DOI: 10.1002/cmdc.200800101

Structure–Antioxidant Activity Relationships in a Series of NO-Donor Phenols

Paolo Tosco,[a] Elisabetta Marini,[a] Barbara Rolando,[a] Loretta Lazzarato,[a] Clara Cena,[a] Massimo Bertinaria,[a] Roberta Fruttero,[a] Marianne Reist,[b] Pierre-Alain Carrupt,[b] and Alberto Gasco*[a]

Recently we reported a new class of NO-donor phenols that could be of interest in the treatment of many forms of cardiovascular disease (CD). Their potencies as inhibitors of ferrous salt/ascorbate-induced peroxidation of membrane lipids of rat hepatocytes were assessed as pIC_{50} values through the TBARS assay. In this work we aimed to find quantitative relationships between the antioxidant activity of these compounds and appropriate molecular descriptors. In particular, we determined their $\log P_{oct}$, their reactivity ($\log Z$) in reaction with the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH•), and the theoretical parameter ΔH_{abs}, which describes the enthalpy of homolytic O–H bond cleavage. The QSAR equations found through the classical Hansch approach allowed us to draw interesting conclusions on the possible mechanisms of reaction with radicals in the various environments, while underlining the role of lipophilicity in antioxidant activity.

Introduction

Reactive oxygen species (ROS) are formed and consumed during cellular metabolism. Though a low concentration of ROS is physiologic, they can undergo a dramatic increase under certain pathological conditions, leading to oxidative stress. ROS are believed to play a major role in many pathologies, such as aging, cancer, arthritis, lung diseases, cardiovascular diseases, ischemia-reperfusion damage, and neurodegenerative disorders.[1] Today, antioxidants have attracted a great deal of attention as therapeutic agents to be used in such pathologies. Phenols represent a class of antioxidants which have been closely studied after the discovery that vitamin E is the main lipid-soluble antioxidant in human blood.[2] In a recent paper[3] we described a new class of phenols, able to release nitric oxide (NO) (NO-donor phenols), which could be of interest in the treatment of many forms of cardiovascular disease (CD), in particular those where ROS-mediated vascular alterations are involved. Experimental evidences indicate that atherosclerotic vessels suffer an impairment of the endogenous production of NO, whereas the responsiveness to the vasodilator actions of exogenous NO is largely preserved.[4,5] NO-donor phenols are potentially able to counteract both vascular degeneration and deficient NO production.[3] These structures (Figure 1) were obtained by joining phenols (Figure 1, compounds **1**–**4**), whose antioxidant activity spans a wide range, with appropriate NO-releasing nitrooxy and furoxan moieties. The potencies of all these compounds as inhibitors of ferrous ion/ascorbate-induced peroxidation of membrane lipids of rat hepatocytes (pIC_{50}, Table 1) were assessed by detecting the 2-thiobarbituric acid reactive substances (TBARS),[6] which are the final metabolites of the auto-oxidation process. The NO-donor phenols were also able to relax rat aorta strips pre-contracted with phenylephrine in a concentration-dependent manner. The effect was cGMP-dependent, and this is in keeping with the NO-mediated activation of the sGC.[3] In this paper we report the results of a study designed to shed light on the structure–antioxidant activity relationships which operate in these dual-action compounds. To this purpose, we determined their lipophilicity ($\log P_{oct}$), their reactivity ($\log Z$) in the reaction with 2,2-diphenyl-1-picrylhydrazyl radical (DPPH•), and the theoretical parameter ΔH_{abs}, which describes the enthalpy of homolytic O–H bond cleavage. The reference phenols **1**–**4** were also considered in the study. The impact of these molecular descriptors on the antioxidant potencies (TBARS assay) was analyzed through the classical Hansch physicochemical approach.

