	1.1	0.0	0.0	0.0	–	–	–	–
C13(H13)–N6–C5–H5	–	–	–	–	+1.9	0.0	0.0	0.0
C13(H13)–N6–C5–N4	–	–	–	–	179.1	180.0	180.0	180.0
C14(H14)–N7–C8–C9	176.8	176.1	169.9	172.9	–119.8	–108.1	–155.1	–178.4

Table IV. ^{13}C NMR Chemical Shifts (ppm) and Coupling Constants (Hz)

compd[22]	C3	C5	C8	C9	C13	C14
1a	152.8	142.9 (dq), ^1J = 212.9, ^3J = 4.0	152.6 (q), ^3J = 3.1	103.8 (m)	33.8 (qd), ^1J = 141.7, ^3J = 1.2	28.7 (q), ^1J = 141.7
2a	158.8	137.2 (dq), ^1J = 216.1, ^3J = 4.4	142.1 (m)	116.2 (dt), ^3J = 9.3, ^3J = 3.4	31.7 (q), ^1J = 142.0	36.2 (q), ^1J = 142.1
2b	158.3	144.6 (m)*[b]	143.1 (m)*	115.2	35.2 (q), ^1J = 145.4	37.9 (q), ^1J = 145.2
1c[a]	152.9	151.8	152.2	107.7	32.5	29.3
2c[a]	158.8	148.1	144.1	107.5	31.7	36.1
1e	153.9	136.9 (d), ^1J = 212.8	147.4	104.3	–	–
1f[a]	154.8	151.1	147.0	110.7	–	–

[a] Decoupled spectra. [b] (*) assignments may be exchanged.

Table V. Atomic Distances (Å) to the Plane Containing the Imidazole Ring and C3

	S1	N12	C13(H13)	C14(H14)
1a exptl	0.542	–0.177	0.028	0.037
1a	0.557	–0.226	0.000	0.088
1d	0.458	0.000	0.000	0.113
1e	0.573	–0.250	0.000	0.160
2a exptl	0.687	–0.412	–0.018	–1.101
2a	0.638	–0.281	0.000	–1.299
2d	0.378	0.000	0.000	–0.024
2e	0.612	–0.240	0.000	0.393

S atom from the plane containing the imidazole ring and C3 is –0.542 (1) Å; this value is less than the corresponding deviation in **2a** (see Table V). The molecular packing is affected by the molecular electronic polarization. The molecules lie in parallel planes and are linked by hydrogen bonds through the amine group and the O and N atoms. (Intermolecular contacts and a projection of the structure along the *A* axis are in the supplementary material.)

Dipole Moments. Unfortunately, the dipole moment of **1a** could not be measured due to its limited solubility in nonpolar solvents. This fact is an indication that **1a** will have a greater dipole moment than **2a**. The experimental dipole moment of **2a** was determined in 1,4-dioxane at 25 °C by the Halverstadt–Kumler[20] (HK) and Guggenheim–Smith[21] (GS) methods. The values obtained were 7.09 D from both methods, in very good agreement. In the Halverstadt–Kumler method, the contribution of the atomic polarization was considered to be 5% of the electronic polarization.

NMR Study. ^{13}C NMR data of described compounds **1a**, **2a**, and **1e** are now reported together with those of new compounds in Table IV.[22] Owing to the prototropic tautomerism, the ^{13}C NMR spectra of **1e** and **1f**, in DMSO, correspond to a mixture of tautomers, among which **1e**, **2e** and **1f**, **2f**, respectively, are present.

In dimethyl isomers **1a** and **2a**, long-range coupling constants could be measured. Thus, the coupling of C5 with the protons of the imidazole NMe could be seen in both isomers, and the coupling of C9 with H5 (^3J = 9.3 Hz) and NH_2 (^3J = 3.4 Hz) could be seen in **2a**. The fact that the coupling between C13 and H5 could only be observed in **1a** indicates that, in DMSO solution, the C13–N4(6)–C5–H5 dihedral angle is different for both isomers.

Theoretical Calculations. Geometries of **1a**, **1e**, **1d**, **2a**, **2e**, and **2d** were fully optimized by following a suitable gradient method,[23] but, due to the size of the systems

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[20] Halverstadt, I. F.; Kumler, W. D. *J. Am. Chem. Soc.* **1942**, *64*, 2988.

