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Relationships between the Electrophilicity Index and Experimental Rate Coefficients for the Aminolysis of Thiolcarbonates and Dithiocarbonates

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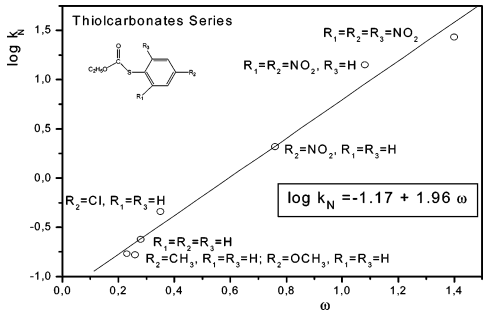

Quantitative relationships are reported between the global electrophilicity index and the experimental rate coefficients for the reactions of thiolcarbonates and dithiocarbonates with piperidine. The validated scale of electrophilicity is then used to rationalize the reaction mechanisms of these systems. This scale also makes it possible to predict both rate coefficients and Hammett substituent constants for a series of systems that have not been experimentally evaluated to date.

Introduction

Although the kinetics of aminolysis of oxyesters and oxycarbonates have been extensively studied and their mechanisms are well-established,[1−4] those for the reactions of the thio analogues have received less attention. From the theoretical point of view, the latter systems have also been less investigated compared to their carbonyl analogues.[5−7] Most of these reactions can be described by a nucleophilic attack at the C═X (X = S,O) group of the substrates, which are in most cases the highest electrophilic site. Depending on the nature of the electrophile/nucleophile pair, two general mechanisms are possible. In the former, the interaction of the nucleophile with the electrophilic carbon may lead to the formation of a tetrahedral intermediate, $T^{\pm}$, from which the leaving group detaches. This mechanism is usually referred to as stepwise.[1,2−8,9] Another possibility is the concerted pathway,[8,9] where the nucleophilic attack at

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(1) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc*. **1974**, *96*, 7018.
(2) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970.
(3) (a) Fife, T. H.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4194. (b) Brunelle, D. J. *Tetrahedron Lett*. **1982**, *23*, 1739. (c) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611. (d) Castro, E. A.; Ibáñez, F.; Lagos, S.; Schick, M.; Santos, J. G. *J. Org. Chem.* **1992**, *57*, 2691. (e) Castro, E. A.; Andujar, M.; Campodónico, P.; Santos, J. G. *Int. J. Chem. Kinet*. **2002**, *34*, 309. (f) Castro, E. A.; Aliaga, M.; Campodónico, P.; Santos, J. G. *J. Org. Chem*. **2002**, *67*, 8911. (g) Castro, E. A.; Andujar, M.; Toro, A.; Santos, J. G. *J. Org. Chem*. **2003**, *68*, 3608. (h) Castro, E. A.; Campodónico, P.; Toro, A.; Santos, J. G. *J. Org. Chem*. **2003**, *68*, 5930.
(4) (a) Kovach, I. M.; Belz, M.; Larson, M.; Rousy, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7360. (b) Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1987**, 159. (c) Yoh, S. D.; Kang, J. K.; Kim, S. H. *Tetrahedron* **1988**, *44*, 2167. (d) Knowlton, R. C.; Byers, L. D. *J. Org. Chem*. **1988**, *53*, 3862. (e) Castro, E. A.; Ureta, C. *J. Org. Chem*. **1990**, *55*, 1676. (f) Koh, H. J.; Lee, H. C.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 839.
(5) Contreras, R.; Andrés, J.; Safont, V. S.; Campodónico, P.; Santos, J. G. *J. Phys. Chem. A* **2003**, *107*, 5588.
(6) Campodónico, P.; Santos, J. G.; Andrés, J.; Contreras, R. *J. Phys. Org. Chem*. **2004**, *17*, 273.
(7) Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B. S. *J. Am. Chem. Soc*. **2000**, *122*, 11162.
(8) Williams A. *Concerted Organic and Bio-Organic Mechanism*; CRC Press: Boca Raton, FL, 2000; Chapter 4 and references therein.
(9) (a) Johnson, S. L. *Adv. Phys. Org. Chem*. **1967**, *5*, 237. (b) Stefanidis, D.; Cho, S.; Dhe-Paganon, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1993**, *115*, 1650.