Results and Discussion

Lipophilicity

The $\log P_{oct}$ values of all the compounds reported in Table 1 were obtained by a RP-HPLC method (see the Experimental Section for details). The RP-HPLC method was first calibrated with 63 reference compounds of known $\log P$ values[7] ranging

[a] *Dr. P. Tosco, Dr. E. Marini, Dr. B. Rolando, Dr. L. Lazzarato, Prof. Dr. C. Cena, Dr. M. Bertinaria, Prof. R. Fruttero, Prof. A. Gasco*
Dipartimento di Scienza e Tecnologia del Farmaco
Università degli Studi di Torino
Via Pietro Giuria 9, 10125 Torino (Italy)
Fax: (+39) 011-670-7286
E-mail: alberto.gasco@unito.it

[b] *Dr. M. Reist, Prof. Dr. P.-A. Carrupt*
Unité de Pharmacochimie, Section des Sciences Pharmaceutiques
Université de Genève, Université de Lausanne
30 Quai Ernest Ansermet, 1211 Genève 4 (Switzerland)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cmdc.200800101.

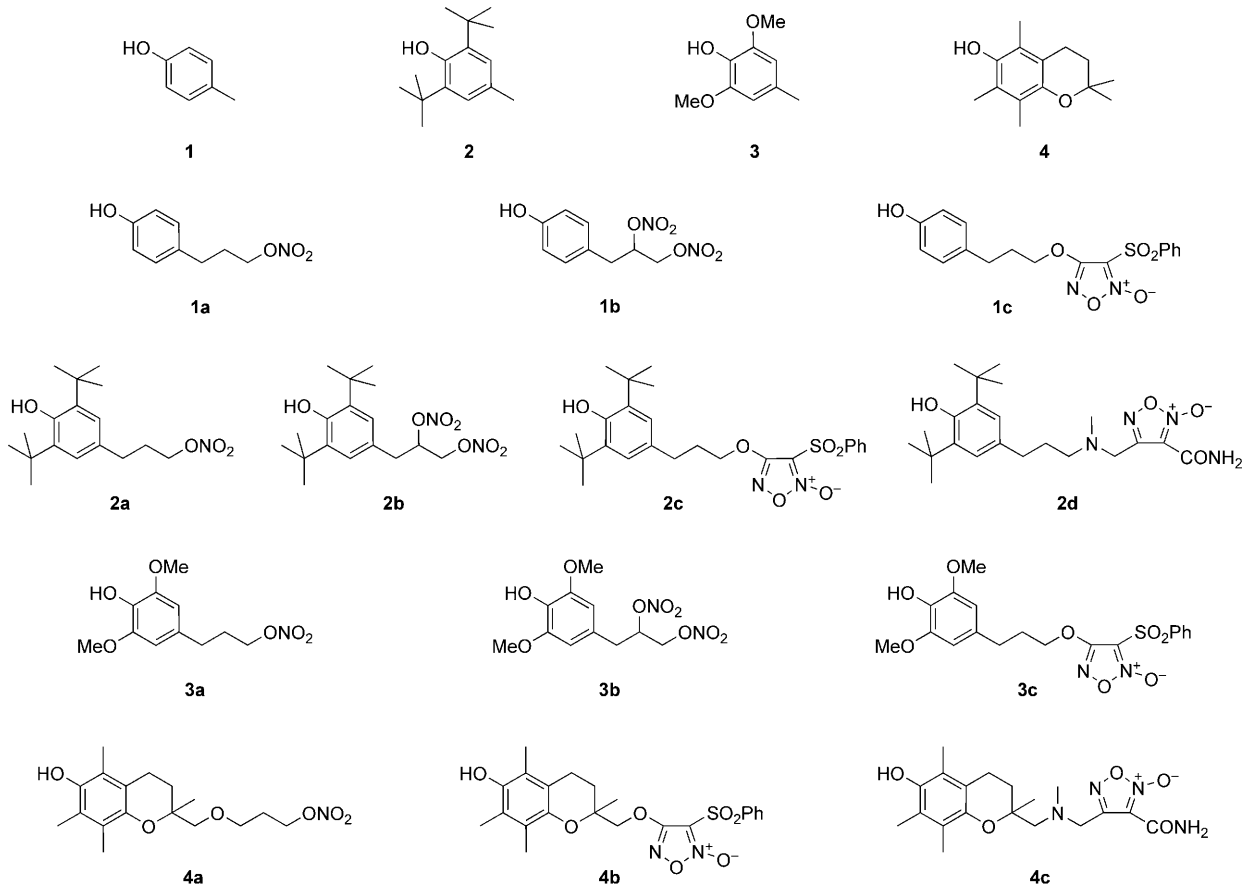


Figure 1. Structures of reference compounds and newly synthesized NO-donor phenols.