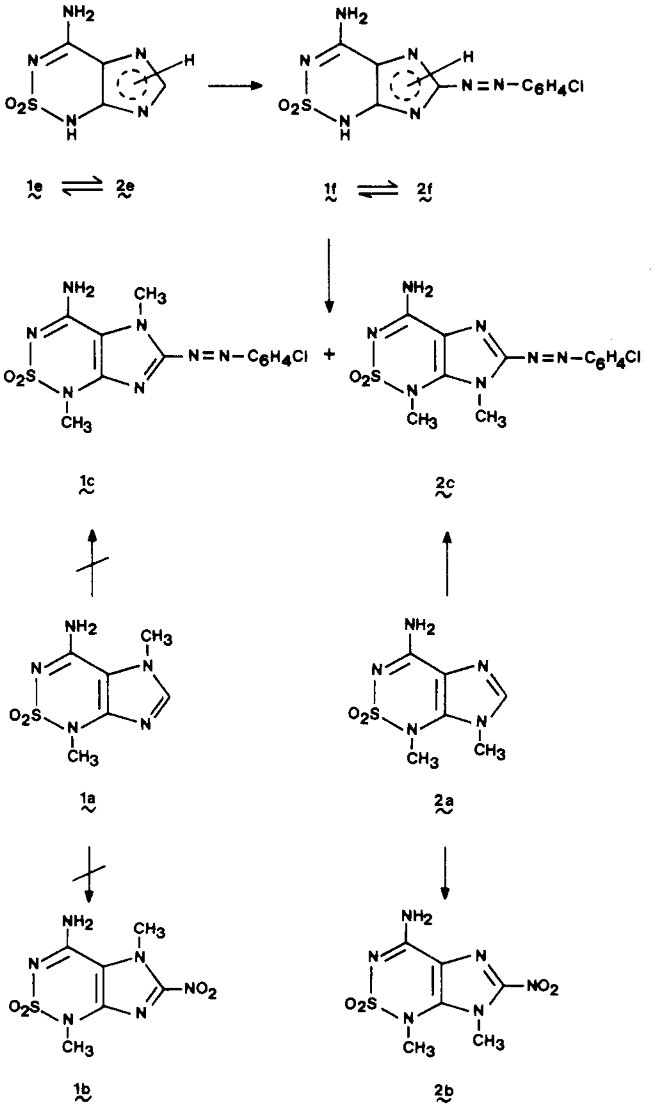
[21] (a) Guggenheim, E. A. *Trans. Faraday Soc.* **1949**, *45*, 714; **1951**, *47*, 573. (b) Smith, J. W. *Ibid.* **1950**, *46*, 394.

[22] In order to simplify the correlation between charge and chemical shift, numbering in Table IV is not the correct numbering but the same as used in the X-ray analysis and theoretical calculations.

Table VI. Mulliken Populations, SCF Energies, and Dipole Moments

	1a	1e	1d	2a	2e	2d
S1	15.512	15.507	15.501	15.529	15.513	15.495
N2	7.284	7.285	7.235	7.299	7.305	7.249
C3	5.753	5.741	5.911	5.725	5.715	5.896
N4	7.238	7.307	7.306	7.259	7.250	7.240
C5	5.848	5.840	5.841	5.870	5.867	5.869
N6	7.279	7.272	7.273	7.243	7.316	7.318
N7	7.276	7.339	7.341	7.268	7.334	7.349
C8	5.815	5.811	5.812	5.805	5.775	5.764
C9	5.981	5.974	5.970	6.000	6.012	6.008
O10	8.244	8.239	8.233	8.251	8.240	8.235
O11	8.255	8.254	8.242	8.253	8.259	8.240
N12(H12)	7.385	7.385	0.905	7.392	7.392	0.893
C13(H13)	6.078	0.763	0.761	6.074	0.761	0.762
C14(H14)	6.078	0.774	0.770	6.091	0.795	0.777
H5	0.903	0.897	0.897	0.907	0.903	0.904
H121	0.803	0.792	–	0.789	0.784	–
H122	0.821	0.817	–	0.782	0.779	–
H131	0.893	–	–	0.905	–	–
H132	0.914	–	–	0.912	–	–
H133	0.906	–	–	0.895	–	–
H141	0.903	–	–	0.927	–	–
H142	0.922	–	–	0.926	–	–
H143	0.907	–	–	0.893	–	–
E (au)	–1039.282 388	–962.120 317	–907.787 637	–1039.290 889	–962.126 477	–907.787 924
μ (D)	6.744	7.159	6.496	6.003	5.948	6.244

Scheme I



under study and taking into account their X-ray structure, the following restrictions were employed: (a) For **1d** and **2d**, atoms 2–9, 12, 13, and H5 were left in the same geometrical plane. (b) For **1e** and **2e**, atoms 2–9, 13, and H5 were left in the same plane. (c) For **1a** and **2a**, atoms 2–9, 13, and H5 were left in the same plane. Also *d* C14–H141 = *d* C14–H143, *d* C13–H131 = *d* C13–H133, and *d* N12–H121 = *d* N12–H122. No other restrictions were imposed (Figure 1).