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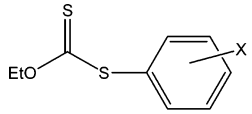
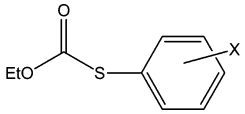
TABLE 1. Global Electrophilicity (in Electronvolts) of Dithiocarbonates and Thiolcarbonates, Evaluated Using Eq 3, at the HF/6-311G (d,p) Level of Theory

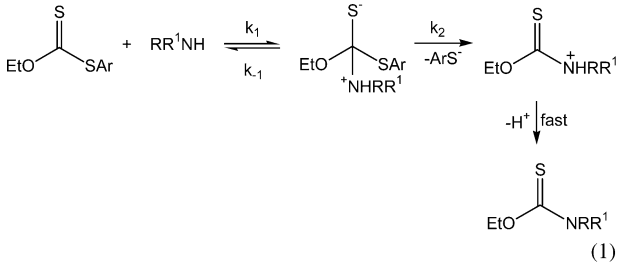




dithiocarbonate			thiolcarbonate		
	X =	ω		X =	ω
1	2,4,6-triNO_2	1.39	**20**	2,4,6-triNO_2	1.40
2	2,4-diNO_2	1.15	**21**	2,4-diNO_2	1.08
3	4-NO_2	0.92	**22**	4-NO_2	0.85
4	3-NO_2	0.84	**23**	3-NO_2	0.76
5	4-CN	0.74	**24**	4-CN	0.72
6	3-CN	0.68	**25**	3-CN	0.67
7	4-CO_2H	0.68	**26**	4-CO_2H	0.66
8	3-CO_2H	0.61	**27**	4-CF_3	0.61
9	4-CF_3	0.60	**28**	3-CO_2H	0.60
10	3-CF_3	0.55	**29**	3-CF_3	0.56
11	4-Cl	0.52	**30**	3-CH_3	0.38
12	3-Cl	0.50	**31**	4-Cl	0.35
13	H	0.46	**32**	3-NH_2	0.29
14	3-CH_3	0.45	**33**	H	0.28
15	4-CH_3	0.44	**34**	4-CH_3	0.26
16	3-OCH_3	0.42	**35**	4-OCH_3	0.23
17	4-OCH_3	0.41			
18	3-NH_2	0.38			
19	4-NH_2	0.36			

the electrophilic carbon occurs concertedly with the leaving group departure within a single step.

The kinetics of the reactions of several dithiocarbonates (**1**−**3**, **12**, **13**, **15**, and **17** in Table 1) with secondary alicyclic amines in water have been experimentally studied, and the reaction mechanisms have been proposed on the basis of Brønsted-type plots.[10] The analysis revealed the presence of an intermediate $T^{\pm}$, consistent with a stepwise mechanism. For the piperidine reaction, the rate-determining step is the nucleophilic attack of the amine.[10] On the other hand, the rate coefficients for the departure of the nucleofuge from the intermediates $T^{\pm}$ formed in the reactions with dithiocarbonates **12**, **13**, **15**, and **17** were not significantly different, probably because of the very similar basicities of the leaving groups involved.[10c] The reactions can be described by the mechanism shown in eq 1, where RR_1NH represents a secondary alicyclic amine.[10]



(1)

Applying the steady-state condition to the zwitterionic tetrahedral intermediate ($T^{\pm}$) in eq 1, we obtained eq 2, where k_N is the macroscopic rate coefficient for aminolysis:[10]

$$k_N = \frac{k_1 k_2}{k_{-1} + k_2} \qquad (2)$$

The curvature of the Brønsted plots can be explained by a change in the rate-limiting step from k_2, for amines of low basicity (where $k_{-1} \gg k_2$, i.e., $k_N = K_1 k_2$, where K_1 is the equilibrium constant for the first step) to k_1 for amines of high basicity ($k_{-1} \ll k_2$, i.e., $k_N = k_1$).[2,11,12]

It has been proposed that the reactions of secondary alicyclic amines with thiolcarbonates **20** and **21** in water proceed via a concerted mechanism.[13a,b] This proposal was based on the fact that linear Brønsted-type plots, with slopes $\beta = 0.56$ and $\beta = 0.48$, respectively, were found.[13a,b] The reactions of these amines with thiolcarbonates **22**, **31**, **33**, **34**, and **35**[13c,d] (see Table 1) in water are consistent with stepwise mechanisms, where breakdown to products of the intermediate $T^{\pm}$ is rate-determining.

On the other hand, Lee and co-workers studied the reactions of some of the above thiolcarbonates with benzylamines in acetonitrile at 45 °C. The failure of the reactivity−selectivity principle was interpreted to indicate a concerted mechanism for these reactions.[14] The same conclusion was reached by the same authors for the reactions of dithiocarbonates with anilines and *N*,*N*-dimethylanilines in acetonitrile at 30 °C.[15] The great instability of the hypothetical tetrahedral intermediate was attributed to the acetonitrile solvent.[14,15]

A useful classification of these processes may also be achieved on the basis of electronic structure information condensed in the form of reactivity indexes. Validated scales of electrophilicity/nucleophilicity[16−21] have proven to be a useful tool to rationalize the observed reaction mechanisms in related systems.[6] They may be further used to predict the degree of polar character at the transition state.[22,23] Within this framework, we have recently proposed a useful empirical rule, based on theoretical electrophilicity/nucleophilicity indexes, to rationalize the reaction mechanism for a series of carbonates with neutral and charged reagents of varying nucleophilicity.[6] This rule states that the greater the electrophilicity/nucleophilicity difference, the greater concerted character the reaction mechanism will possess. Conversely, a small electrophilicity/nucleophilicity gap will in general be associated with a stepwise reaction mechanism. Other attempts to relate electronic properties and reactions mechanisms have been reported.[20,21]