from 0.40 to 4.78 (see Supporting Information). A very good linear correlation ($r^2 = 0.98$) was found between the log *P* and log k_w values of these compounds [Eq. (1)]; the standard error of regression coefficients is given within parentheses):

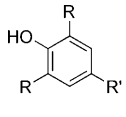
$$\log P = 1.098(\pm 0.022) \log k_w + 0.335(\pm 0.047)$$
$$n = 63,\ r^2 = 0.98,\ s = 0.15,\ F = 2531 \qquad (1)$$

This equation was used as a calibration curve for the evaluation of the log *P* of our phenols from their log k_w values, which were determined under the same conditions as the reference compounds. Experimental log *P* values are in good accordance with the calculated ones (CLOGP).[8] Analysis of the data reported in Table 1 shows that the lipophilicity of the reference phenols is modified by the NO-donor moiety; this is particularly evident in the furoxan derivatives. Consequently, this molecular descriptor is widely modulated across the series.

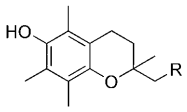
Reaction of phenols with DPPH

The stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH$^\bullet$) is a useful reagent for investigating the scavenger properties of phenols, catechols, and aromatic amines. It is widely accepted that the reaction between phenols and DPPH$^\bullet$ proceeds through two essentially different, nonexclusive mechanisms, namely direct hydrogen atom transfer (HAT) and sequential proton loss electron transfer (SPLET).[9–11] Whereas the first mechanism is predominant in apolar media, the second gains importance in polar solvents supporting ionization, for example alcohols (Scheme 1). The phenoxyl radical thus formed undergoes secondary reactions producing a complex mixture of products which alter the stoichiometry of the first reaction. To assess the reactivity of the phenols in Figure 1 against DPPH$^\bullet$, we measured the kinetic parameter log *Z*, according to a previously described procedure.[12] Standard solutions of the phenol antioxidants were prepared in methanol and rapidly mixed with a methanolic solution of DPPH$^\bullet$. The progress of the reaction was followed by determining the decrease of the DPPH$^\bullet$ absorbance at 517 nm. This decrease was plotted against time (Figure 2). Plots of 1/[DPPH$^\bullet$] versus time, obtained in the first 15 seconds during which the reaction follows second order kinetics, afforded straight lines (Figure 3). The slopes of these lines were plotted against the ratio [antioxidant]/[DPPH$^\bullet$] (Figure 4); linear regression analysis afforded the parameter *Z* (slope of the line in $L\,mol^{-1}\,s^{-1}$). Log *Z* values (Table 1) of the NO-donor derivatives are similar to those of the respective reference phenols. This means that the NO-donor moieties joined to the phenolic leads to obtain the final hybrid drugs have a moderate influence on the reactivity with DPPH$^\bullet$.

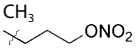
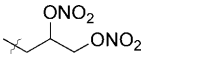
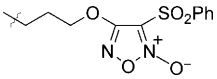
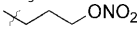
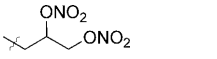
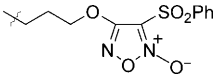
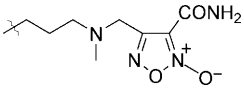
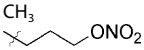
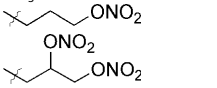
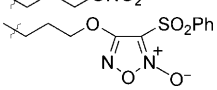
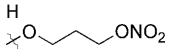
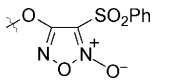
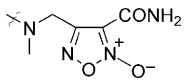
Table 1. pIC_{50} (antioxidant potency), log *P*, log *Z*, and calculated ΔH_{abs} values for reference and NO-donor phenols.[a]



