Tetrahedron Letters 53 (2012) 553–556

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

On the choice of optimal conformation in linear free-energy relationships. Reactivity of 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids with diphenyldiazomethane

Branko J. Drakulić [a,*], Aleksandar D. Marinković [b], Ivan O. Juranić [a]

[a] Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia
[b] Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, 11000 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 12 August 2011
Revised 5 November 2011
Accepted 18 November 2011
Available online 25 November 2011

Keywords:
Conformational space
Rate constants
Linear free-energy relationships
Frontier orbitals

ABSTRACT

Rate constants for the esterification of eleven 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids with diphenyldiazomethane in ethanol at 30 °C were determined, and correlated with substituent constants using classical Hammett and related methods. Statistically valid results for the *para*-substituted compounds were obtained by the Swain–Lupton approach. The compounds studied had significant conformational mobility due to seven rotatable bonds in their backbone. Going beyond the classical Hammett approach, we established a relatively fast procedure to find the optimal conformations that can be used in linear free-energy relationships, combining molecular dynamics with semiempirical calculations, and calculations using a higher level of theory (DFT and MP2). Fair correlations were observed with frontier orbitals, allowing inclusion of *ortho*-substituted derivatives and clarifying artifact-like data, as perceived by the Hammett-type approach.

2-[(Carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids exert antiproliferative activity and significant selectivity (tumor vs healthy human cells).[1] The title compounds are a unique chemotype so far, although reasonably similar compounds have been reported as immunosuppressors,[2] and recently as allosteric ligands for 3-phosphoinositide-dependent protein kinase 1 (PDK1).[3] Within an ongoing study on the structure–activity relationships of the title compounds, we examined the transmission of substituent effects through the molecular skeleton, and the reactivity of the carboxyl groups. With this rationale, the rate constants of esterification of eleven compounds **1**–**11** (Table 1) with diphenyldiazomethane (DDM) were determined using the spectrophotometric method introduced by Roberts et al.[4,5] DDM reacts with carboxylic acids as shown in Scheme 1a. In an alcohol as solvent, a competing reaction (etherification of the alcohol) occurs[6] as shown in Scheme 1b.

The compounds chosen for this study had a simple substitution pattern, comprising alkyl and halogen substituents, mainly in *para* positions.[7] Still, a straightforward relationship between the rate constants and a substituent effect was not observed. Probably this can be attributed to two factors. The first is lack of conjugation between the aryl moiety and the carboxyl groups that underwent esterification, and the second is the flexibility of the molecules studied. Transmission of electronic effects through –S–CH_2–[8] and –CH_2–CH_2–[9] moieties has been documented. Rate constants for esterification of dicarboxylic acids with DDM have been reported.[10]

Using classical Hammett and related approaches, a statistically fair correlation was derived using the Swain–Lupton method,[11,12] excluding the *ortho*-substituted derivative **11**, see (Eq. 1), Table S1, and Figure S1 in the Supplementary data.

$$\log k_2 = 0.0395\ (\pm 0.0166)\ F - 0.3031\ (\pm 0.0265)\ R - 0.5592\ (\pm 0.0066) \quad (1)$$

$r = 0.9807$, sd = 0.0098, $n = 10$, $F = 88.50$, $F_{\text{significance}} = 1.1 \times 10^{-5}$; compound **11** is anomalous.

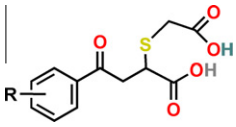
The resonance effect appears to be one order of magnitude higher than the field effect. For the 3,4-di-Me-substituted derivative **10**, doubled values for both F and R were used, because the Swain–Lupton substituent constants are position independent. For compounds **3**, **4**, **5,** and **9**, R^+ values were used; this can be explained by hyperconjugation for alkyl-substituted compounds. The R^- fits compound **6** best to (Eq. 1), an inconsistency that will be discussed below.

The title compounds are significantly flexible in standard solvents. To illustrate this, the range of surface area[14] of molecules obtained from 15 nanosecond molecular dynamics (MD) trajectories in an implicit solvent is given in Table S1 in the Supplementary data. The majority of the conformations obtained had energies higher than 5 kcal/mol compared to the global minimum, as perceived by

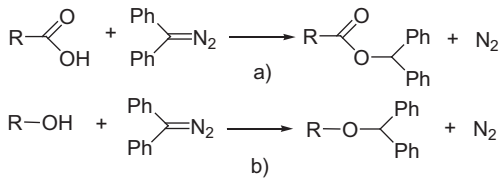
* Corresponding author. Tel.: +381 11 3336738; fax: +381 11 2636061.
E-mail address: bdrakuli@chem.bg.ac.rs (B.J. Drakulić).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.097

Table 1
Logarithmic values of second-order rate constants for esterification of **1**–**11** with DDM; polar surface area of molecules in chosen conformation (PSA); values of highest occupied molecular orbitals (HOMO) obtained at the semiempirical PM6 level; and HOMO–LUMO differences obtained by DFT and MP2 calculations