(10) (a) Castro, E. A.; Ibáñez, F.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1993**, *58*, 459. (b) Cabrera, M.; Castro, E. A.; Salas, M.; Santos, J. G.; Sepúlveda, P. *J. Org. Chem.* **1991**, *56*, 5324. (c) Castro, E. A.; Cubillos, M.; Ibáñez, F.; Moraga, I.; Santos, J. G. *J. Org. Chem.* **1993**, *58*, 5400.
(11) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.
(12) (a) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869. (b) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.
(13) (a) Castro, E. A.; Ibáñez, F.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1991**, *56*, 4819. (b) Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 30. (c) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 3572. (d) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 6342.
(14) Oh, H. K.; Lee, Y. H.; Lee, I. *Int. J. Chem. Kinet.* **2000**, *32*, 131.
(15) Oh, H. K.; Lee, J. Y.; Yun, J. H.; Park, Y. S.; Lee, I. *Int. J. Chem. Kinet.* **1998**, *30*, 419.
(16) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.
(17) Mayr, H.; Kempf, B.; Ofial, A. A. *Acc. Chem. Res.* **2003**, *36*, 66.
(18) Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *76*, 1540.
(19) Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1819.
(20) Pearson, R. G. *J. Org. Chem.* **1987**, *52*, 2131.
(21) Ritchie, C. D. *Can. J. Chem.* **1972**, *5*, 348.
(22) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523.
(23) Domingo, L. R.; Aurrel, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *48*, 4417.

In the present case, however, an additional simplification may be introduced, considering the reactions of several electrophiles with the same reference nucleophile (piperidine). In such a case, the effect of the nature of the nucleophile may be neglected, and the prediction of both rate coefficients and reaction mechanism may be described on the basis of an absolute scale of electrophilicity for the thiocarbonates derivatives. In this work, we present a theoretical scale of electrophilicity based on the Parr et al. definition of global electrophilicity[24] for a series of thiocarbonates derivatives. The electrophilicity numbers are then used to derive an empirical equation by comparing the global electrophilicity values with the experimental rate coefficients for the aminolysis of these compounds with piperidine. The resulting equation is then used to predict the rate coefficients for aminolysis of compounds not kinetically evaluated to date. A useful additional result is that the electrophilicity index may also be used to account for substituent effects,[25,26] in the form of a linear relationship between the global electrophilicity and Hammett substituent constants.[27]

Model Equations and Computational Details

The quantitative definition of electrophilicity is based on a second-order model for the change in electronic energy as a function of the change in the number of electrons, ΔN, at constant external potential $v(r)$, namely.[24,28,29] On the basis of this expression, Parr and co-workers[24] performed a simple variational calculation to obtain the global electrophilicity index $\omega = -\Delta E$. The resulting equation is:

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

which is expressed in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities are easily obtained from a finite difference method together with Koopman's theorem, in terms of the one electron energy level of the frontier molecular orbitals HOMO and LUMO,[24] namely, eqs 4 and 5, respectively. In general, Koopman's theorem yields a correct ordering of IPs as compared to the adiabatic approximation that evaluates this quantity from the total energy difference between the cation and the neutral species. The numbers are obviously different, but the ordering within a family of related compounds is essentially the same.[23]

$$\mu = \frac{\epsilon_H + \epsilon_L}{2} \tag{4}$$

$$\eta \cong \epsilon_L - \epsilon_H \tag{5}$$

With the μ and η values, the electrophilicity index was evaluated using eq 3. The global electrophilicity is not sensitive to solvent effects,[30] and therefore the gas-phase value suffices to establish an absolute hierarchy of the electron-accepting ability of these systems.

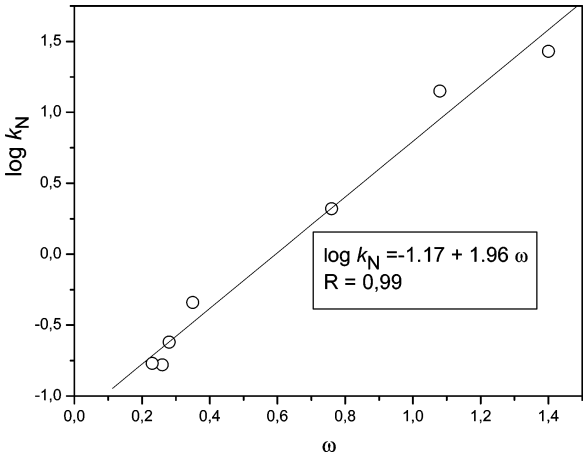


FIGURE 1. Comparison between the experimental nucleophilic rate coefficient, k_N, for the reactions of the thiolcarbonates series with piperidine and the electrophilicity index obtained at the HF/6-311G(d,p) level of theory.