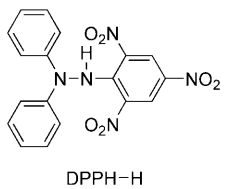
A



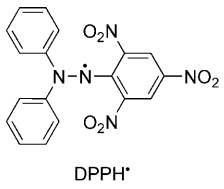
B

Compd	Scaffold	R	R′	pIC_{50}[b]	log *P*[c]	log *Z*[d]	ΔH_{abs}[e]
1	A	H	CH_3	3.54	1.88	0.31	13.58
1a	A	H		3.84	2.85	−0.15	15.58
1b	A	H		3.73	2.99	–[f]	17.36
1c	A	H		4.33	4.18	−0.09	15.38
2	A	*t*Bu	CH_3	5.77	5.36	1.62	5.24
2a	A	*t*Bu		5.70	6.02	1.48	8.19
2b	A	*t*Bu		5.58	6.16	1.57	9.57
2c	A	*t*Bu		5.70	7.32	2.02	6.97
2d	A	*t*Bu		5.92	5.53	1.77	5.02
3	A	OCH_3	CH_3	4.74	1.87	3.24	5.11
3a	A	OCH_3		5.23	2.81	3.11	7.05
3b	A	OCH_3		5.27	3.04	2.78	8.28
3c	A	OCH_3		5.47	3.99	3.13	5.99
4	B	H	–	6.77	3.58	3.17	0.00
4a	B		–	6.82	4.45	3.10	0.70
4b	B		–	6.31	5.21	2.84	1.25
4c	B		–	6.85	3.96	3.08	−0.54

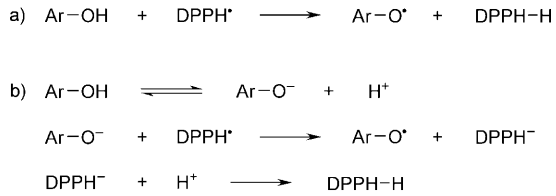
[a] See text for details of experimental and theoretical methods. [b] Antioxidant potency evaluated by TBARS assay, as previously described.[3] [c] Log P_{oct} assessed through an RP-HPLC method. [d] Measured from DPPH• absorbance quenching in the first 15 s of reaction. [e] Calculated by an ab initio QM method. [f] The low reactivity with DPPH• did not permit the measurement of a reliable log *Z* value.



DPPH−H



DPPH•



Scheme 1. Reaction of phenols with DPPH•: a) HAT and b) SPLET mechanisms.

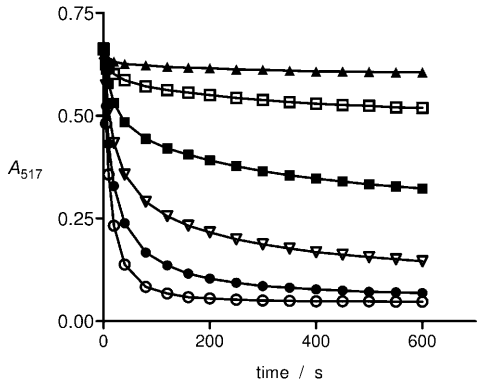


Figure 2. Reaction of **4c** with DPPH•, monitored at 517 nm. Curves corresponding to different starting concentrations of **4c** are reported (▲: 0.044 equiv; □: 0.15 equiv; ■: 0.30 equiv; ▽: 0.46 equiv; ●: 0.75 equiv; ○: 0.90 equiv).

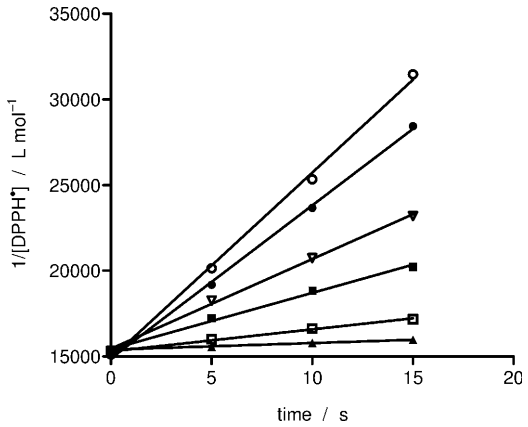


Figure 3. Kinetics of the reaction of **4c** with DPPH•. Curves corresponding to different starting concentrations of **4c** are reported (▲: 0.044 equiv; □: 0.15 equiv; ■: 0.30 equiv; ▽: 0.46 equiv; ●: 0.75 equiv; ○: 0.90 equiv).