Compound	R-	$\log k_2$	$\log(k/k_0)$	PSA (Å^2)	PM6 HOMO (eV)	DFT HOMO–LUMO diff (eV)	MP2 HOMO–LUMO diff (eV)
1	H-	−0.5498	–	220.8	−9.660	−4.6458	−11.4538
2	4-Me-	−0.5017	0.9125	215.6	−9.662	−4.5438	−11.1254
3	4-Et-	−0.4698	0.8545	222.9	−9.694	−4.6575	−11.1863
4	4-*i*-Pr-	−0.4609	0.8383	227.4	−9.731	−4.9868	−11.3050
5	4-*n*-Bu-	−0.4908	0.8927	224.6	−9.692	−4.8537	−11.2236
6	4-*t*-Bu-	−0.5560	1.0112	192.0	−9.445	−4.1190	−10.8930
7	4-F-	−0.4225	0.7685	221.7	−9.898	−5.0610	−11.7102
8	4-Cl-	−0.4828	0.8781	204.1	−9.605	−4.5242	−11.4141
9	4-Br-	−0.4547	0.8270	213.6	−9.776	−4.7500	−11.3616
10	3,4-Di-Me-	−0.4342	0.7897	237.7	−9.583	−4.9122	−11.2554
11	2,5-Di-Me-	−0.4145	0.7540	228.4	−9.428	−5.1182	−11.8775



Scheme 1. (a) General reaction for the esterification of carboxylic acids with diphenyldiazomethane (DDM). (b) General reaction for the etherification of alcohols with diphenyldiazomethane (DDM).

the ABF procedure used, see Figure S2 in the Supplementary data. All the compounds exerted similar conformational mobility. This is illustrated by the ratio of the range of 3D dependent surface areas to the molecular weights of the compounds (Table S1 in the Supplementary data), and is expected for the molecules having the same core structure and a similar number of rotatable bonds. Some successful attempts to account for the conformational mobility of molecules in linear free-energy relationships (LFER) can be found in the literature.[15] Such studies describe molecules having not more than two rotatable bonds; substituent effects were accounted for by using classical Hammett substituent constants and the Yukawa–Tsuno equation. The conformational adaptation of substituents was also described.[16]

As no other literature reports exist on transmission of substituent effects for flexible, partially conjugated molecules, we tried to find a way to establish a correlation on rational grounds. We aimed first to find the conformations that could be used for the correlations, and then to obtain descriptors that are specific for particular conformations, and that describe the entire molecule. Frontier orbitals, often used to quantify the electrophilicity or nucleophilicity of entire molecules in their reactions, appeared to be a logical choice. Classical geometry optimization using fast semiempirical methods, or significantly slower and computationally more demanding methods on a higher level of theory (DFT, ab initio) when applied to compounds having significant conformational mobility have obvious drawbacks. The main obstacle is the heavy dependence of the output conformation on the choice of the starting one. Local minima can be readily obtained in this way, and for semiempirical methods the difference of energies among the minima obtained is within the confidence limit of the method. Methods using a higher level of theory are free of the drawback of the uncertainty in the energy differences among local minima, but are very time-demanding. Inspired by our on-going study of the free-energy landscapes of the title compounds in various explicit solvents, aimed to derive biologically relevant conclusions,[17] we employed a similar procedure,[18] using implicit solvation, to find the global energy minima, and to speed-up the computation. Each molecule was submitted to a 15 ns MD simulation in implicit ethanol at 300 K. To enhance sampling and to map the free energy surface, an adaptive biasing force (ABF)[26] calculation was used. Two collective variables that map the conformational space of molecules in the most comprehensive way, were chosen on the basis of previous calculations (data not shown): the distance between centroids defined on aroyl phenyl and distal carboxyl groups; and the radius of gyration of all heavy atoms, including substituents (Figure S3 in the Supplementary data). Energy minima were extracted from free-energy surfaces. The conformation closest to the free-energy minimum was found from the collective variables trajectory file. To remove artifacts stemming from molecular mechanics (small deviations of planarity in phenyl rings, bond lengths), and to retain the conformations most similar to those obtained by molecular dynamics, all structures were optimized at the semiempirical PM6 level[27] to acceptable root-mean-square gradients in the implicit solvent,[28] and in a vacuum. Comparing the initial conformations obtained as MD minima and the corresponding optimized ones, the largest root-mean-square deviation (RMSD) of the backbone atoms (excluding substituents) was 0.92 (Table S1 in Supplementary data). The main contribution to RMSD, for all molecules, arose from the position of atoms in the phenyl rings, that is, Ph to C(O) torsion (Figure S4 in the Supplementary data). The highest occupied molecular orbitals (HOMOs) derived from the semiempirical calculations correlated well with experimentally obtained rate constants for the *para*-substituted congeners **2**–**9** ((Eq. 2) and Figure S5 in the Supplementary data).

$$\log(k/k_0) = 0.5197\ (\pm 0.0660)\ \mathrm{HOMO}_{(\mathrm{PM6})} + 5.9080\ (\pm 0.6392) \quad (2)$$

$r = 0.9549$, sd = 0.023, $n = 8$, $F = 62.066$, $F_{\mathrm{significance}} = 2 \times 10^{-4}$; outliers **10** and **11**.

Compounds having *meta*–*para* (**10**) and *ortho*–*meta* (**11**) substitution patterns are obviously anomalous. Single point calculations,