Ab inito HF/6-311G (d,p) calculations were performed using the Gaussian 98 suite of programs[31] to evaluate the electronic quantities required to calculate the ground-state electrophilicity index for the series of thiocarbonates derivatives considered in the present study.

Results and Discussion

(a) Absolute Scale of Electrophilicity. Table 1 summarizes the global electrophilicity evaluated for a series of thiolcarbonates and dithiocarbonates. As in the case of carbonates previously reported,[6] the whole series may be arbitrarily ordered into three groups. A first series, group I, which we classify as strong electrophiles, shows electrophilicity numbers $\omega > 1.0$. The second series, group II, presenting electrophilicity numbers within the range $0.5 < \omega < 1.0$, is classified as moderate electrophiles, and those compounds possessing electrophilicity values $\omega < 0.5$, group III, are classified as marginal electrophiles. The theoretical scale was validated against the rate coefficient values reported by Castro and co-workers for the reactions of secondary alicyclic amines with thiolcarbonates and dithiocarbonates.[10,13] The comparisons are shown in Figures 1 and 2, respectively. The first comparison (regression coefficient $R = 0.990$) is carried out for thiolcarbonates **20**−**22**, **31**, **33**, **34**, and **35**, for which the kinetic information is available.[13] The second analysis ($R = 0.965$) is carried out for dithiocarbonates **2**, **3**, **11**, **13**, **15**, and **17**, which have been kinetically evaluated.[10] The little difference in electrophilicity between dithiocarbonate and thiolcarbonate series may be traced to the fact that the former

(24) Parr, R. G.; Szentpály, L. V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
(25) Domingo, L. R.; Pérez, P.; Contreras R. *J. Org. Chem.* **2003**, *68*, 6060.
(26) Hammett, L. P. *Physical Organic Chemistry; Reaction Rates, Equilibria, and Mechanism*, 2nd ed.; McGraw-Hill: New York, 1970.
(27) Hansch, C.; Leo, A.; Taft, W. *Chem. Rev.* **1991**, *91*, 165.
(28) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(29) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.
(30) Pérez, P.; Toro-Labbe, A.; Contreras, R. *J. Am. Chem. Soc.* **2001**, *123*, 5527.
(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision x.x; Gaussian, Inc.: Pittsburgh, PA, 1998.

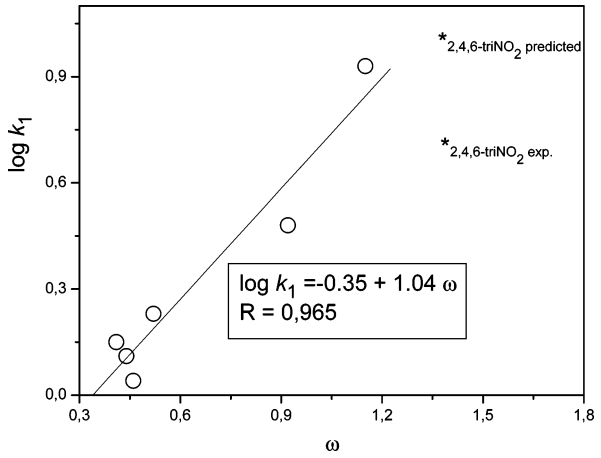


FIGURE 2. Comparison between the experimental nucleophilic rate coefficient for amine attack, k_1, for the reaction of the dithiocarbonates series with piperidine and the electrophilicity index obtained at the HF/6-311G(d,p) level of theory.

is expected to be softer than the latter because of the presence of a second S atom in the structure. Since the electrophilicity index is inversely proportional to chemical hardness (see eq 3) and, therefore, directly proportional to global softness, a soft molecule will be, in general, more electrophilic than a hard molecule.

It can be observed that, for thiocarbonate **33**, which is a marginal electrophile ($\omega = 0.28$ eV), substitution at the para position of the ring by a methyl group results in a slight electrophilic deactivation in compound **34** ($\omega = 0.26$ eV). Substitution at the same site by a stronger electron-releasing group, $-OCH_3$, results in further electrophilic deactivation in compound **35** ($\omega = 0.23$ eV). Electrophilic activation induced by chemical substitution by strong electron-withdrawing groups such as the $-NO_2$, on the other hand, increases the electrophilicity number of the reference compound **33** ($\omega = 0.28$ eV) to $\omega = 0.85$, 1.08, and 1.40 eV in compounds **22**, **21**, and **20**, respectively. Note that increasing substitution by one, two, and three $-NO_2$ groups makes an almost additive contribution per group.