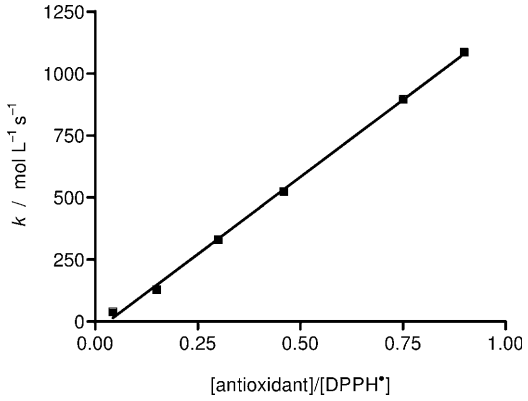
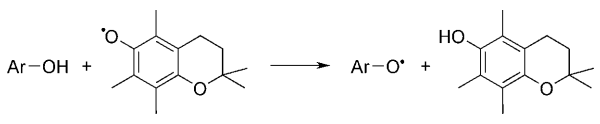


Figure 4. Calculation of Z for **4c** (regression parameters: slope $Z = 1243$, $r^2 = 0.999$).

Relative O–H bond dissociation enthalpy (ΔH_{abs})

As already pointed out, the HAT mechanism is favored in apolar media such as hydrocarbon solvents and the lipidic core of biological membranes.[9,13] In light of this, we decided to explore whether a correlation existed between the experimental pIC_{50} values determined through the TBARS assay and the relative O–H bond dissociation enthalpy ΔH_{abs}, defined by Equation (2) and related to the isodesmic reaction depicted in Scheme 2.[12]

$$\Delta H_{abs} = \Delta H_f(\mathrm{HPMC}) + \Delta H_f(\mathrm{ArO^{\cdot}}) - \Delta H_f(\mathrm{HPMC^{\cdot}}) - \Delta H_f(\mathrm{ArOH}) \quad (2)$$



Scheme 2. Isodesmic reaction between a generic phenol and the α-tocopheryl radical.

ΔH_{abs} describes the enthalpy of homolytic O–H bond cleavage and provides a quantitative estimate of the capacity of each product to donate a H atom to the radical 6-hydroxy-2,2,5,7,8-pentamethylchroman (HPMC), used as reference. ΔH_f values represent the calculated enthalpies of formation of the different species involved in the reaction. These values were computed by ab initio quantum mechanics using the RHF/6-31G(d) level for geometry optimizations and vibrational analysis, and the RB3LYP/6-311+G(2d,2p) level for single-point energy calculations; the restricted open-shell method was adopted for radicals. Analysis of the data reported in Table 1 shows that the ΔH_{abs} values of the NO-donor derivatives are similar to the values of the respective reference phenols. This means that the NO-donor moieties do not significantly influence the O–H bond dissociation energies.

Quantitative structure–antioxidant activity relationships

A good quality linear correlation was obtained between pIC_{50} and ΔH_{abs} [Eq. (3); QSAR Equations (3)–(10) along with the respective statistical parameters are reported in Table 2]. By contrast, a feeble linear correlation ($r^2 = 0.50$) was obtained when the dependence of pIC_{50} on $\log Z$ was checked [Eq. (4)]. The correlation between the two reactivity parameters $\log Z$ and ΔH_{abs} is not very strong either ($r^2 = 0.73$, equation not reported). These results reflect the fact that in the TBARS assay, which assesses the antioxidant power in a lipidic matrix, the HAT mechanism is expected to be largely predominant; therefore ΔH_{abs} is a good predictor of the antioxidant activity. The $\log Z$ parameter describes the reactivity of antioxidants with DPPH• in methanol, where both HAT and SPLET mechanisms are known to come into play. This may well provide a sound explanation to the imperfect agreement between the antioxidant potencies assessed by the two different experimental methods. If $\log P$ is introduced in Equations (3) and (4) as a new independent variable, the quality of the equations is significantly improved [Eq. (5) and (6)]. When normalized data (mean-centered, then divided by the standard deviation) are used, Equations (5) and (6) turn into Equations (7) and (8). Analysis of the coefficients of the two independent variables shows that the reactivity parameters ΔH_{abs} and $\log Z$ are more important than lipophilicity ($\log P$) in describing antioxidant potencies. An additional small increment in the quality of the correlation occurs if the parabolic dependence from $\log P$ is explored [Eq. (9) and (10); Figure 5]. The use of the bilinear model yields similar results. Equations (9) and (10) are able to explain a large amount of variance in the data and display a high predictive power. It would be necessary to take into account additional members of the series characterized by a very high lipophilicity in order to confirm this parabolic behavior; however, the probable very low solubility of such products discourages this approach. Consequently, a conclusive word on the nature (linear or quadratic) of the dependence on the lipophilicity of the antioxidant potencies across this series of products cannot be given. If we trust the parabolic dependence of the antioxidant activity on the lipophilicity indicated by Equations (9) and (10), we could speculate that when the lipophilic–

Table 2. Summary of QSAR Equations (3)–(10).