Selected geometrical parameters are given in Tables II, III, and V. Mulliken electronic populations, SCF energies, and dipole moments are in Table VI.

Geometries. Bond lengths are in agreement with experimental data (error < 0.04 Å) except for S1–N2, S1–N7, and C3–N12. Most significative angle distortions are in the O–S–O, N2–C3–C9, and S1–N2–C3–C9 angles. In general, STO-3G* structures are in good agreement with the experimental ones. The significative discordance in the S–N bond length in the O–S–O angle or in the O–S–N–C dihedral angle may be explained by the lack of flexibility of the STO-3G* basis set for describing long-distance interactions and due to crystal structure distorsions which are not in the gas phase.

The sulfur atom is out of the molecular plane in both **1a** and **2a**, and the C14 of **2a** is below this plane, in good agreement with experimental findings (see Figure 2 and Table V), showing that STO-3G* reflects fairly well N7 hybridization.

Energies. In all cases, compounds 1 are less stable than 2. The NH_2 substitution in C3 favors compounds 1, and the methyl substitution (**2e**–**2a** or **1e**–**1a**) increases the predominance of compounds 1. HOMO energies are higher in compounds **1a** and **1e** than in **2a** and **2e** (supplementary material).

Charges and Dipole Moments. In all cases, compounds 1 have greater dipole moments than 2, in agreement with experimental indications. The NH_2 substitution increases the dipole moment but dimethyl substitution decreases the dipole moment in **1a**, although its dipole moment is greater than that of **2a**. It may be explained with a simple addition of the individual methyl group dipole moment to the dipole moments of **2e** and **1e**.

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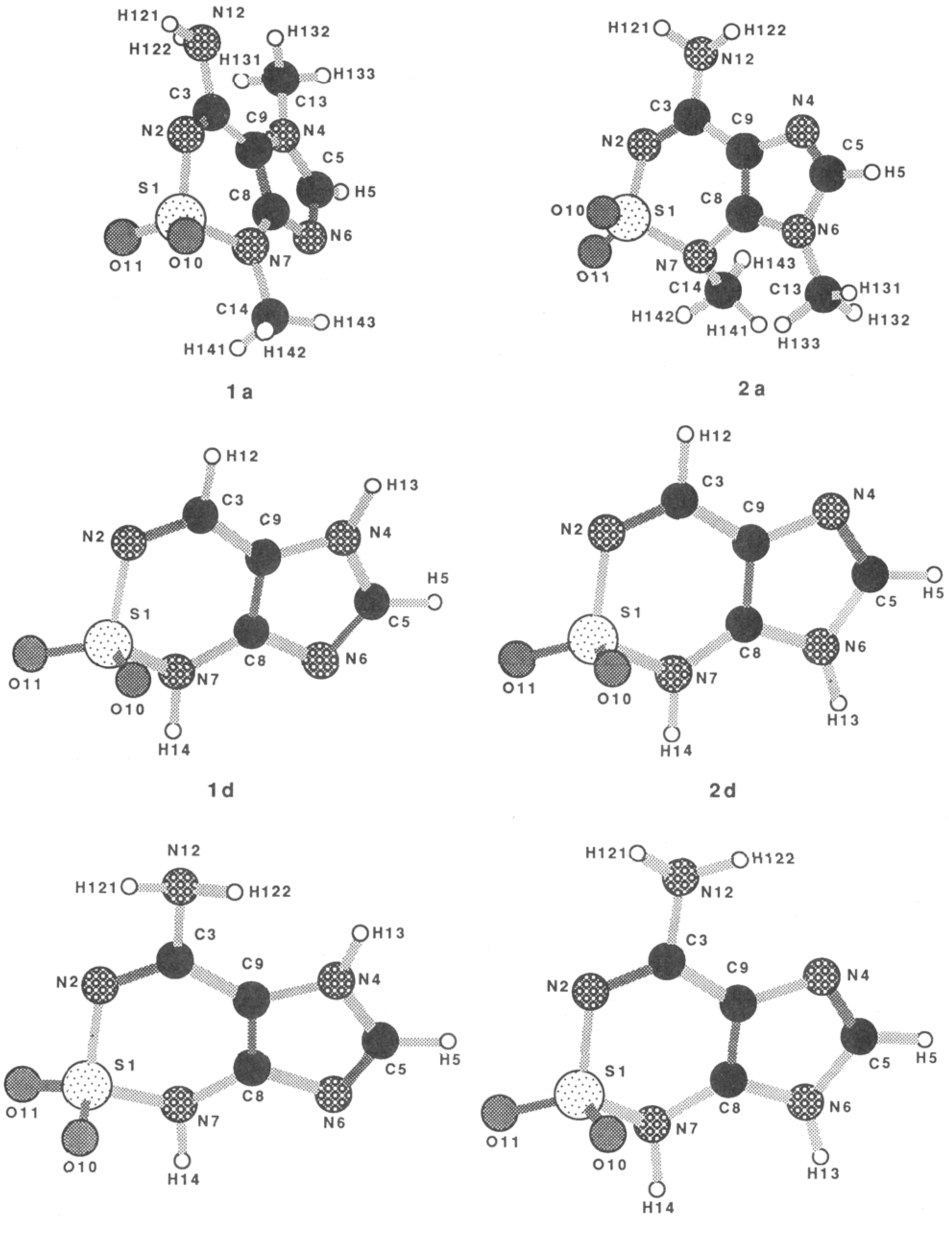
(23) (a) Murtagh, B. A.; Sargent, R. W. H. *Comput. J.* **1982**, *131*, 185–194. (b) Schelegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214–218.