A similar trend is observed for the series of dithiocarbonates. For instance, starting with compound **13** as reference ($\omega = 0.46$ eV), increasing substitution by one, two, and three $-NO_2$ groups at the ring enhances the electrophilicity, ω, to 0.92, 1.15, and 1.39 eV in compounds **3**, **2**, and **1**, respectively. Note again that increasing substitution by one, two, and three $-NO_2$ groups makes an almost additive contribution of about 0.24 eV per group. Other electrophilic deactivation patterns induced by electron-releasing groups, such as methyl and methoxy, in the aromatic ring can be confirmed in Table 1 for both series of thiocarbonates.

(b) Relationship between the Electrophilicity Index and Rate Coefficients. The result of the comparison between the electrophilicity index and the nucleophilic rate coefficient k_N for the reactions of the thiolcarbonates series with piperidine is displayed in Figure 1. The resulting empirical equation is:

$$\log k_N = -1.17 + 1.96\omega \quad (R = 0.990) \qquad (6)$$

From this equation, the rate coefficient for the nucleophilic attack k_N may be predicted from the knowledge of the global electrophilicity index. These values are compiled in Table 2. In the absence of experimental values for compounds marked with (*) in Table 2, the reliability of the predictions made from eq 6 may be reinforced by using the empirical rules about substituent effects at the aromatic ring of the leaving group in these systems,[26] based on Hammett substituent constants. In the analysis that follows, the substitution pattern at the ring of the leaving group and the values of k_N for each compound are given in parentheses. For the series of thiolcarbonates depicted in Table 2, it may be seen that compound **22** (p-NO_2, $k_N = 3.40$ s^{-1} M^{-1}) is upper bounded by compound **21** (2,4-diNO_2, $k_N = 14.8$ s^{-1} M^{-1}) and lower bounded by compound **23** (m-NO_2, $k_N = 2.20$ s^{-1} M^{-1}). This result is in agreement with the substituent effect expected for the strong electron-withdrawing $-NO_2$ group, which is known to have its greatest effectiveness at the para position.[27] Note further that compounds **24** (p-CN, $k_N = 1.85$ s^{-1} M^{-1}) and **25** (m-CN, $k_N = 1.46$ s^{-1} M^{-1}) are both predicted to display nucleophilic rate constants smaller than those for the $-NO_2$ group at the meta and para positions of the phenyl ring, respectively. Compounds **26** (p-CO_2H, $k_N = 1.39$ s^{-1} M^{-1}), **28** (m-CO_2H, $k_N = 1.05$ s^{-1} M^{-1}), **27** (p-CF_3, $k_N = 1.10$ s^{-1} M^{-1}), and **29** (m-CF_3, $k_N = 0.87$ s^{-1} M^{-1}), on the other hand, are predicted to display nucleophilic rate constants even smaller than those displayed by the $-NO_2$ and $-CN$ groups at these positions. Other derivatives containing electron-releasing groups such as **30** (m-CH_3, $k_N = 0.37$ s^{-1} M^{-1}) and **32** (m-NH_2, $k_N = 0.24$

TABLE 2. Predicted and Experimental Rate Coefficients for the Aminolysis of Thiolcarbonates with Piperidine, and Predicted and Experimental Hammett Substituent Constants[a]

compound	k_N^{exptl} (s^{-1} M^{-1})	k_N^{pred}	σ_p	σ_m
33	0.24	0.23	0.00	0.00
			−0.05*	−0.05*
31	0.46	0.32	0.23	
			0.11*	
34	0.17	0.21	−0.17	
			−0.11*	
35	0.17	0.18	−0.27	
			−0.20*	
22	2.10	3.40	0.78	
			0.78*	
21	14.0	14.8	−	−
			0.96*	0.96*
20	27.0	27.7	−	−
			1.15*	1.15*
23		2.20*		0.71
				0.69*
24		1.85*	0.66	
			0.65*	
25		1.46*		0.56
				0.60*
26		1.39*	0.45	
			0.59*	
28		1.05*		0.37
				0.52*
27		1.10*	0.54	
			0.53*	
29		0.87*		0.43
				0.46*
30		0.37*		−0.07
				0.17*
32		0.24*		−0.16
				−0.03*

[a] Predicted values marked with (*) were obtained from a reduced regression analysis for compounds 22, 31, and 33−35 in Figure 5. The regression equation is: $\log k_N = -1.21 + 2.05\ \omega$; $R = 0.985$.

