

Hydrophobicity and Structure of 1,2,4-Triazole Derivatives Bearing 1-Carbamoyl and 3-Sulfonyl Groups

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Various 3-sulfonyl-1,2,4-triazole-1-carboxamides (**5a**–**h**) were synthesized and their hydrophobicities were evaluated from their retention time in reversed-phase HPLC chromatography. Although the compounds have rather complex structures, a good linear relationship was observed between log k' of these compounds derived from the retention time of HPLC and log P_H for water–hexadecane partition coefficients of related alcohols. In regards with the rotation about the O_2S–C(ester part) single bond, the preference for a *gauche* conformer relative to the *anti* form was revealed by both X-ray structural analysis of **5a** and calculations at the AM1 level. In this conformation, substituents are arrayed to have the largest separation between the hydrophilic and hydrophobic parts. This can be rationalized as the primary reason for the good linearity.

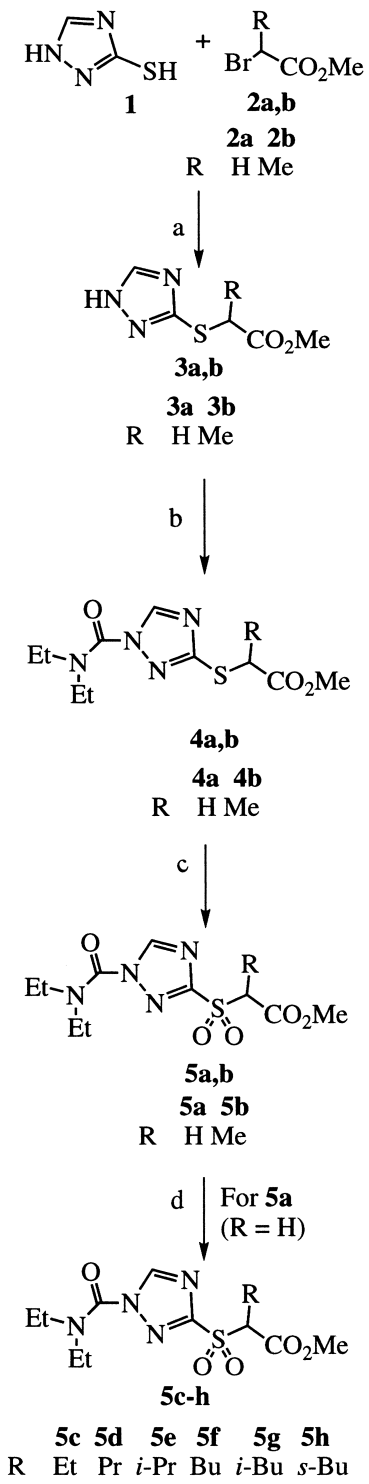
The unique properties of 1,2,4-triazole derivatives make them an interesting group of compounds from the viewpoint of theoretical and industrial chemistry.[1] Various 1,2,4-triazoles have commercial applications as herbicides, defoliants, photographic reagents, rubber chemicals, and polymer components. Of these 1,2,4-triazoles, those having a tertiary carbamoyl group on a nuclear nitrogen have been found to exhibit particularly high herbicidal activities and excellent crop selectivity.[2] The degree of hydrophobicity has often been found to be a delicate factor in altering the activity of biologically active molecules. Thus, hydrophobicity has been regarded as an essential parameter in quantitative structure–activity relationship (QSAR) analysis,[3] which is a frequently used method to establish quantitative relationships between the chemical structure and the bioactivity of certain groups of compounds.[4] Various hydrophobic parameters (usually expressed as the logarithm of partition coefficients, log k_i for 50 organic compounds in the solvent systems of higher alcohols and water, log P_{oct} for octanol–water, and log P_H for water–hexadecane) have been proposed so far.[5] Arising from our interest in 1,2,4-triazole herbicides, we have carried out a systematic examination of the hydrophobicities of a series of 3-sulfonyl-1,2,4-triazole-1-carboxamides. In this paper, we describe the structural features of these compounds in terms of their hydrophobicity evaluated from retention time in HPLC chromatography.

Results and Discussion

Synthesis of Substrates. All of the 1,2,4-triazole derivatives (**5a**–**h**) were prepared by the procedure outlined in Scheme 1.[2a,b] The reaction of 3-mercapto-1,2,4-1*H*-triazole (**1**) with various α-bromo carboxylic esters **2a,b** afforded the corresponding sulfides **3a,b**, which by treatment with diethylcarbamoyl chloride gave 2-(1-diethylcarbamoyl-1,2,4-triazole-3-ylthio)acetic esters **4a,b**. Oxidation of the triazoles **4a,b** with *m*CPBA gave the sulfonyl derivatives **5a,b**. Alkylation of **5a** with alkyl iodides afforded the corresponding triazole derivatives **5c**–**h**. Although the carbonylation of **3a,b** could give rise to three regioisomers as 1-, 2-, and 4-substituted derivatives, the 1-substituted derivative was obtained as the major product after separation of the crude product by column chromatography. Tentative regioisomeric assignments of **5a,b** were carried out by ^{1}H NMR, in which the ring proton at the 5-position of **5a,b** appeared at δ 8.8–9.0. It has been reported that the ring proton at the 5-position has a tendency to appear at lower field (δ 8.9) for the 1-carbamoyl derivative compared with those of the other isomers (2-substituted derivative: δ 8.0, 4-substituted derivative: δ 8.5).[6] The difference has been attributed to the magnetic deshielding anisotropy caused by the carbonyl group in the carbamoyl moiety.

