13. Choy, J. H.; Demazeau, G.; Byeon, S. H.; Dance, J. M. *J. Phys. Chem. Solids* **1990**, *51*, 391.
14. Choy, J. H.; Demazeau, G.; Hong, S. T. *Jpn. J. Appl. Phys.* **1992**, *31*, 3649.
15. Goodenough, J. B. *Phys. Rev.* **1967**, *164*(2), 785.
16. Choy, J. H.; Hong, S. T.; Kim, S. J. *J. Korean Ceram. Soc.* **1991**, *28*(8), 603.
17. Choy, J. H.; Hong, S. T. *Bull. Korean Chem. Soc.* **1991**, *12*(3), 349.
18. Galasso, F. S.; Katz, L.; Ward, R. *J. Am. Chem. Soc.* **1959**, *81*, 820.
19. Takeda, T.; Watanabe, A.; Sugihara, K. *Phys. Lett.* **1968**, *A27*, 114.
20. Dernov-Pigarev, V. F.; Zaripov, M. M.; Samoiloich, M. I.; Stepanov, V. G. *Fiz. Tverd. Tela.* **1965**, *7*, 3688.
21. Kim, E.; Demazeau, G.; Dance, J. M.; Pouchard, M.; Hagenmuller, P. *C.R. Acad. Sci.* Ser. 2, **1985**, *16*, 491.
22. Müller, K. A. *Helv. Phys. Acta.* **1960**, *33*, 497.
23. Müller, K. A. *Phys. Rev. Lett.* **1959**, *2*, 341.
24. Geschwind, S.; Kisliuk, R.; Klein, M. P.; Remeika, J. P.; Wood, D. L. *Phys. Rev.* **1962**, *126*, 1684.
25. Henderson, B. *Proc. Phys. Soc.* **1967**, *92*, 1064.
26. Carrington, A.; Ingram, D. J. E.; Lott, K. A. K. *Proc. Roy. Soc. London.* **1960**, *A254*, 101.
27. Luwig, G. W.; Woodbury, H. H. *Solid State Physics*; Vol. 1, eds. Seitz, F. and Turnbull, D.; Academic Press: New York, 1962.
28. Goodenough, J. B. *Phys. Rev.* **1955**, *100*, 564.
29. Goodenough, J. B.; Loeb, A. L. *Phys. Rev.* **1955**, *98*(2), 391.
30. Selwood, P. W. *Magnetochemistry*; 2nd ed.; chap. 5; Interscience: New York, 1967.
31. Figgis, B. N. *Introduction to Ligand Fields*; Interscience: New York, 1966.

Modified LOGIT(MLOGIT) Transformation: Prediction of IC_{50} Value from Two Arbitrary Concentration Data

Sung-Eun Yoo* and Ok Ja Cha

Korea Research Institute of Chemical Technology, Daedeog-Danji, Taejon 305-606, Korea
Received September 9, 1994

A LOGIT transformation is a method to estimate IC_{50} values with two arbitrary concentration data when complete dose response curves (DRCs) are not available. We propose a modified LOGIT transformation (MLOGIT) which predicts IC_{50} values more accurately than the conventional LOGIT method.

Introduction

In a QSAR (Quantitative Structure Activity Relationship) analysis, a thermodynamic property representing biological responses is commonly expressed in IC_{50} value which is the molar concentration of a compound resulting in a half-maximum inhibition response. The IC_{50} is normally obtained experimentally from dose response curves. However, it is troublesome to obtain complete dose response curves due to several practical reasons.

Therefore, a logit transformation[1,2] has been developed as a way of predicting IC_{50} when only two arbitrary concentration data are available. A logit transformation is carried out as follows:[2]

1. The logit transformed formula at the concentrations C is: $\log [R_c/(100-R_c)]$

R_c = Response in % at the concentration C

2. $L_c = \log [R_c/(100-R_c)] - \log C$

L_c = logit value at the concentration C

3. LOGIT = $(L_{c1}+L_{c2})/2$

L_{c1} and L_{c2} are logit values at concentrations $C1$ and $C2$.

This transformation is based on the assumption that all compounds would have the same shape of dose response curves and that the response would be within the linear part of the sigmoidal dose response curve. Also it is based on the assumption that one response is less than 50% and the other one is more than 50%.

Table 1. LOGIT and MLOGIT value[a]

#	$C1$	R_{c1}	$C2$	R_{c2}	L_{c1}	L_{c2}	LOGIT	MLOGIT
1	3	29	10	64	5.13	5.25	5.19	5.20
2	3	29	32	88	5.13	5.36	5.25	5.21
3	10	64	32	88	5.25	5.36	5.31	5.19

[a] $C1$ and $C2$ are concentration in μm of compound **6** in reference 3. R_{c1} and R_{c2} are response in % at concentration $C1$ and $C2$. L_{c1} and L_{c2} are logit value at concentration $C1$ and $C2$. Observed pI_{50} of compound **6** is 5.20.