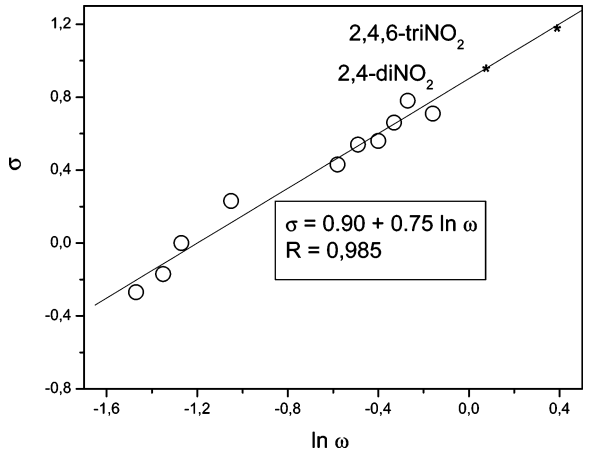


FIGURE 3. Comparison between the experimental Hammett substituent constants and the electrophilicity index in a logarithmic scale for the reaction of thiolcarbonates series with piperidine.

s^{-1} M^{-1}) are predicted to have rate coefficients greater than the reference compound **33** ($k_N = 0.23$ s^{-1} M^{-1}) and compounds **31** (p-Cl, $k_N = 0.32$ s^{-1} M^{-1}), **34** (p-CH_3, $k_N =$ 0.21 s^{-1} M^{-1}), and **35** (p-OCH_3, $k_N = 0.18$ s^{-1} M^{-1}), but smaller that those predicted for the $-NO_2$ and $-CN$ substituted derivatives. This analysis may be further confirmed by the use of the available experimental Hammett substituent constants included in the last two columns of Table 2. The values of σ_P for each compound are given in parentheses. For instance, starting with the reference compound **33** ($\sigma_P = 0.0$) substitution with a $-CH_3$ group at the para position of the leaving group results in a slight decrease of the rate coefficient in compound **34** ($\sigma_P = -0.17$; see both the experimental and predicted values in Table 2). Substitution with a $-OCH_3$ group at the same position results in further decrease of the rate coefficient in compound **35** ($\sigma_P = -0.27$). Note that substitution by chlorine at the para position of the ring of the leaving group results in an enhancement in the rate coefficient in compound **31** ($\sigma_P = 0.23$).

For the nitro derivatives, the relationship between k_N and σ_P is conserved, at least for compounds **22** ($\sigma_P = 0.78$) and **23** ($\sigma_m = 0.71$) for which experimental σ values are available (see Table 2). Note further that compounds **24** ($\sigma_P = 0.66$) and **25** ($\sigma_m = 0.56$) are both predicted to display nucleophilic coefficients smaller than those shown by the $-NO_2$ group at the meta and para positions of the phenyl ring, respectively. Compounds **26** ($\sigma_P = 0.45$) and **28** ($\sigma_m = 0.37$), on the other hand, are predicted to display nucleophilic rate constants even smaller than those shown by the $-NO_2$ and $-CN$ groups at these positions. The σ values for the remaining derivatives containing electron-releasing groups such as **30** ($\sigma_m = -0.07$) and **32** ($\sigma_m = -0.16$) are consistently predicted to have rate coefficients greater than the reference compounds. It is also noteworthy that Hammett substituent constants also correlate with the electrophilicity index in a logarithmic scale. The correlation is shown in Figure 3. The resulting empirical equation using compounds **22**–**25**, **27**, **29**, **31**, and **33**–**35** is:

$$\sigma = 0.90 + 0.75 \ln \omega \quad (R = 0.985) \qquad (7)$$

TABLE 3. Predicted and Experimental Rate Coefficients for Amine Attack for the Aminolysis of Dithiocarbonates with Piperidine, and Predicted and Experimental Hammett Substituent Constants[a]

compound	k_1^{exptl} (s^{-1} M^{-1})	k_1^{pred}	σ_p	σ_m
13	1.10	1.34	0	0
			−0.06**	−0.06**
11	1.70	1.55	0.23	
			0.23**	
15	1.30	1.28	−0.17	
			−0.17**	
17	1.40	1.19	−0.27	
			−0.34**	
3	3.00	4.04	0.78	
			0.78*	
2	8.50	7.01	–	–
			0.93*	0.93*
1	5.12	12.46	–	–
			1.06*	1.06*
4		3.34*		0.71
				0.72*
5		2.63*	0.66	
			0.64*	
6		2.28*		0.56
				0.59*
7		2.28*	0.45	
			0.59*	
8		1.92*		0.37
				0.51*
9		1.88*	0.54	
			0.50*	
10		1.67*		0.43
				0.44*
12		1.48*		0.37
				0.14**
14		1.31*		−0.07
				−0.12**
16		1.22*		0.12
				−0.28**
19		1.06*	−0.66	
			−0.65**	
18		1.11*		−0.16
				−0.52**

[a] Predicted values marked with (*) and (**) were obtained from eqs 9 and 10, respectively.

From this correlation, the values of the Hammett substituent constant for compounds **21** and **20** may be predicted. For instance, the value $\sigma = 0.96$ obtained for compound **21** (2,4-diNO_2) is consistent with the larger rate coefficient value ($k_N = 14.8$ s^{-1} M^{-1}) compared to that of compounds **22** ($k_N = 3.4$ s^{-1} M^{-1}, predicted $\sigma_P =$ 0.78, and experimental $\sigma_P = 0.78$) and **23** ($k_N = 2.2$ s^{-1} M^{-1}, predicted $\sigma_m = 0.69$, and experimental $\sigma_m = 0.71$). Note that compound **20** (2,4,6-triNO_2), which displays the largest experimental value of the rate coefficient, is consistently predicted to have the greatest value of Hammett substituent constant ($\sigma = 1.15$, see Table 2).