	Equation[a]	*n*	r^2	*s*	*F*	$q^{2[b]}$
(3)	$pIC_{50} = -0.18(\pm0.04)\ \Delta H_{abs} + 6.67(\pm0.36)$	17	0.85	0.42	87.44	0.82
(4)	$pIC_{50} = 0.59(\pm0.16)\ \log Z + 4.28(\pm0.37)$	16	0.50	0.73	13.91	0.34
(5)	$pIC_{50} = -0.16(\pm0.03)\ \Delta H_{abs} + 0.20(\pm0.10)\ \log P + 5.74(\pm0.55)$	17	0.93	0.29	99.51	0.89
(6)	$pIC_{50} = 0.60(\pm0.25)\ \log Z + 0.32(\pm0.19)\ \log P + 2.89(\pm1.00)$	16	0.76	0.53	20.11	0.63
(7)	$pIC_{50} = -0.85(\pm0.15)\ \Delta H_{abs} + 0.29(\pm0.15)\ \log P$	17	0.93	0.29	99.51	0.89
(8)	$pIC_{50} = 0.73(\pm0.30)\ \log Z + 0.51(\pm0.30)\ \log P$	16	0.76	0.53	20.11	0.63
(9)	$pIC_{50} = -0.079(\pm0.05)\ (\log P)^2 + 0.90(\pm0.43)\ \log P - 0.15(\pm0.02)\ \Delta H_{abs} + 4.29(\pm0.96)$	17	0.97	0.21	126.40	0.94
(10)	$pIC_{50} = -0.13(\pm0.09)\ (\log P)^2 + 1.44(\pm0.81)\ \log P + 0.56(\pm0.20)\ \log Z + 0.83(\pm1.67)$	16	0.86	0.41	25.08	0.79

[a] 95% Confidence intervals of regression coefficients are given within parentheses. [b] Calculated by the leave-one-out method.

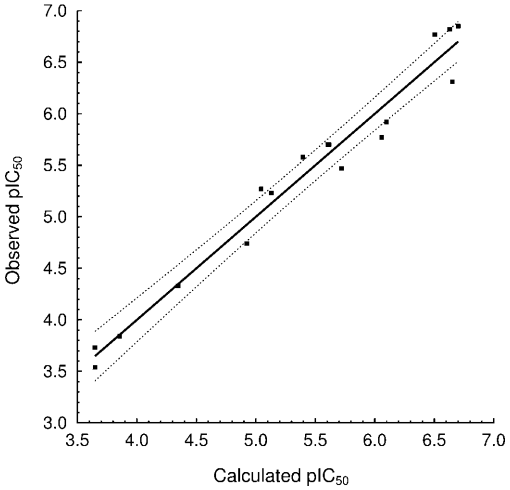


Figure 5. Plot between the observed and calculated pIC_{50} values using Equation 9. Dashed lines represent confidence bands (95% limits).

hydrophilic balance of the products is higher than the optimal value [$\log P_0 = 5.70$ from Eq. (9)] they still penetrate well into the membrane, but their strong interactions with the hydrophobic phospholipid tails greatly limit their mobility, with the result that their antioxidant capacity is decreased as well.[14] The ability of Equation (9) to explain about 97% of the variance of data is in keeping with the finding that the NO-donor moieties we used to design the title NO-donor phenols, in general, do not display antioxidant properties per se under the experimental conditions used (TBARS method).[3]

Conclusions

Herein we have shown that the antioxidant potencies in a series of NO-donor phenols derived from the respective phenolic leads, assessed by the TBARS assay, are principally dependent on their capacity to undergo hydrogen abstraction from the O–H group and on their lipophilicity ($\log P$). The relative O–H bond dissociation enthalpy (ΔH_{abs}) is a better predictor than $\log Z$; this may well be connected with the prevalence of the HAT mechanism in lipidic matrices. In addition to reactivity descriptors, lipophilicity also plays an important role. The QSAR equations obtained indicate that, in this series of products, the antioxidant activities evaluated by the TBARS method can be reasonably predicted by simple experimental and theoretical parameters.