Results and Discussion

The LOGIT values calculated using data from Table 1 in reference 3 are plotted against the observed pI_{50}, $\log(1/IC_{50})$, to show a good correlation ($r^2 = 0.994$) in Figure 1.[4]

However, as shown in Figure 1, the LOGIT values vary depending on the response values used. For example, if

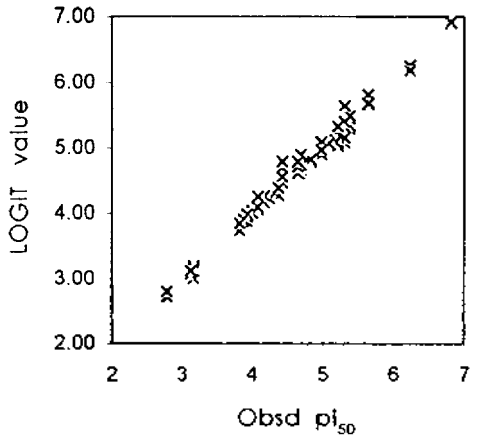

Figure 1. The plot of the LOGIT value versus observed pI_{50}. The observed pI_{50} are from ref. 3. The LOGIT values were calculated by LOGIT transformed equation using the data from ref. 3.

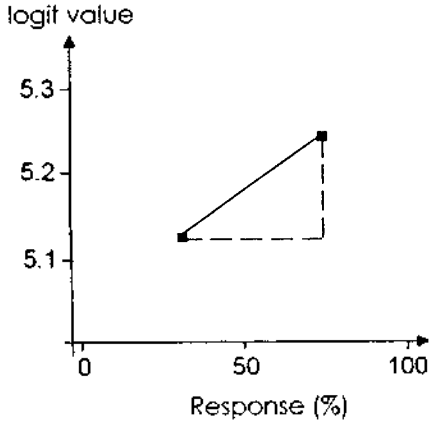

Figure 2. The plot of the logit value versus response in %.

three response values are 29%, 64%, and 88% at the concentrations of 3, 10, and 32 μm, and then the logit values would be 5.13, 5.25, and 5.36 respectively (Table 1). From these, the LOGIT values of #1 and #2 would be either 5.19 or 5.25, while the observed pI_{50} is 5.20. These results show that the logit value increases with the response value.

Therefore, it is desirable to modify the conventional LOGIT transformation equation to minimize the deviation. Our assumption is that if the logit value is linear to the response in %, then a linear equation would be expressed by Equation 1, which can be expressed graphically in Figure 2.

$$L_c=[(L_{c2}-L_{c1})/(R_{c2}-R_{c1})]R_c+b \quad (1)$$

R_{c1} and R_{c2} are responses in % at concentrations $C1$ and $C2$. b is an intercept on Y axis.

Therefore, the logit value for 50% response would be then a new equation 2, which is the formula for the Modified LOGIT (MLOGIT) transformation.

$$\text{MLOGIT}=L_c+(50\%-R_c)[(L_{c2}-L_{c1})/(R_{c2}-R_{c1})] \quad (2)$$

In order to demonstrate the usefulness of the new method,

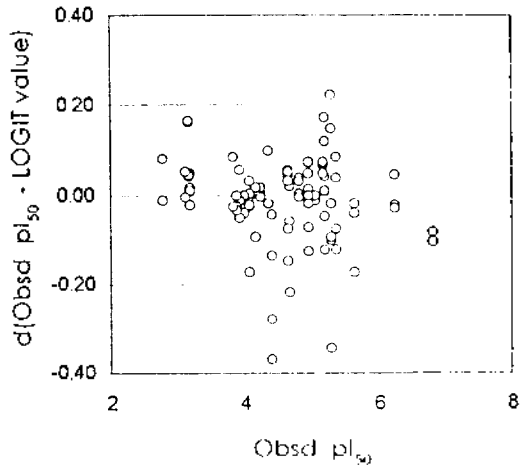

Figure 3. The plot between the difference observed pI_{50} and LOGIT value versus observed pI_{50}. See the legend of Figure 1 for the pI_{50} and the LOGIT values.

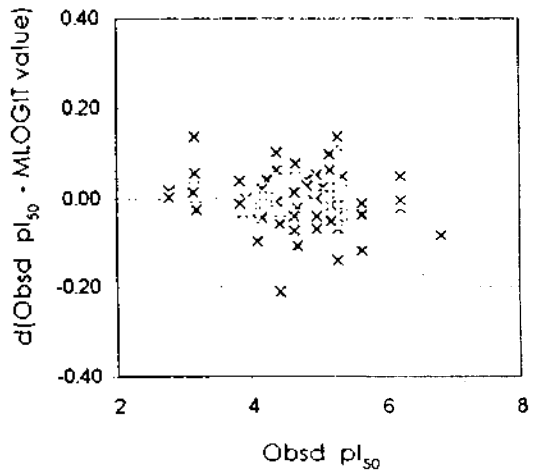

Figure 4. The plot between the differences observed pI_{50} and MLOGIT value versus observed pI_{50}. The observed pI_{50} are from ref. 3. The MLOGIT values were calculated by MLOGIT transformed equation using the data from ref. 3.

we calculated the MLOGIT values with two arbitrary selected concentrations from the data[4] of Table 1 in reference 3. The results showed that the predictability of the LOGIT method and the MLOGIT method is almost same when the response is in the range of 20-80%. However, when the response is either less than 20% or higher than 80%, the predictability of the MLOGIT method is much higher than that of the LOGIT method. Figures 3 and 4 show the difference between the observed pI_{50} and the estimated pI_{50} values by the LOGIT method and the MLOGIT method, respectively. Comparing Figure 3 with Figure 4, we can see that the deviation by the MLOGIT method is smaller than the deviation by the LOGIT method.

