Communications to the Editor

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MOLECULAR ORBITAL CONSIDERATION OF THE COOPERATIVE EFFECT OF MULTIPLE SUBSTITUENTS IN SOME BIOLOGICALLY ACTIVE CINNAMATE DERIVATIVES

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Molecular orbital quantities of several cinnamate derivatives were calculated by the CNDO/2 method to evaluate the influence of the cooperative effect of multiple hydroxy substituents on their electronic features. The pathways undergone in TFA have been differentiated from each other by such substituents, which were totally consistent with the indices deduced from the calculated quantum chemical quantities.

KEYWORDS —— MO calculations; CNDO/2; FMO; cooperative substituent effect; dimerization; cationic polymerization; cinnamic acid; p-coumaric acid; cafferic acid

Various studies of the oxidative dimerization of cinnamic derivatives have been reported, in part from the biological and pharmacological interest. Oxidative phenolic coupling with ferric chloride and oxygen,[1, 2] anodic oxidation,[3] and non-phenolic coupling[4] with thallium (III) trifluoroacetate of 4-hydroxy cinnamic derivatives have been shown to afford various types of dimeric products such as asatone-type dimers,[3] pinorecinol-type bis-lactones[3,4] and others.

The substituted cinnamic derivatives such as p-coumaric, cafferic, ferulic and sinapic acid are widely distributed in plants and are found in various combined forms, some of which have biological and pharmacological activities. For instance, ferulic acid and its derivatives such as γ-oryzanol are well known to have a variety of such activities.

Our interest in the physicochemical properties of cinnamate derivatives began with the question of whether the cooperative substituent activity intrinsic in the 3,4-disubstitution by the hydroxy and/or alkoxy groups is effective on the aromatic rings of the cinnamic derivatives, since many biologically active aromatic compounds are known to have the ring substituents capable of rendering the cooperative effect. Thus, as we felt it worthwhile to evaluate the nature and magnitude of such effects exerted on the electronic features of cinnamic derivatives, we have undertaken the molecular orbital calculations, supported by CNDO/2 approximation,[5] on several hydroxy cinnamate derivatives.

We report here some quantum chemical properties and quantities disclosed by such calculations. Also, the predictions derived from the computed quantities were found to be consistent with the reaction course in strong acid differentiated by the substituent effects.

The two highest occupied and lowest unoccupied molecular orbitals for several cinnamate derivatives were shown in Figure 1.