Evaluation of Hydrophobicity by Means of a Chromatographic Method. It has been demonstrated that the hydrophobic parameters, log P, for various organic compounds are highly correlated to the retention times in chromatography on silica gel, cellulose plates, and HPLC.[7–9] The hydrophobicities for the triazoles described here were evaluated as the log k' values (logarithm of capacity factors) derived from the retention time in reversed-phase HPLC.[7c,e] The capacity factor is derived from

$$k' = (t_r - t_0) / t_0 \quad (1)$$



Scheme 1. Reagents and conditions: (a) **2a,b**, K_2CO_3, MeCN, reflux. (b) Et_2NCOCl, K_2CO_3, MeCN, 50–60 °C. (c) *m*CPBA, $CHCl_3$, 0 °C. (d) RI, NaH, DMF, rt.

where t_r is the retention time of the examined sample (the solute) and t_0 is the solvent front.

The hydrophobic parameters, log P_{calc}, were calculated on a personal computer using the "SciLogP" software developed by SCIVISION Co.[10] The experimental log k' values and the calculated log P_{calc} values for **5a**–**h** along with the water-hexadecane partition coefficients (log P_H) for water and related alcohols (ROH), where the R group is common, are summarized in Table 1.[2b,c,5c] Linear relationships were observed between log k' and log P_{calc} for **5a**–**h** (log $k' = 0.25 \log P_{calc} + 0.22$, $r^2 = 0.957$) and between log k' for **5b**–**h** and log P_H for related alcohols (ROH) (log $k' = 0.14 \log P_H + 0.81$, $r^2 = 0.992$), as shown in Fig. 1 and Fig. 2, respectively.

The linearity in Fig. 1 indicates that the hydrophobic properties of **5a**–**h** are highly related to retention time in reversed-phase HPLC. In Fig. 2, there can be observed a very good linear relationship between the log k' values of **5b**–**h** in HPLC and the water–hexadecane partition coefficients (log P_H) of aliphatic alcohols (ROH). These results indicate that practically only the properties of the R moieties are essential for establishing the hydrophobic tendency of the whole molecule of compounds **5b**–**h**, although there is a possibility for the complexity of the remaining part to alter the hydrophobicities. That is, as the molecule becomes complex, more conformations (which should vary in hydrophobicities) could arise. However, the behavior of these R groups is the same as that of the R group for simple alcohols (ROH).

In reversed-phase chromatography, the retention of a solute (S), i.e., the triazole derivatives, is viewed as the reversible association of the solute with the octadesyl functions (L) at the chromatographic surface, to form the complex (SL). Solute retention is governed by the average value of the contact surface area arising from the plurality of such binding configurations.[7c,f] The capacity factor (k') is related to the equilibrium constant (K) for the distribution of the solute between the bulk mobile phase and the stationary phase by

$$k' = K\varphi, \tag{2}$$

where φ is the phase ratio of the column. The energetics of retention are determined by the standard free energy change (ΔG°) associated with solute transfer from the mobile phase to the stationary phase as

$$\Delta G^\circ = -RT \ln K. \tag{3}$$

The relative free energy ($\delta\Delta G_{ret}$) of partition is derived from

$$\begin{aligned}\delta\Delta G_{ret} &= -RT \ln (K_R/K_S) \\ &= -RT [\ln (V_e - V_0)_R - \ln(V_e - V_0)_S],\end{aligned} \tag{4}$$

where K_R/K_S is the equilibrium constant relative to that of the standard compound **5a** (K_S), V_e: elution volume, V_0: column volume in HPLC. The values of $V_e - V_0$ are evaluated from the corresponding retention time t_r and t_0. Combining Eqs. 2 and 4 yields

$$\delta\Delta G_{ret} = -RT \ln (k'_R/k'_S) = -2.303\, RT\, (\delta \log k'), \tag{5}$$

where k'_R/k'_S is the capacity factor relative to that of the standard compound **5a** and $\delta \log k'$ is the difference in the log k' values with that of **5a**. The relative free energy values of partition ($\delta\Delta G_{ret}$) are summarized in Table 1. As an inevitable consequence, good linear relationships were observed between the

Table 1. Hydrophobicity log k' and Related Partition Coefficients log P_{calc} and log P_H.