Table 3 shows the values of k_1 for the reactions of dithiocarbonates with piperidine and the theoretical electrophilicity index ω. The comparison between these parameters for the reactions of the series of dithiocarbonates is shown in Figure 2. The resulting empirical equation is:

$$\log k_1 = -0.35 + 1.04\omega \quad (R = 0.965) \qquad (8)$$

The predicted k_1 values obtained from eq 8 are compiled in Table 3. A similar analysis to that performed for the thiolcarbonates series shows that the rate coefficients

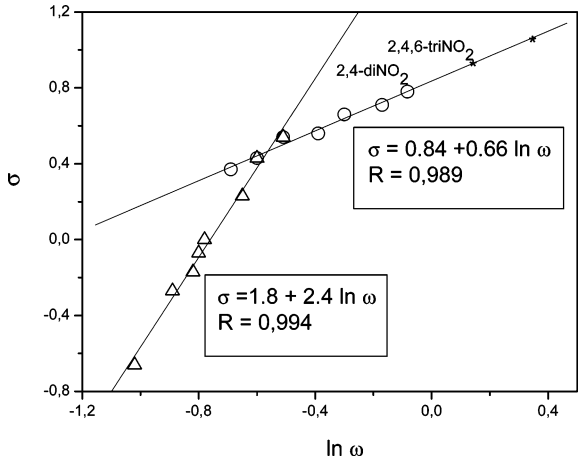


FIGURE 4. Comparison between the experimental Hammett substituent constants and the electrophilicity index in a logarithmic scale for the reactions of the dithiocarbonates series with piperidine. (*) predicted values.

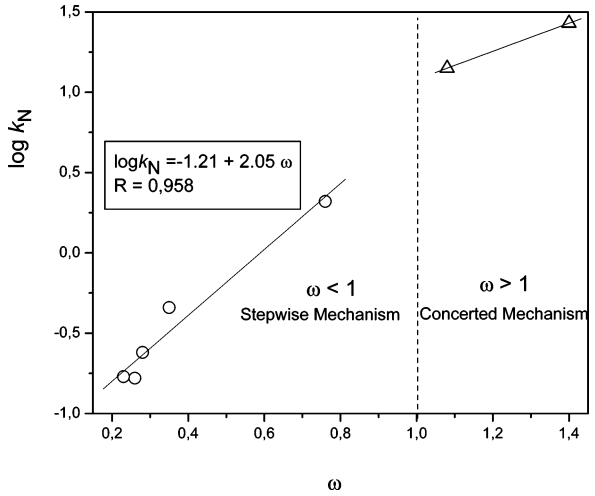


FIGURE 5. The dividing line between compounds with $\omega < 1$ and $\omega > 1$ is defined for $\Delta NE \approx \omega$ index for the thiolcarbonates series.

for compounds **3** (p-NO_2, $k_1 = 4.04\ s^{-1}\ M^{-1}$, predicted $\sigma_P = 0.78$, and experimental $\sigma_P = 0.78$) and **4** (m-NO_2, $k_1 = 3.34\ s^{-1}\ M^{-1}$, predicted $\sigma_m = 0.72$, and experimental $\sigma_m = 0.71$) are consistent with the substituent effect expected for the strong electron-withdrawing $-NO_2$ group.

Hammett substituent constants for this series were compared with the electrophilicity index in logarithmic scale (see Figure 4). The comparison shows this time two linear relationships for the nucleofuge: one for strong electron-withdrawing substituents and another for electron-releasing substituents. For strong electron-withdrawing substituents (compounds **3**−**6**), the following equation holds:

$$\sigma = 0.84 + 0.66 \ln \omega \quad (R = 0.989) \qquad (9)$$

From this equation, σ values for compounds **1** (2,4,6-triNO$_2$ derivative) and **2** (2,4-diNO$_2$ derivative) may be predicted (see Table 3).

A second straight line was obtained for the leaving groups substituted with electron-releasing groups using compounds **11**, **13**−**15**, **17**, and **19**. The regression equation in this case is:

$$\sigma = 1.80 + 2.40 \ln \omega \quad (R = 0.994) \qquad (10)$$

The presence of two linear relationships may be traced to the fact that in the aminolysis of these compounds, the rate-determining step is the attack of the amine. In this case, compounds presenting electron-withdrawing groups will significantly activate the carbocation site, and they will consistently show greater values of electrophilicity σ parameter and rate constant than those compounds substituted with electron-releasing groups. Note further that the predicted σ values for multiple substitution in compounds **21** and **20** (0.96 and 1.15, respectively) of the series of dithiocarbonates and compounds **2** and **1** (0.93 and 1.06) of the series of thiolcarbonates are approximately the same, thereby proving the stability and consistency of the theoretical σ index.

