SHORT PAPER

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Octan-1-ol / water partition coefficients of *p*-benzo- and *p*-naphthoquinones corrected for pH effect†

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A method was developed to quench the effect of pH on the determination of octan-1-ol / water partition coefficients (k_{ow}) of *p*-benzo- and *p*-naphthoquinones by using a mildly buffered aqueous phase.

Keywords: log*P*, pH effect, k_{ow}, quinones, octanol/water coefficient

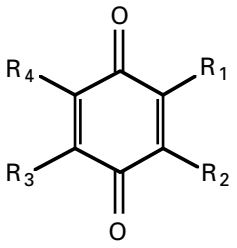
Quinones are important multifunctional biomolecules that are involved in many processes necessary for living organisms. One of their primary functions is to serve as electron acceptors/donors in redox cycles of cellular energy metabolism such as mitochondrial respiration and photosynthesis.[1–3] The diversity of structures found in natural quinones forms the basis for their versatility of functions. Many of the redox cycles involving quinones are localised within membranes to protect other biochemical processes from the potential deleterious effects of the highly reactive nature of some of the intermediate steps. As a result, biological quinones have specific lipophilic properties that allow them to remain compartmentalised.[4,5]

In spite of their biological importance, relatively little information is available on the lipophilicity of quinones,[6,7] and the limited amount of published data on these molecules contains inconsistencies. We postulated that contamination in the samples altered the pH of the aqueous phase during octan-1-ol/water partition coefficient (k_{ow}) determination.

When tested, the log*P* values (log10 k_{ow}) of 2,5-dichloro-*p*-benzoquinone (**2**) and 2-hydroxy-3-methyl-*p*-naphthoquinone (**21**) were indeed strongly affected by the pH of the aqueous phase used in the shake-flask experiment. For **2**, log*P* values at pHs 5, 7, and 9 were 1.8, 1.5 and 1.1, respectively, whereas the log*P* values were 2.5, 1.1, and 1.0 for **21**, respectively. Increasing the pH yielded apparent decrease in the lipophilicity of the quinones.

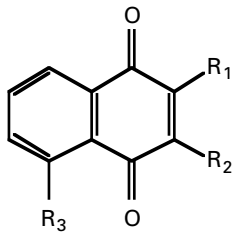
Therefore, a modified octan-1-ol/water partition protocol using slightly buffered water (1 mM Hepes) to maintain the pH at 7.0 was developed for reliable determination of the log*P* for a series of *p*-benzo- and *p*-naphthoquinones. Using this

Table 1 Log*P* of selected *p*-benzoquinones.



	Substitutions				
id	R_1	R_2	R_3	R_4	Log*P*
1	H	H	H	H	0.20
2	Cl	H	Cl	H	1.59
3	*t*-butyl	H	H	H	1.65
4	*t*-butyl	Cl	CH_3	H	1.80
5	Cl	Cl	Cl	Cl	2.29
5	I	I	I	I	2.47
7	H	phenyl	H	H	2.51
8	Br	Br	Br	Br	2.53
9	*t*-butyl	H	CH_3	H	2.65
10	Cl	Br	*t*-butyl	H	2.66
11	Br	CH_3	Br	Br	3.01
12	H	*p*-tolyl	H	H	3.01
13	Br	CH_3	H	H	3.10
14	OH	pentadecanyl	OCH_3	H	2.73
15	OH	8,11,14-pentadecatrienyl	OCH_2CH_3	H	3.28
16	OH	8,11,14-pentadecatrienyl	OCH_3	H	3.56
17	OCH_3	8,11,14-pentadecatrienyl	OCH_3	H	4.32

Table 2 Log*P* of selected *p*-naphthoquinones.



	Substitutions			
id	R_1	R_2	R_3	Log*P*
18	OH	Br	H	0.66
19	OH	H	H	0.67
20	OH	Cl	H	0.88
21	OH	CH_3	H	1.06
22	H	H	H	1.85
23	H	H	OH	2.05
24	H	Br	H	2.11
25	OH	3-Cl-3-methylbutyl	H	2.22
26	OH	2-methylbutyl	H	2.46
27	H	*n*-butyl	H	2.46
28	OH	dodecylaminomethyl	H	2.69
29	Cl	CH_3	H	2.69
30	OH	$CH_2CHC(CH_3)_2$	H	2.77
31	OH	*i*-butyl	H	2.77
32	Br	Br	H	2.87
33	OH	2-phenylbutyl	H	2.94
34	OH	3-methylbutyl	H	3.08
35	OH	2,3-dimethylbutyl	H	3.17
36	Cl	Cl	H	3.22
37	CH_3	H	OH	3.69
38	OH	4-tolylpropyl	H	3.89
39	OH	5-methylhexyl	H	4.09

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

method, the log*P* values of several of the quinones were within a narrow range of their published values. For example, the log*P* values of compounds **1**, **21**, **22**, **23**, **24**, **29**, and **32** (Tables 1 and 2) were within 0.15 units of their published values.[6,7] In cases where erroneous log*P* values had been noticed in the literature, such as with the *p*-naphthoquinones **19** and **21**, our protocol enabled accurate measurement of the log*P* (Table 2). The published log*P* of **19** (1.38) is greater than that of **21** (1.20),[6] whereas the presence of the methyl group on **21** would dictate that its log*P* should be greater than that of **19**. Using our protocol, the log*P* value of **21** remained within 0.14 unit at 1.06, whereas the value for 19 was significantly lower, at 0.67. This value also falls nicely within the range of similar *p*-naphthoquinones such as **18** and **20**, with log*P* of 0.66 and 0.88, respectively.

The published value for the dichloro-*p*-naphthoquinone **36** was listed as approximately 2.56[7] but the value measured using mildly buffered aqueous phase was significantly higher, at 3.22. The log*P* values for all remaining compounds, including those of the natural *p*-benzoquinones ethoxysorgoleone (**15**) and sorgoleone (**16**), and the natural *p*-naphthoquinones lawsone (**19**), juglone (**23**), lapachol (**30**), and plumbagine (**37**), have to our knowledge never been published previously.

The use of a mildly buffered aqueous phase during the measurement of octan-1-ol/water coefficient prevents undesirable changes in pH. The advantage of this modified shake-flask protocol is evident in this model study using quinones, and may also have broad applications for the determination of log*P* of any samples that contain impurities that affect pH.

Experimental

Octan-1-ol was mixed with 1 mM Hepes (*N*-2-hydroxyethylpiperazine-*N*′-2-ethane-sulfonic acid, sodium salt, pK_a 7.55) buffer, pH 7.0, 1:1 v/v and allowed to separate at room temperature (25°C). Stock solutions of each quinone were prepared in the water saturated octan-1-ol and their respective calibration curves (based on half-log incremental dilution from 333 to 3.3 μM) were obtained spectrophotometrically at A_{280} on a Shimadzu model UV3101PC spectrophotometer with the cell thermostabilised at 25°C. The k_{ow} was obtained either in 1/25 or 1/50 (octan-1-ol/buffer) ratios and all measurements were triplicated. The effect of pH on the octan-1-ol/water coefficient of quinones was determined as described above, except that the pH of the aqueous phase was adjusted to 5, 7 and 9 with either 0.1N NaOH or HCl.

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