Compound Substituent	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**
(R)	H	Me	Et	Pr	*i*-Pr	Bu	*i*-Bu	*s*-Bu
log k'[a]	0.36	0.41	0.49	0.58	0.56	0.69	0.68	0.66
$\delta\Delta G_{ret}$[b]	0.00	−0.29	−0.74	−1.26	−1.14	−1.88	−1.83	−1.71
log P_{calc}[c]	0.52	0.77	1.10	1.58	1.54	1.91	1.73	1.66
log P_H[d]	(−4.38)[e]	−2.82	−2.19	−1.46	−1.66	−0.86	−0.90	−1.05

a) Values of log k' were derived from retention time of reversed-phase HPLC analysis.[2b] b) Values $\delta\Delta G_{ret}$ are relative to that of **5a**. The values of $\delta\Delta G_{ret}$ (kJ/mol) at 298 K were derived from log k' values. c) Values of log P_{calc} were calculated on a personal computer using the "SciLogP" software developed by SCIVISION Co.[10] d) Values of log P_H are the data of related alcohols (ROH), which have been reported.[5c] e) Value for H_2O.

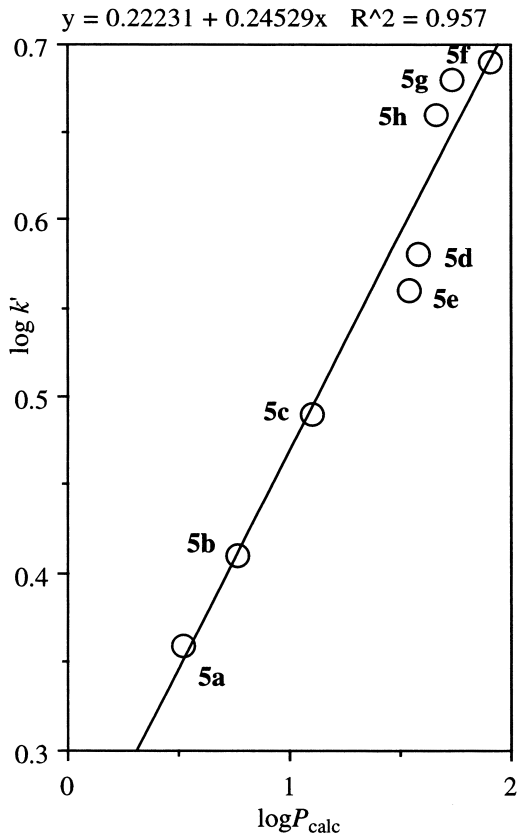


Fig. 1. Hydrophobicity (log k') vs the calculated partition coefficient log P_{calc}. Numbering (**5a–h**) indicates the corresponding compounds.

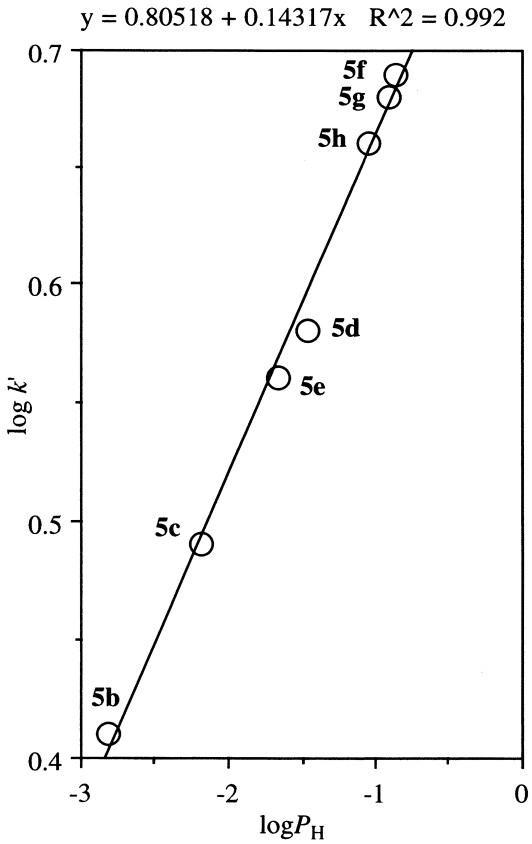


Fig. 2. Hydrophobicity (log k') vs the partition coefficient log P_H. Numbering (**5b–h**) indicates the corresponding compounds.

experimental $\delta\Delta G_{ret}$ values and log P_{calc} for **5a–h** ($\delta\Delta G_{ret} = -1.40 \log P_{calc} + 0.78$, $r^2 = 0.957$) and between $\delta\Delta G_{ret}$ for **5b–h** and log P_H for related alcohols (ROH) ($\delta\Delta G_{ret} = -0.82 \log P_H - 2.54$, $r^2 = 0.993$).

The linearity between $\delta\Delta G_{ret}$ and log P_H indicates that the free energy of the partition of **5b–h** in HPLC is related to the water–hexadecane partition coefficients of the aliphatic alcohols (ROH). Even though the molecular structure becomes complex, the hydrophobic effect of the aliphatic side chain in **5b–h** is similar to that of the alkyl group in simple alcohols (ROH) from the point of view of the free energy of partition.