1a 2a

1d 2d

1e 2e

Figure 1. View of ab initio structures of **1a**, **1d**, **1e**, **2a**, **2e**, and **2d** with the atomic numbering.

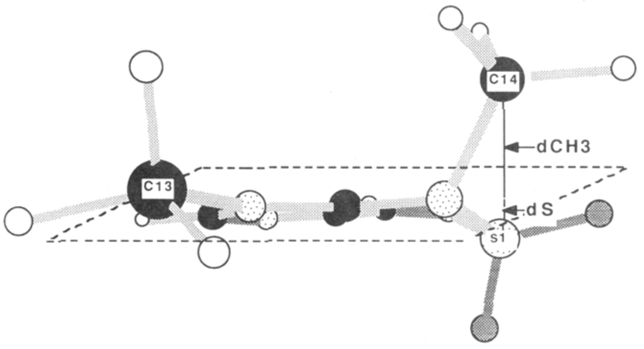


Figure 2. Compound **2a** perspective of distances of C14 and S1 to the plane containing the imidazole ring and C3.

The electronic populations move from S to O atoms and from C to N atoms, and H atoms are always positively charged. There is a greater positive charge on C5 in compounds **1** than in **2**. The charge in C5 is nearly constant under NH_2 and CH_3 substitution.

A good correlation could be established (eq 1) between the total charges of carbon atoms and experimental ^{13}C chemical shifts of **1a** and **2a**:

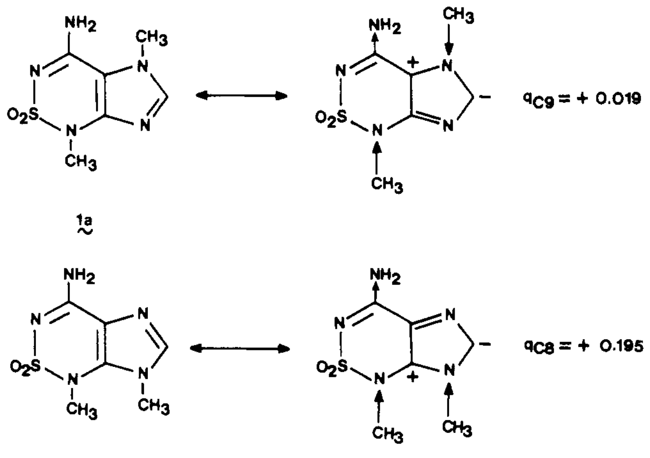
$$q_c = -(4.87 \times 10^{-3})\delta C + 6.52 \qquad n = 8, r^2 = 0.90 \qquad (1)$$

Reactivity. Experimentally no evidence of nitration nor diazonium coupling reactions for **1a** was found. In order to find an explanation for this fact, we studied the following points: (a) dipole moment differences, (b) q_{C5}, (c) resonance structures, and (d) protonation energies in C5.

