Shortcomings and Complexities of Macrocycle Modeling: Salvaging AlogP and Identifying Structural Changes in Triazine-Containing Macrocycles

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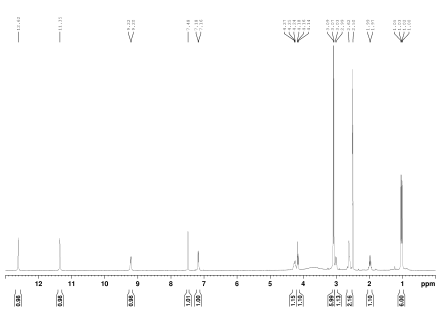
Abstract

Octanol/water partition coefficients guide drug design, but algorithms do not always accurately predict these values. For cationic triazine macrocycles that adopt a conserved folded shape in solution, common algorithms fall short. The logD values for 12 macrocycles differing in amino acid choice were predicted and then measured experimentally. On average, AlogP, XlogP, and ChemAxon predictions deviate by 0.9, 2.8, and 3.9 log units, with XlogP overestimating lipophilicity and AlogP and ChemAxon underestimating lipophilicity. Importantly, however, a linear relationship ($R^2 > 0.98$) exists between the values predicted by AlogP and the experimentally determined logD values, thus enabling more accurate predictions.

N-Alkylation is a common strategy to improve the permeability of cyclic peptides. Three isosteres of naturally occurring amino acids were incorporated into the macrocycles (*N*-Me glycine, *N*-Et glycine, *N*-Bn glycine). While the intuitive relationship between increasing hydrophobicity of a sidechain leading to a molecule with an overall larger logD value holds true for α-substituted amino acids, this relationship is not consistent with *N*-alkylated amino acids. Depending on the protonation state of the macrocycle, *N*-alkylation yields either more hydrophilic (pH ~ 7) or less hydrophilic (pH ~ 2) logD values with respect to the *N*-alkyl amino acid's isostere. This pH-dependent behavior is hypothesized to arise from differences in shape or population distribution. Protonation leads to a more static, folded conformation for macrocycles incorporating α-amino acids, but interruption of the hydrogen-bond network yields a different conformation for the *N*-alkyl macrocycles.

Previous paradigm: 24-membered triazine macrocycles adopt a folded, compact conformation within solution.



^{1}H Spectrum of **V-V**

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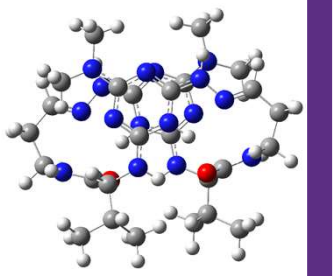


V-V
B3LYP/6-31G*
Optimized Structure

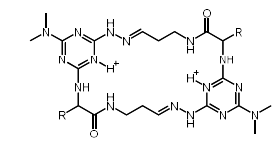
References

G-G:
ACS Omega **2022**, *7* (34), 30291-30296

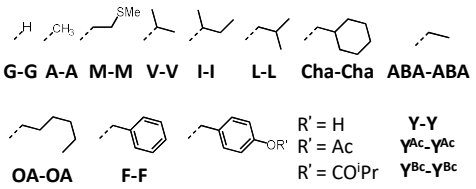
V-V, I-I:
J. Org. Chem. **2023**, *88* (5), 2692-2702

LogP Computation:
ACS Med. Chem. Lett. **2023**, *14* (10), 1378-1382

LogD Predictions With Empirical Computation Methods



A library of macrocycles used to investigate accuracy of empirical computational algorithms.

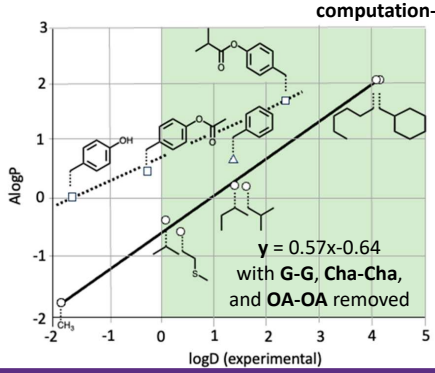


Computed logD values vary greatly from experimental values.