Structural Considerations of Substituents in the Triazole Derivatives. The structure–activity relationship is a useful methodology in searching for biologically active compounds. Conformation as well as the skeleton of the compound influences this activity. Thus, in order to gain insight concerning stable conformations, we carried out X-ray crystal structure analysis of **5a**. An Ortep drawing is shown in Fig. 3. Selected interatomic distances and dihedral angles around the sulfur atom are summarized in Table 2. A conformational analysis of **5a** in which semiempirical optimization was carried out at the AM1 level of theory implemented in Chem 3D Pro. was also conducted, as described below (Fig. 4).[11]

According to AM1 calculations for the carbamoyl part of

Table 2. Selected Interatomic Distances and Dihedral Angles

X-ray analysis		AM1 calculation[a)]	
		gauche-1 form	*anti* form
Interatomic distance			
O(3)···S(1)	3.120(2)	3.343	3.828
O(3)···C(1)	2.976(3)	3.123	4.847
O(1)···C(4)	3.088(3)	3.097	3.047
N(1)–C(6)	1.458(2)	1.458	1.456
N(4)–C(6)	1.329(2)	1.378	1.378
N(4)–C(7)	1.481(3)	1.456	1.447
Dihedral angle			
C(1)–S(1)–C(3)–C(4)	61.0(2)	67.2	157.7
S(1)–C(3)–C(4)–O(3)	−46.2(3)	−57.9	−137.0
O(1)–S(1)–C(1)–N(2)	−1.5(2)	15.3	−17.3
O(1)–S(1)–C(3)–C(4)	−53.9(2)	−48.7	43.9
O(3)–C(4)–O(4)–C(5)	−4.7(4)	1.6	1.9
O(5)–C(6)–N(1)–C(2)	48.1(3)	25.5	−12.5
N(2)–C(1)–S(1)–C(3)	−117.8(2)	−99.4	−131.9

a) The AM1 calculations were made with Chem 3D Pro.[11c]

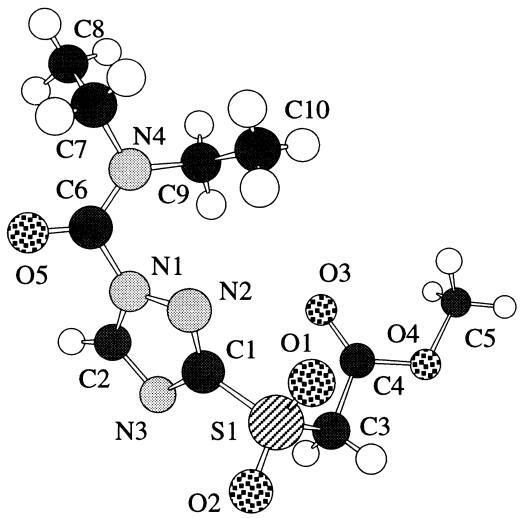
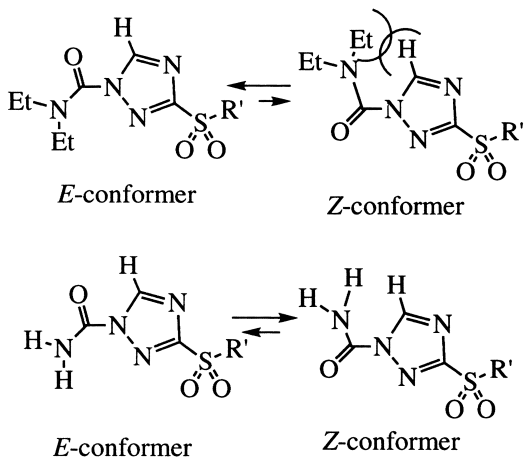
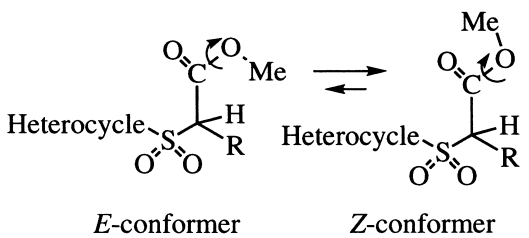


Fig. 3. Crystal structure of **5a** by X-ray analysis.



Scheme 2.

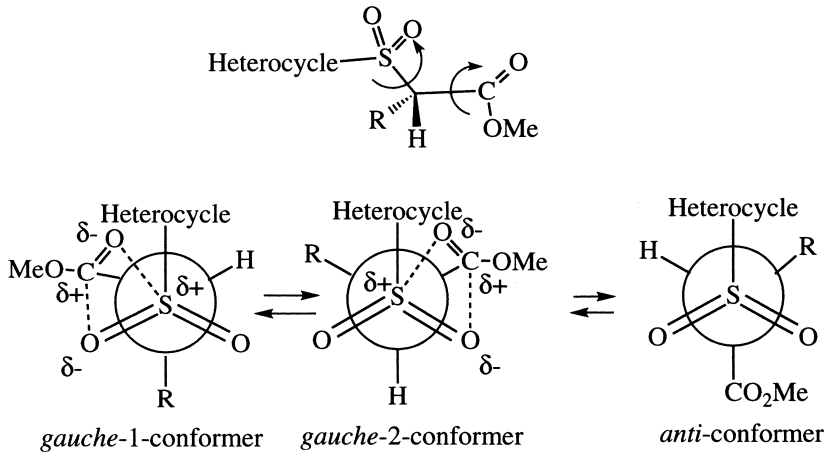


Scheme 3.