In this study we have demonstrated that the MLOGIT transformation method is a better method than the conventional LOGIT one in predicting pI_{50} values. In particular, it was found that this method is more useful than the LOGIT

method when the response value is either 10-20% or 80-90%.

Acknowledgment. We thank Tripos Associates for providing us the SYBYL® program.

References

1. (a) McPherson, G. A. *J. Pharmacol. Meth.* **1985**, *13*, 125. (b) Schaper, K. J. *Pharmacochem. Libr.* **1987**, *10*, 58.
2. SYBYL 6.0 Manual, **1992**, p. 2271-2273, Tripos Associates, Inc.
3. Fuller, R. W.; Molloy, B. B.; Day, W. A.; Roush, B. W.; Marsh, M. M. *J. Med. Chem.* **1973**, *16*, 101.
4. We used the data which fall in the range of 10-90% from Table 1 in reference 3.

Semiempirical MO Study on Malonyl-CoA. 1. Malonic Acid and Malonyl Methyl Sulfide

In Kee Yoo, Young Ju Kim, Shi Choon Kim, Yu Sam Kim†, and Young Kee Kang*‡

Department of Chemistry, Hanyang University, Seoul 133-791, Korea
†Department of Biochemistry and Bioproducts Research Center, Yonsei University, Seoul 120-749, Korea
‡Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 360-763, Korea
Received September 14, 1994

The conformational study on malonic acid, hydrogen malonate, malonate, malonyl methyl sulfide, and malonyl methyl sulfide anion, as the model compounds of malonyl-CoA, was carried out using the semiempirical MO methods (MNDO, AM1, and PM3) and hydration shell model. On the whole, the feasible conformations of malonic acid, hydrogen malonate, and malonate seem to be similar to each other. In malonic acid and malonate, two carboxyl groups are nearly perpendicular to the plane of the carbon skeleton, despite of different orientation of two carboxyl groups themselves. In particular, two carboxyl groups of hydrogen malonate are on the plane formed by carbon atoms with an intramolecular hydrogen bond. The calculated results on the geometry and conformation of three compounds are reasonably consistent with those of X-ray and spectroscopic experiments as well as the previous calculations. The orientation of two carbonyl groups of malonyl methyl sulfide is quite similar to that of malonic acid, but different from that of its anion. Especially, the computed probable conformations of the sulfide anion by the three methods are different from each other. The role of hydration seems not to be crucial in stabilizing the overall conformations of malonic acid, hydrogen malonate, malonate, and malonyl methyl sulfide. However, the probable conformations of the unhydrated sulfide anion obtained by the MNDO and AM1 methods become less stabilized by including hydration. The AM1 method seems to be appropriate for conformational study of malonyl-CoA and its model compounds because it does not result in the formation of too strong hydrogen bonds and significant change in conformational energy from one compound to another.

Introduction

Malonyl-CoA synthetase catalyses the formation of malonyl-CoA directly from malonate and CoA in the presence of ATP and Mg^{2+}, which was first purified and characterized from *Bradyrhizobium japonicum*.[1] This enzyme has been proposed to play a role in regulation of glutamate in rat brain mitochondria[2] and in symbiotic nitrogen metabolism between soybean and *B. japonicum*.[3] In spite of the recent kinetic studies on malonyl-CoA synthetase,[4] the catalytic mechanism was not established yet. In addition, the substrate malonyl-CoA is known to participate in the biosynthesis of fatty acids.[5a]

Malonate, an analog of succinate, is a strong competitive inhibitor of succinate dehydrogenase and therefore blocks the citric acid cycle.[5b] The structure of malonate was studied by X-ray experiments and theoretical methods.[6] In particular, considerable experiments and calculations have been carried out on the conformations of malonic acid[7] and hydrogen malonate[8] in order to interpret the anomalous ratio of the first and second dissociation constants of malonic acid in terms of the formation of intramolecular hydrogen bonds.[9]

In the present study, the conformations of malonic acid, hydrogen malonate, malonate, and malonyl methyl sulfide in the unhydrated and hydrated states were studied using the semiempirical MO methods and hydration shell model to determine the detailed structure of the malonyl-CoA and the hydration effect as a first step in understanding the biochemical functions of malonyl-CoA synthetase.

Methods

The chemical structure and torsion angles of malonic acid and malonyl methyl sulfide are shown in Figure 1. The same

*To whom correspondence should be addressed.