Experimental Section

Lipophilicity measurements

The $\log P_{oct}$ of all the compounds was obtained by a RP-HPLC method. HPLC analyses were performed with a HP1100 chromatograph system (Agilent Technologies, Palo Alto, CA, USA) equipped with a quaternary pump (model G1311A), a membrane degasser (model G1379A), and a diode-array detector (DAD) (model G1315B). Data analysis was accomplished using a HP ChemStation system (Agilent Technologies). Retention time measurements were performed on a Discovery RP-amide-C_{16} column (150×4.6 mm i.d., 5 μm; Supelco, Bellefonte, PA, USA) thermostated at 30 °C, by a UV detector operating at 226 and 254 nm. The mobile phase consisted of mixtures of 0.02 M pH 7.4 phosphate buffer and methanol in proportions varying from 40 to 70% (*v/v*). The phosphate buffer was filtered under vacuum through a 0.45 μm HA Millipore filter (Millipore, Milford, MA, USA). The flow rates ranged from 0.8 mL min^{-1} to 1.0 mL min^{-1}. Stock solutions (10^{-2} M) of compounds were prepared in methanol and diluted (10^{-3}–10^{-4} M) in the mobile phase for injection (20 μL). All samples were injected at least three times for each mobile phase. Uracil was used as the non-retained compound. The logarithms of the capacity factor ($\log k$) were measured for each compound using a minimum of four different methanol/buffer ratios. $\log k_w$, namely the logarithm of the capacity factor corresponding to 0% methanol modifier, was obtained by linear extrapolation.

Reaction of phenols with DPPH•

All spectrophotometric measurements were performed with a Varian Cary 50BIO UV/Vis spectrophotometer, under controlled temperature (37 °C). Standard solutions of the antioxidants were prepared in methanol and rapidly mixed (volumes from 0.015 mL to 0.2 mL) with a methanol solution of DPPH• (final volume 3 mL). Initial concentrations of DPPH• taken between 5.8×10^{-5} M and 6.4×10^{-5} M were used. The decrease in absorbance at 517 nm was recorded every 0.1 s. Six to ten measurements per potential antioxidant were recorded with [antioxidant]/[DPPH•] ratios varying from 0.015 to 320. In parallel, a blank solution of DPPH• was screened to estimate DPPH• decomposition during the time of measurement.

Theoretical ΔH_{abs} calculations

All molecular models were constructed using standard bond lengths and angles with the MOE software package.[15] Following truncated Newton–Raphson geometry optimization with the MMFF94s force field (MMFF94 charges, dielectric constant $\varepsilon = 1r$) until the gradient was lower than 0.001 kcal mol^{-1}, a conformational search by means of quenched molecular dynamics (QMD) was performed to find low-energy starting conformers for subsequent quantum-mechanical (QM) calculations. Molecular dynamics simulations (100 ps) in vacuum were carried out at 1000 K with the MMFF94 force field as implemented in MOE, starting with a Boltzmann distribution of the atomic velocities. A time step of 1 fs was used, and a snapshot was taken every 0.5 ps, to accumulate 200 conformers for each run. Each conformer underwent a truncated Newton–Raphson energy minimization with the same protocol as described above. After eliminating duplicate conformers, the lowest-energy conformer was chosen for further optimization by an ab initio RHF/6-31G(d) method; vibrational frequencies were determined at the same level of theory to obtain the zero-point energy and the thermal contribution to the enthalpy at 298.15 K, scaled by a factor of 0.9135 as suggested by Scott and Radom.[16] All QM calculations were accomplished with the GAMESS-US software package.[17] As previous investigators found that the Hartree–Fock method leads to enthalpies which are significantly lower than the experimental values,[18] on the RHF geometry a single-point DFT calculation was run at the RB3LYP/6-311 + G(2d,2p) level, which was proven to give good results.[19] The electronic energy thus obtained was then corrected by the scaled zero-point vibrational energy and the thermal contribution to enthalpy at 298.15 K, yielding ΔH_f for the parent phenolic molecules. The radicals ArO$^{\bullet}$ were built by H-atom abstraction from the parent phenols ArOH. Geometry optimizations, vibrational analysis, and single-point energy calculations were run at the same level of theory used for the parent phenols, adopting the restricted open-shell method, yielding ΔH_f for the radical species. ΔH_{abs} for each compound was then calculated according to Equation (2). The values thus obtained represent O–H bond homolytic cleavage enthalpies relative to 6-hydroxy-2,2,5,7,8-pentamethylchroman (HPMC). All computations were performed on a Linux cluster (Intel Pentium IV 2.4–3.0 GHz; AMD Athlon XP 1.8–2.4 GHz).