the triazole ring of **5a**, the *E*-conformer, with regards to rotation about the Et_2NCO–N(ring) single bond, is considered to be more stable than the *Z*-conformer due to unfavorable Et_2N/CH(ring) interactions in the *Z*-form, as shown in Scheme 2. On the other hand, the *Z*-conformer was preferred over the *E*-form in the corresponding primary NH_2CO derivative. An X-ray structural analysis of **5a** revealed that it assumes a conformation where the carbamoyl group is of *E*-geometry, as shown in Fig. 3, in full agreement with calculations. The dihedral angle [O(5)–C(6)–N(1)–C(2)] was 48.1°. The conformation was also consistent with that speculated from NMR analysis, as described above.

As for the sulfonyl moiety at the 3 position on the other side of the heterocycle, the *Z*-conformer, with regards to rotation about the CO–OMe single bond of the methyl ester part, is expected to be strongly favorable compared with the *E*-isomer, as shown in Scheme 3, since in the parent methyl formate, the *Z*-conformer is 20–25 kJ/mol (5–6 kcal/mol) more stable than the *E*-form with a barrier to rotation of 42–45 kJ/mol (10–13 kcal/mol).[12] In the crystal structure, as shown in Fig. 3, the conformation of the methyl ester moiety of **5a** was confirmed to be of *Z*-form. The dihedral angle [O(3)–C(4)–O(4)–C(5)] was −4.7(4)°, showing that the ester part is practically planar.

As for rotation about the O_2S–C(ester part) bond, there are three possible staggered conformers, two (*gauche*-1 and



Scheme 4.

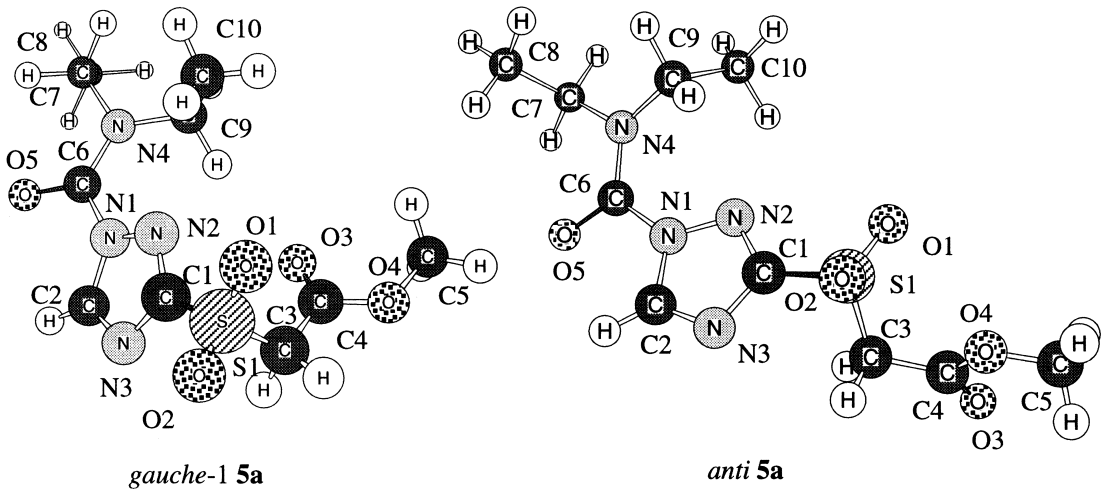


Fig. 4. Molecular structure of **5a** simulated by AM1 level calculations.

gauche-2) of which the ester part is *gauche* to the ring, and one (*anti*), with the ester part anti to the heterocyclic ring, as shown in Scheme 4. In the CH_2CO_2Me derivative, the *gauche*-1 and *gauche*-2 conformers are degenerate.

According to the structural parameters derived from X-ray analysis (Table 2), the interatomic distance between the carbonyl carbon (C4) and a sulfone oxygen (O1) is 3.088(3) Å, which is less than the sum of van der Waals radii of 3.22 Å. That between the carbonyl oxygen (O3) and sulfur (S1) is 3.120(2) Å, which is also slightly shorter than the sum of the van der Waals radii of 3.32 Å. Furthermore, the distance between the carbonyl oxygen (O3) and a carbon (C1) in the heterocycle is 2.976(3) Å. This is also less than the sum of van der Waals radii. The dihedral angles around the sulfone and ester moieties are $-46.2(3)°$ for S(1)–C(3)–C(4)–O(3) and $-53.9(2)°$ for O(1)–S(1)–C(3)–C(4), which indicate the partial presence of $\pi^*CO/\sigma C–S$ and $\pi CO/\sigma^*C–S$ orbital interactions.[13] All of these attractive interactions may contribute to the stabilization of the *gauche* conformer, as shown in Scheme 4. Furthermore, in the IR spectrum of **5a** in $CHCl_3$, there is observed a carbonyl stretching band at 1749.6 cm^{-1} which could be assigned to the *gauche* conformer. In the ^{13}C NMR spectrum of **5a** in $CDCl_3$, the carbonyl carbon of the ester appears at δ 162.1, which is also in agreement with the *gauche* conformation.[13b] Since it is expected that the preference for the *gauche*-form relative to the *anti*-form results in an increase of hydrophobic character (ΔG_{ret}), we believe that the predominant presence of the gauche conformers is responsible for the hydrophobic trend of our series of **5**.