Cmpd	Exp.	AlogP	XlogP	ChAxon
G-G	-3.6	-2.6	0.1	-6.3
A-A	-1.9	-1.9	0.9	-5.4
Y-Y	-1.7	0.0	3.4	0.1
Y^{Ac}-Y^{Ac}	-0.3	0.5	3.6	-2.9
M-M	0.1	-0.4	2.2	-4.2
V-V	0.4	-0.6	2.9	-4.0
I-I	1.4	0.2	3.6	-3.3
F-F	1.4	0.6	4.1	-2.3
L-L	1.6	0.2	3.6	-3.5
Y^{Bc}-Y^{Bc}	2.4	1.7	5.7	-0.4
Cha-Cha	4.1	2.1	4.9	-1.4
OA-OA	4.1	2.1	6.0	-1.5

[a]Color indicates deviation from experimental values in log units: green (±1), yellow (±2), red (>2).

A linear regression can be drawn to give an experimentally corrected model for computation-directed prediction.



method	logD G−G	logD Cha−Cha	logD OA−OA	Error MAE	Error RMSE
expt	−3.6	4.1	4.1	–	–
AlogP	−2.6	2.1	2.1	1.0	1.2
AlogP-C	**−3.5**	**4.8**	**4.8**	**0.5**	**0.6**
XlogP	0.1	4.9	6.0	2.8	3.0
XlogP-C	**−3.1**	**3.4**	**4.8**	**0.6**	**0.6**
ChemAxon	−6.3	−1.4	−1.5	3.8	4.3
ChemAxon-C	**−3.7**	**5.0**	**5.0**	**0.6**	**0.7**

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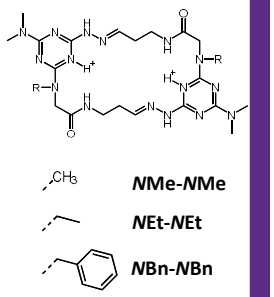
N-Alkylation and Lipophilicity

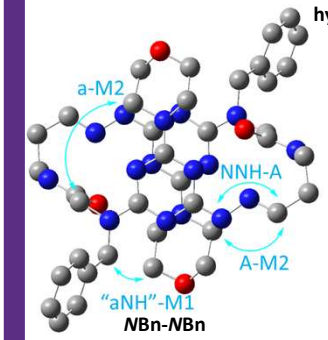
Isosteres investigate impact of *N*-alkylation on lipophilicity



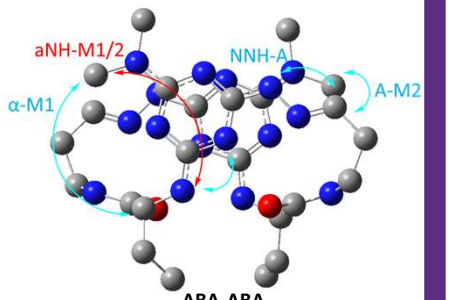
***N*-Alkyl isosteres are more hydrophobic when neutral, but more hydrophilic when protonated.**

Compound	logP (pH 10)	logD (pH 2)
G-G	-0.95	-3.60
A-A	-0.20	-2.29
*N*Me-*N*Me	0.43	-3.37
ABA-ABA	0.35	-1.03
*N*Et-*N*Et	1.24	-1.93
F-F	0.73	1.44
*N*Bn-*N*Bn	1.59	-1.93

***N*-Alkylation yields a different conformation by disruption of an intramolecular hydrogen-bond network.**



***N*Bn-*N*Bn**
("αNH"-M1 present)



ABA-ABA
(αNH-M1/2 missing)

^{1}H NMR indicates the presence of subpopulations for *N*-alkyl macrocycles