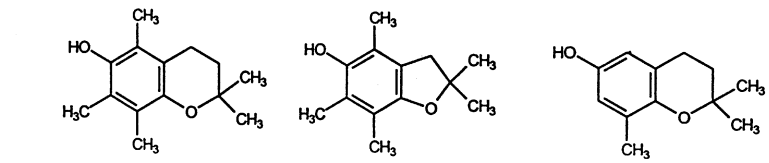
Investigation on the Effectiveness of HOMO to Characterize Antioxidant Activity

Sir:

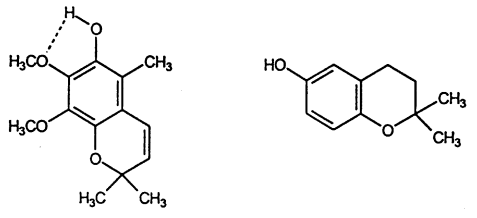
Owing to the importance and the difficulty of selecting applicable antioxidants, theoretical methods capable of accelerating the selection process are paid much attention. Various parameters have been found appropriate to characterize the free-radical scavenging activities of antioxidants, such as the difference in the heat of formation (ΔHOF) between the antioxidant and its free radical (1,2), the dissociation energy of the O-H bond [D(O-H) or ΔH_{abs}] (3–5), and the highest occupied molecular orbit (HOMO) (5–7). The effectiveness of ΔHOF, D(O-H), and ΔH_{abs} can be understood easily, as they all represent the strength of the O-H bond. The lower strength of the O-H bond corresponds to a higher scavenging activity. However, it is somewhat astonishing to see that HOMO, a parameter representing the molecular electron-donating ability, is also a good index predicting antioxidant activity. van Acker *et al.* have found a poor correlation between the ionization potential (IP) and the logarithm of the free-radical scavenging activity (log k_s) for tocopherolic antioxidants (TA) (1). Of course, HOMO is of great advantage in practice because the calculation of ΔHOF, D(O-H) or ΔH_{abs} is a much more time-consuming process compared with the calculation of HOMO. And the good correlation between HOMO and log k_s suggests that an electron transfer mechanism is involved in the antioxidative process (5), which is helpful in understanding the H-abstraction reaction of antioxidants. Perhaps unfortunately, the effectiveness of HOMO is only a superficial phenomenon to a certain extent.

TA compounds are similar in structure, and all possess para-methoxyphenol as an active center. The difference between TA mainly arises from the number and properties of the substituting groups. Taking into consideration that electron-donating groups enhance the HOMO level and reduce the strength of the O-H bond at the same time (1,8), we believe that the correlation between HOMO and log k_s only re-



I II III

	I	II	III
HOMO	-8.33eV	-8.37eV	-8.41eV
ΔH_{abs}	0.00kcal/mol	-0.31kcal/mol	2.51kcal/mol
log k_s	3.71	3.84	3.00



IV V

	IV	V
HOMO	-8.41eV	-8.49eV
ΔH_{abs}	3.23kcal/mol	2.38kcal/mol
log k_s	2.75	2.75

FIG. 1. Structures of some tocopherols. See Reference 5 for more illustrations and data.

Copyright © 1999 by AOCS Press

flects a correlation between the parameters characterizing the strength of the O-H bond, e.g., ΔH_{abs}, and log k_s. Indeed, a correlation has been found between them ($r = -0.812$) (5). Thus, to a certain extent, the effectiveness of HOMO is only a superficial phenomenon. Consequently, the conclusion that an electron-transfer mechanism must be involved in an H-abstraction reaction of antioxidants cannot be based only on the effectiveness of HOMO.

Further analysis indicates that a slight difference exists between HOMO and ΔH_{abs}. Firstly, ΔH_{abs} is better than HOMO in predicting free-radical scavenging activity differences between six-membered tocopherol analogs and five-membered tocopherol analogs. For instance, ΔH_{abs} of molecule **II** is lower than that of molecule **I** (Fig. 1), so the former is more active than the latter, which is consistent with the experiment (5). But the prediction based on HOMO gives an opposite result (5). Secondly, ΔH_{abs} is better than HOMO in characterizing antioxidant activity with the formation of hydrogen bonds. For example, in contrast to the invalidity of HOMO, ΔH_{abs} can give a correct prediction for activity differences between molecules **III** and **IV**, in which a hydrogen bond is formed (5). In fact, HOMO is invalid for predicting the antioxidative activities of flavonoid antioxidants that possess many intramolecular hydrogen bonds (9). Finally, HOMO is better than ΔH_{abs} in predicting the activity of TA in the presence of a *meta*-methyl group. For example, HOMO can give a correct prediction for the difference between molecules **III** and **V**, but ΔH_{abs} cannot (5). This difference between ΔH_{abs} and HOMO can be explained by high-level quantum chemical calculation.

Therefore, although the correlation between HOMO and log k_s arises from the correlation between HOMO and ΔH_{abs} to a certain extent, HOMO is better than ΔH_{abs} in some situations. The invalidity of ΔH_{abs} suggests that an electron-transfer mechanism really exists in H-abstraction for antioxidants, but the extent of the mechanism involved must be determined by calculation on the transition states of the H-abstraction process.

REFERENCES

1. van Acker, S.A.B.E., L.M.H. Koymans, and A. Bast, Molecular Pharmacology of Vitamin E: Structural Aspects of Antioxidant Activity, *Free Radical Biol. Med. 15*:311–328 (1993).
2. Zhang, H.-Y., Selection of Theoretical Parameter Characterizing Scavenging Activity of Antioxidants on Free Radicals, *J. Am. Oil Chem. Soc. 75*:1705–1709 (1998).
3. Tomiyama, S., S. Sakai, T. Nishiyama, and F. Yamada, Factors Influencing the Antioxidant Activities of Phenols by an *ab initio* Study, *Bull. Chem. Soc. Jpn. 66*:299–304 (1993).
4. Yamamura, T., K. Suzuki, T. Yamaguchi, and T. Nishiyama, Antioxidant Activities of Phenothiazines and Related Compounds: Correlation Between the Antioxidant Activities and Dissociation Energies of O-H or N-H Bonds, *Bull. Chem. Soc. Jpn. 70*:413–419 (1997).
5. Migliavacca, E., P.A. Carrupt, and B. Testa, Theoretical Parameters to Characterize Antioxidants. Part 1. The Case of Vitamin E and Analogs, *Helv. Chim. Acta 80*:1613–1626 (1997).
6. He, D., Z. Wang, and F. Mo, Studies on the Relationship Between Electronic Structure and Antioxidant Activity of Vitamin E, *Chin. J. Med. Chem. 6*:157–161 (1996).
7. Liu, S.L., J.H. Pan, D.Y. Shi, K.X. Chen, Q.M. Wang, S.M. Chen, and X.M. Yan, Relationship Between Structure and Anti-Oxidation of Tocopherol with Molecular Orbit Theory, *Acta Pharmacol. Sin. 19*:513–518 (1998).
8. Zhang, H.-Y., Theoretical Elucidation of Structure-Activity Relationships of Flavonoid Antioxidants, *Sci. China, Ser. B 42*:106–112 (1999).
9. Zhang, H.-Y., Theoretical Methods Used in Elucidating Activity Differences of Phenolic Antioxidants, *J. Am. Oil Chem. Soc. 76*: 745–748 (1999).

Hong-Yu Zhang
Department of Biology
Shandong Teachers' University
Jinan, 250014
People's Republic of China

[Received March 25, 1999; accepted May 5, 1999]