It has been demonstrated by Olivato and his co-workers that some β-carbonyl sulfoxides, $XCOCH_2SO_2R$, prefer a *gauche* conformation between the C=O and CH_2S bonds.[13] The stability of the *gauche* conformers has been ascribed to electrostatic and charge transfer interactions between oppositely charged atoms, i.e., O (of SO_2) to C (of C=O) and/or O (of C=O) to S (of SO_2), along with hyperconjugation.[13b]

Figure 4 shows the AM1 optimized structures of *gauche*-1 and *anti* for **5a**. The calculated geometry of the *gauche*-1 conformer of **5a** was very close to that determined by X-ray structural analysis.

For most of compounds **5**, one of the *gauche* conformers was found to be ca. 4 kJ/mol (1 kcal/mol) more stable than the *anti* form. Thus, the linear relationship depicted in Figs. 1 and 2 can be attributed to the predominance of one of the *gauche*

conformations.

In summary, we have observed for a series of 3-sulfonyl-1,2,4-triazole-1-carboxamides (**5a–h**), that the hydrophobicity (log k'), evaluated from their retention time in reversed-phase HPLC chromatography, is highly correlated with log P_H, water–hexadecane partition coefficients of related alcohols. We could rationalize this result by assuming that the predominant conformer of these compounds is a common gauche conformation with regards to rotation about the O_2S–C(ester part) single bond. X-ray analysis of **5a** and AM1 calculations were supportive of our assumptions.

Experimental

NMR spectra were recorded on JEOL JNM-A500 and JNM-LA500 NMR instruments, and ^{1}H and ^{13}C NMR spectra were observed in $CDCl_3$ solutions with TMS as an internal reference. IR spectra were recorded on a SHIMADZU FT IR-4200 instrument and MS spectra were recorded on a JMS-SX 102A instrument. FAB spectra were obtained by using glycerol as a matrix. The melting points were determined on a Yanagimoto or a Büchi melting-point apparatus.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-acetate (5a). An acetonitrile solution (90 mL) of 3-mercapto-1,2,4-1*H*-triazole (**1**, 3.04 g, 30.1 mmol), methyl bromoacetate (**2a**, 2.85 mL, 30.1 mmol), and potassium carbonate (3.11 g, 22.5 mmol) were refluxed for 2 h and then cooled to room temperature. Potassium carbonate (3.11 g, 22.5 mmol) and diethylcarbamoyl chloride (4.2 mL, 33.3 mmol) were then added to the mixture, followed by stirring at 50–60 °C for 1.5 h. The resulting mixture was added to a 1 M hydrochloric acid solution (100 mL) and extracted with diethyl ether (40 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/2) to give **4a** as a white solid (5.85 g, 71.4%): mp 90–90.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 6.8 Hz, 6H), 3.59 (q, J = 6.8 Hz, 4H), 3.75 (s, 3H), 3.93 (s, 2H), 8.74 (s, 1H).

To prepare **5a**, **4a** was oxidized without further purification by the following procedure. To a chloroform solution (20 mL) of **4a** (1.08 g, 3.96 mmol) was added *m*CPBA (70%, 3.65 g, 14.8 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for an additional 6 h. To the resulting mixture was added a saturated sodium hydrogen carbonate aqueous solution (50 mL), and then the organic layer was separated. The aqueous layer was extracted with chloroform (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/3) to give **5a** as a white solid (1.08 g, 89.6%): mp 58.5–59.0 °C; IR ($CHCl_3$) 1749.6, 1714.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.3 Hz, 6H), 3.61 (q, J = 7.3 Hz, 4H), 3.75 (s, 3H), 4.44 (s, 2H), 9.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.36, 14.04, 44.19 (×2), 53.43, 58.38, 147.59, 148.10, 161.08, 162.17. HR-FABMS Found: *m*/*z* 305.0918. Calcd for $C_{10}H_{17}N_4O_5S$: M + H, 305.0920.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-propionate (5b). By a procedure similar to that for **5a**, The treatment of **1** (2.53 g, 25.0 mmol) with methyl 2-bromopropionate (4.18 g, 25.0 mmol) and potassium carbonate (2.59 g, 18.7 mmol), followed by the treatment with potassium carbonate (2.59 g, 18.7 mmol) and diethylcarbamoyl chloride (3.48 mL, 27.6 mmol) gave rise to methyl 2-(1-diethylcarbamoyl-1,2,4-triazole-3-ylthio)propionate **4b**. Column chromatographic purification (silica gel, ethyl acetate/hexane = 1/3) gave **4b** as a white solid (5.38 g, 75.2%): mp 48.5–49.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.3 Hz, 6H), 1.65 (d, J = 7.3 Hz, 3H), 3.64 (q, J = 7.3 Hz, 4H), 3.74 (s, 3H), 4.39 (q, J = 7.3 Hz, 1H), 8.75 (s, 1H).