Acknowledgements

This work was supported by a grant from the Italian Ministry for Education, University and Research (MIUR), Studi e Ricerche Finalizzate 40% Roma, and Regione Piemonte Ricerca Scientifica Applicata, CIPE 2004. We gratefully acknowledge the ShareGrid management team for the computing power provided through the ShareGrid distributed platform.[20]

Keywords: antioxidants · DPPH · phenols · radical reactions · structure–activity relationships

[1] M. K. Eberhardt, *Reactive Oxygen Metabolites*, CRC, Boca Raton, **2001**.
[2] "Phenols as antioxidants": L. Ross, C. Barclay, M. R. Vinqvist in *The Chemistry of Phenols, Part 2* (Ed.: Z. Rappoport), Wiley, New York, **2003**, pp. 839–908, and references therein.
[3] D. Boschi, G. C. Tron, L. Lazzarato, K. Chegaev, C. Cena, A. Di Stilo, M. Giorgis, M. Bertinaria, R. Fruttero, A. Gasco, *J. Med. Chem.* **2006**, *49*, 2886–2897.
[4] G. A. Dillon, J. A. Vita in *Contemporary Cardiology, Vol. 4* (Eds.: J. Loscalzo, J. A. Vita), Humana, Totowa, **2000**, pp. 207–226.
[5] C. A. Shaw, I. L. Megson, A. G. Rossi, *Anti-Inflammatory Anti-Allergy Agents Med. Chem.* **2006**, *5*, 27–33.
[6] M. Antolovich, P. D. Prenzler, E. Patsalides, S. McDonald, K. Robards, *Analyst* **2002**, *127*, 183–198.
[7] C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR—Hydrophobic, Electronic, and Steric Constants*, American Chemical Society, Washington DC (USA), **1995**.
[8] Bio-Loom for Windows v. 1.5, BioByte Corp., Claremont, CA (USA).
[9] M. C. Foti, C. Daquino, C. Geraci, *J. Org. Chem.* **2004**, *69*, 2309–2314.
[10] G. Litwinienko, K. U. Ingold, *J. Org. Chem.* **2004**, *69*, 5888–5896.
[11] M. Musialik, G. Litwinienko, *Org. Lett.* **2005**, *7*, 4951–4954.
[12] J. Ancerewicz, E. Migliavacca, P. A. Carrupt, B. Testa, F. Brée, R. Zini, J. P. Tillement, S. Labidalle, D. Guyot, A. M. Chauvet-Monges, A. Crevat, A. Le Ridant, *Free Radical Biol. Med.* **1998**, *25*, 113–120.
[13] O. Friaa, D. Brault, *Org. Biomol. Chem.* **2006**, *4*, 2417–2423.
[14] N. Noguchi, E. Niki, *Free Radical Biol. Med.* **2000**, *28*, 1538–1546.
[15] MOE version 2007.09, Chemical Computing Group Inc., Montreal, QC (Canada), 2008.
[16] A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502–16513.
[17] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.* **1993**, *14*, 1347–1363.
[18] H.-F. Ji, G.-Y. Tang, H.-Y. Zhang, *QSAR Comb. Sci.* **2005**, *24*, 826–830.
[19] J. S. Wright, E. R. Johnson, G. A. DiLabio, *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183.
[20] ShareGrid project, http://dcs.di.unipmn.it/ (Last accessed June 25, 2008).

Received: March 28, 2008
Revised: June 6, 2008
Published online on July 14, 2008