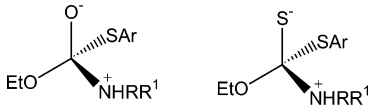
Nature of the Reaction Mechanisms. It has been previously shown that the experimental and theoretical scales of electrophilicity/nucleophilicity are useful to discuss reaction feasibility,[16] inter- and intramolecular reactivity,[17] and reaction mechanisms.[6] The nucleophilicity number ω^- has been represented using the critical points of the molecular electrostatic potential.[6,32] For the aminolysis of carbonates, we recently reported an empirical rule stating that the larger the electrophilicity/nucleophilicity difference, the greater the concerted character of the reaction mechanism. Conversely, a small electrophilicity/nucleophilicity gap will, in general, be associated with a stepwise reaction mechanism. This model uses the nucleophilicity/electrophilicity difference index $\Delta NE = |\varpi^- - \omega|$[6] as a criterion to predict the degree of ionic character of the electrophile/nucleophile interaction. The parameter ϖ^- is the average nucleophilicity evaluated for a set of nucleophiles reacting with a series of electrophiles.[6] In the present case, however, this analysis is simpler, since a unique nucleophile (piperidine) is employed, so that the ΔNE sequence is the same as that for electrophilicity (i.e., $\Delta NE = \omega$, to within a constant term).

Figure 5 shows the dividing line between the compound with $\omega < 1$ and $\omega > 1$, based on the $\Delta NE \approx \omega$ index for the thiolcarbonates. These compounds have been kinetically shown to react with piperidine via concerted (**20** and **21**) or stepwise (**22**, **31**, **33**−**35**) mechanisms. It can be seen that those electrophiles that react via a stepwise route display ω values smaller than 1.0 eV. Compounds reacting via a concerted route consistently show ω values greater than 1.0 eV. On the other hand, the dithiocarbonate derivatives shown in Figure 2 react via stepwise mechanism (compounds **1**−**3**, **11**, **13**, **15**, and **17**). Note that compounds **1** and **2** show ω values greater than 1.0 eV, and therefore they are predicted to react via a concerted mechanism, thereby indicating that the intermediate (Ar = 2,4-dinitrophenyl or 2,4,6-trinitrophenyl) is not readily formed.[13a,b]

A possible explanation for this result is the greater electronegativity of the oxygen as compared to that of the sulfur atom, which favors the formation of the double

(32) (a) Sen, K. D.; Politzer, P. *J. Chem. Phys.* **1989**, *90*, 4370. (b) Sen, K. D.; Seminario, J. M.; Politzer, P. *J. Chem. Phys.* **1989**, *90*, 4373.

CHART 1



I **II**

bond with the electrophilic carbon, thereby facilitating the departure of the nucleofuge[13b,33] (−SAr unity in Chart 1). The replacement of O^- in I by S^- in II stabilizes the intermediate by size effects due to its higher polarizability that better accommodates the negative charge. Therefore, compounds **20** and **21** whose aminolysis proceed through intermediates of type I will react via an enforced concerted mechanism.[8,13] Compounds **1** and **2**, on the other hand, which yield a stable intermediate of type II, will react via a stepwise mechanism. These results reveal the influence of the leaving group basicity, the electronegativity, and polarizability of the CO and CS groups on the stability of the intermediate, $T^{\pm}$,[13] and the reaction mechanism.

The stability of the intermediate $T^{\pm}$ can be interpreted in Figure 5 as a change of slope in the Brønsted plot, thereby confirming the change of mechanism in the thiolcarbonates series. The zone of higher electrophilicity values is in agreement with a concerted mechanism,[13a,b] and the zone of lower electrophilicity values is consistent with a stepwise mechanism.[13c,d]

(33) Castro, E. A.; Cubillos, M.; Aliaga, M.; Evangelisti, S.; Santos, J. G. *J. Org. Chem*. **2004**, *69*, 2411.

Concluding Remarks

The reactivity of thiocarbonates with piperidine has been examined for a wide series of molecules. The electrophilicity of the thio derivatives may be conveniently described in terms of the electronic reactivity index proposed by Parr et al.[24] The global electrophilicity index assesses well the substituent effects induced by different functional groups on a given thiocarbonate frame. Activation/deactivation patterns induced by electron-withdrawing and electron-releasing groups at the aromatic ring in both series of thiocarbonates are consistently ordered with respect to Hammett substituent constants. The electrophilicity scale may also be used to rationalize reaction mechanisms in these systems: while high electrophilic thiocarbonates will in general undergo aminolysis via a concerted route, those marginally electrophilic thiocarbonates will react with piperidine via a stepwise route. Some deviations to this empirical rule may be explained on the basis of the stability of the tetrahedral intermediates, which depends on the leaving group basicity and the electronegativity and polarizability of the CO and CS groups.

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