To prepare **5b**, **4b** was oxidized without further purification by the following procedure. To a chloroform solution (20 mL) of **4b** (0.859 g, 3.0 mmol) was added *m*CPBA (70%, 1.85 g, 7.5 mmol) at 0 °C. Ordinary work-up gave **5b** as a colorless oil (0.88 g, 92.1%): IR ($CHCl_3$) 1747.7, 1712.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.3 Hz, 6H), 1.73 (d, J = 7.3 Hz, 3H), 3.63 (q, J = 7.3 Hz, 4H), 3.75 (s, 3H), 4.19 (q, J = 7.3 Hz, 1H), 8.92 (s, 1H). HR-FABMS Found: *m*/*z* 319.1070. Calcd for $C_{11}H_{19}N_4O_5S$: M + H, 319.1076.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-butanoate (5c). To a suspension (1 mL) of sodium hydride (60%, 0.06 g, 1.50 mmol) in DMF was added a solution of methyl 2-(1-diethycarbamoyl-1,2,4-triazole-3-ylsulfonyl)acetate (**5a**, 0.295 g, 0.97 mmol) in the same solvent (2 mL) at 0 °C under an argon atmosphere; the resulting mixture was stirred for 30 min. To the resulting suspension was added ethyl iodide (0.08 mL, 0.98 mmol), and then the mixture was stirred for 3 h with gradual warming to room temperature. To the reaction mixture was added a 1M hydrochloric acid solution (15 mL); the resulting mixture was extracted with diethyl ether (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/2) to give **5c** as a colorless oil (0.16 g, 49.6%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3H), 1.32 (t, J = 7.0 Hz, 6H), 2.26 (m, 2H), 3.60 (q, J = 7.0 Hz, 4H), 3.76 (s, 3H), 4.16 (t, J = 7.6 Hz, 1H), 8.90 (s, 1H). HR-FABMS Found: *m*/*z* 333.1237. Calcd for $C_{12}H_{21}N_4O_5S$: M + H, 333.1233.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-pentanoate (5d). Following the procedure for **5c**, the reaction of **5a** (0.761 g, 2.50 mmol) with propyl iodide (0.245 mL, 2.51 mmol) and sodium hydride (60%, 0.1 g, 2.50 mmol) in DMF gave **5d** as a white solid (0.26 g, 30.0%) after column chromatographic purification (silica gel, ethyl acetate/hexane = 1/4): mp 77.0–77.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.0 Hz, 3H), 1.29 (m, 2H), 1.31 (t, J = 7.0 Hz, 6H), 2.07 (m, 2H), 3.60 (q, J = 7.0 Hz, 4H), 3.75 (s, 3H), 4.24 (t, J = 7.5 Hz, 1H), 8.90 (s, 1H). HR-FABMS Found: *m*/*z*, 347.1370. Calcd for $C_{13}H_{23}N_4O_5S$: M + H, 347.1389.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-3-methylbutanoate (5e). Following the procedure for **5c**, the reaction of **5a** (0.761 g, 2.50 mmol) with isopropyl iodide (0.25 mL, 2.5 mmol) and sodium hydride (60%, 0.1 g, 2.50 mmol) in DMF gave **5e** as a pale-yellow solid (0.34 g, 39.3%) after column-chromatographic purification (silica gel, ethyl acetate/hexane = 2/5): mp 79–80 °C; IR ($CHCl_3$) 1743.8, 1712.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.31 (t, J = 7.0 Hz, 6H), 2.69 (m, 1H), 3.60 (q, J = 7.0 Hz, 4H), 3.74 (s, 3H), 4.17 (d, J = 7.5 Hz, 1H), 8.89 (s, 1H). HR-FABMS Found: *m*/*z* 347.1388. Calcd for $C_{13}H_{23}N_4O_5S$: M + H, 347.1389.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-hexanoate (5f). Following the procedure for **5c**, the reaction of **5a** (0.608 g, 2.00 mmol) with butyl iodide (0.23 mL, 2.02 mmol) and sodium hydride (60%, 0.08 g, 2.0 mmol) in DMF gave **5d** as a