(a) The greater dipole moment for series **1** shows these compounds will be more stabilized than **2** by solvation in the aqueous phase. However, aqueous stability in all compounds will be great due to their high dipole moment (>6.0 D in the six compounds).

(b) Positive charge in C5 is greater for series **1** (+0.15 e) than for **2** (+0.13 e); this would indicate that in family **1** electrophilic reactions are slightly less favored.

(c) Compound **1a** has a resonance structure, with the C5 negatively charged, less favored than that of **2a**, because the positive charge in C9 is destabilized by the inductive



1a

2a

Figure 3. Selected resonance structures of 1a and 2a.

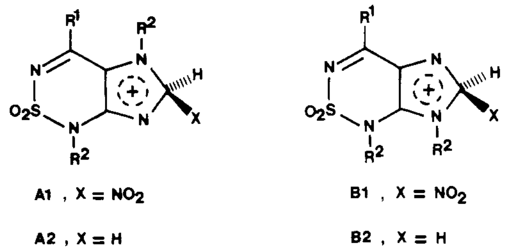


Figure 4. Arenium ions of 1a, 1e, 1d, 2a, 2e, and 2d.

effect of the NH_2 and stabilized by the CH_3. In **2a**, two CH_3 inductive effects contribute to stabilize the positive charge on C8. The near-zero value of q_{C9} in **1a** and the positive value of q_{C8} in **2a** are indicative of this fact (Figure 3).

(d) Since the most common mechanism in aromatic electrophilic substitution involves a positively charged intermediate (the arenium ion),[24] an attempt to calculate the formation energies of the transition state taking the 6-nitro-6*H*-arenium ions (A1 and B1) was carried out. No SCF convergence was obtained (Figure 4).

In a simpler model, NO_2^+ would be substituted by H^+ (A2, B2). In order to obtain approximate protonation energies, we made single point calculations using the geometry of neutral species and placing the carbocation group in the same relative position as obtained for the 2*H*-imidazolium ion with the STO-3G basis set. Only SCF convergence was achieved for the arenium ions corresponding to **1d** and **2d**, obtaining E_P = 210.9 kcal/mol for **1d** and 196.5 kcal/mol for **2d**. Their fairly near protonation energies do not give any thermodynamical explanation why compound **1a** does not show any reactivity against electrophile reagents such as the nitronium ion.

It may be concluded from points a–d that, although compound **2a** has somewhat more affinity toward electrophilic attack than **1a**, there is not any thermodynamic reason that explains why compound **1a** does not show any reactivity under electrophilic reaction conditions. This is an indication that there would be kinetic hindrances for this kind of reaction. In any case, it is not very surprising because relative stabilities of the products in aromatic electrophilic substitutions are determined by the rates at which they are formed.[25]

Conclusions

We have found that 1,7-dimethyl derivative **2a** reacts with electrophiles to give its 6-substituted derivatives while 1,5-dimethyl isomer **1a** does not react under the same experimental conditions. The demethylated compound **1e** suffers diazonium coupling, but there is no evidence whether the reaction only goes through 1*H*,7*H* tautomer **2e**. The ab initio study of these molecules shows the difference found in their reactivity is not clearly due to thermodynamic aspects but kinetics, although the former suggest a lower reactivity of **1a**. Theoretical calculations using the STO-3G* basis set are in good agreement with the experimental results of **1a** and **2a**, indicating this basis set is adequate to study such complex molecules, including sulfur hypervalent atoms.

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Supplementary Material Available: Coordinates, anisotropic thermal parameters, experimental bond distances, bond angles, and torsion angles, possible hydrogen bonds and short intermolecular contacts, obtained by X-ray, and perspective view of **1a**, projection of structure **1a** along *A* axis, HOMO of compounds **1a**, **2a**, **1d**, **2d**, **1e**, and **2e**, and LUMO and 55th and 54th MO of compounds **1a** and **2a** (9 pages). Ordering information is given on any current masthead page.

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[24] Roberts, J. D.; Stewart, R.; Caserio, M. C. *Organic Chemistry*; W. A. Benjamin: Menlo Park, CA, 1971; p 569.

[25] March, J. *Advances in Organic Chemistry: Reactions, Mechanism and Structure*: McGraw-Hill Inc.: London, 1979; p 453.