colorless oil (0.500 g, 69.4%) after column chromatographic purification (silica gel, ethyl acetate/hexane = 2/5): IR ($CHCl_3$) 1745.7, 1714.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3H), 1.20–1.40 (m, 10H), 2.10–2.20 (m, 2H), 3.45–3.60 (m, 4H), 3.76 (s, 3H), 4.20–4.30 (m, 1H), 8.93 (s, 1H). HR-FABMS Found: m/z 361.1550. Calcd for $C_{14}H_{25}N_4O_5S$: M + H, 361.1546.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-4-methylpentanoate (5g). Following the procedure for **5c**, the reaction of **5a** (0.761 g, 2.50 mmol) with isobutyl iodide (0.29 mL, 2.52 mmol) and sodium hydride (60%, 0.1 g, 2.50 mmol) in DMF gave **5d** as a white solid (0.58 g, 64.4%) after column chromatographic purification (silica gel, ethyl acetate/hexane = 2/5): mp 65–66 °C; IR ($CHCl_3$) 1743.8, 1714.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 6.2 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 1.20–1.30 (m, 1H), 1.31 (t, J = 7.0 Hz, 6H), 1.96–2.12 (m, 2H), 3.60 (q, J = 7.0 Hz, 4H), 3.75 (s, 3H), 4.30 (dd, J = 4.6 and 11.3 Hz, 1H), 8.90 (s, 1H). HR-FABMS Found: m/z 361.1529. Calcd for $C_{14}H_{25}N_4O_5S$: M + H, 361.1546.

Methyl 2-(1-Diethylcarbamoyl-1,2,4-triazole-3-ylsulfonyl)-3-methylpentanoate (5h). Following the procedure for **5c**, the reaction of **5a** (1.22 g, 4.00 mmol) with *s*-butyl iodide (0.48 mL, 4.03 mmol) and sodium hydride (60%, 0.16 g, 4.0 mmol) in DMF gave **5d** as a colorless oil (0.365 g, 25.3%) after column chromatographic purification (silica gel, ethyl acetate/hexane = 2/5): ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 and 0.93 (each t, J = 7.4 Hz, total 3H), 1.23 and 1.32 (each d, J = 6.8, total 3H), 1.32 (t, J = 7.1Hz, 6H), 1.45–1.73 (m, 2H), 2.47 (m, 1H), 3.60 (q, J = 7.1 Hz, 4H), 3.73 and 3.74 (each s, total 3H), 4.25 and 4.36 (each d, J = 8.0 and 5.6 Hz, total 1H), 8.90 and 8.90 (each s, total 1H). HR-FABMS Found: m/z 361.1545. Calcd for $C_{14}H_{25}N_4O_5S$: M + H, 361.1546.

X-ray Crystallographic Analysis.[14,15] Crystallographic data were collected on a Mac Science DIP2030 imaging-plate diffractometer employing graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å). The unit-cell parameters were determined by auto-indexing several images in each data set separately with the DENZO program. For each data set, rotation images were collected in 3 ° increments with exposures of 21 min per frame, covering a total of 60 frames (rotation of 180 ° about ϕ). Oscillation images were processed by using the SCALEPACK program. The structures were solved by direct methods using the teXsan structure-solving program package. All non-hydrogen atoms were refined anisotropically by full-matrix least squares. Hydrogen atoms were placed in calculated positions and refined isotropically.

Crystal data for **5a**—colorless plates; $C_{10}H_{16}N_4O_5S$, M_r = 304.32, monoclinic, space group $P2_1/c$ (No.14); a = 8.5530(3) Å, b = 8.7940(3) Å, c = 18.9780(7) Å, β = 92.197(2)°, V = 1426.38(8) $Å^3$, Z = 4, D_c = 1.492 g cm^{-3}, T = 298 K. Final R = 0.0582 (R_w= 0.1073) for 2957 reflections out of 3416 collected (181 parameters) with $I > 2\sigma(I)$. GOF = 1.204.

Determination of the Capacity Factor k' and Relative Free Energy of Partition $\delta\Delta G_{ret}$. HPLC measurements were performed on a Shimadzu Model LC-6A liquid chromatogram, equipped with a C-R5A recorder and a SOD-10AV UV detector. The column was an ODS reversed-phase column (150 × 4.6 mm, Tosoh ODS 120T). The mobile phase (1.0 mL/min) was constituted with acetonitrile–water (60:40). The capacity factor (k') was used as a hydrophobicity index. The retention time of reversed-phase HPLC was used to calculate the capacity factor (k') as follows: $k' = (t_r - t_0) / t_0$, where t_r was retention time of the test compound and t_0 was the solvent front.

The relative free energy of partition was derived from the following equation: $\delta\Delta G_{ret} = -2.303RT(\delta \log k') = -2.303RT[(\log k')_R - (\log k')_0]$. The values of $[(\log k')_R - (\log k')_0]$ were obtained with **5a** as the standard compound. The log k' values and the relative free energy of partition ($\delta\Delta G_{ret}$) are summarized in Table 1.

Calculation of Hydrophobic Parameter log P_{calc}. The values of log P_{calc} were calculated on a personal computer using the "SciLogP" software developed by SCIVISION Co.[10] The values are summarized in Table 1.

Semiempirical Geometry Optimization. The AM1 calculations were made with Chem 3D Pro Ver. 5.0.[11c]

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