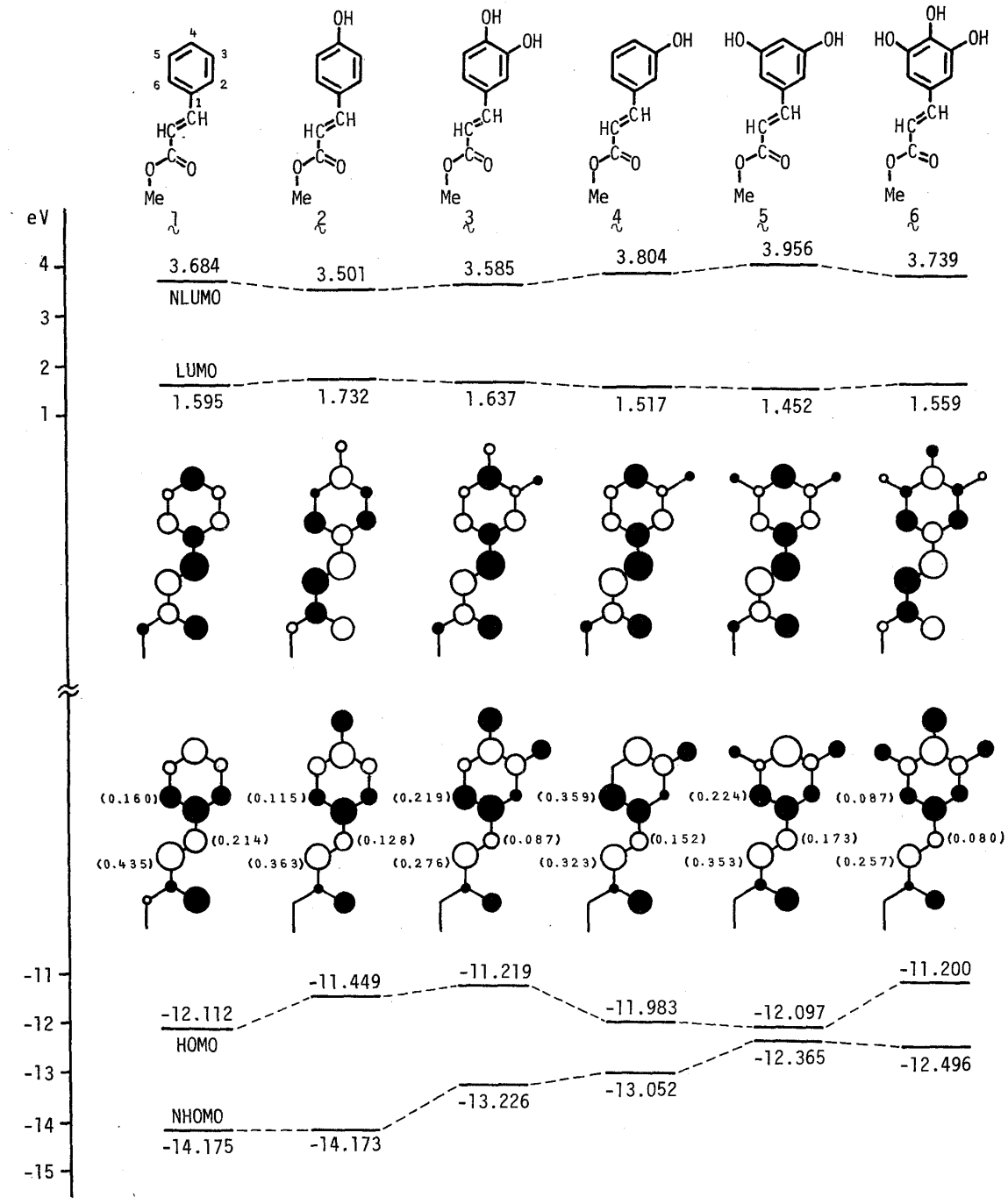

Fig. 1. Frontier Molecular Orbital Energies and Coefficient Distribution of some Hydroxy Derivatives of Methyl Cinnamates Calculated by the CNDO/2 Method

The numbers in parentheses are frontier electron densities ($f_r=2xC_r^2$). NHOMO and NLUMO denote Next Highest Occupied Molecular Orbital and Next Lowest Unoccupied Molecular Orbital, respectively.

Inspection of Figure 1 shows that the HOMO and NHOMO energies and the HOMO nodal properties were more affected than those of the LUMO and NLUMO by the introduction of electron donating hydroxy substituents into the methyl cinnamate (1). The HOMO energies of hydroxy cinnamates (2-6) were all raised relative to that of 1, as expected. Thus, a primary concern of the present study is analysis of the reaction with the electrophilic reagents where the HOMO plays an important role. It can also be seen that α-carbon to the carbonyl function of 1 has the largest HOMO coefficient, i.e. the largest frontier electron densities, among the relevant sites of the reaction with a "soft" electrophilic reagent. The 4-hydroxy substituent raises the HOMO energy level enough to enhance the reactivity and stabilizes the benzyl-type carbocation formed by a protonation of a "hard" strong acid to the carbonyl oxygen due to the largest electron density, whereas the 3-hydroxy substituent raises the NHOMO energy level; but the resulting level is still considerably lower than that of HOMO. Thus, the NHOMO may be of minor importance in FMO term. The 3-hydroxy substituent may also enhance the reactivity of the aromatic C_6-position as indicated by the largest HOMO coefficient in 4. Furthermore, one of the interesting features is that the HOMO energy raise caused by the 3,4-dihydroxy substitution is higher than the total raise by 4-hydroxy- and 3-hydroxy substitution, although the coefficient distribution is of an additive feature between 2 and 4. This cooperative effect may lead to a higher reactivity of 3 with electrophiles.

Thus, the reactions of several cinnamate derivatives (7a-d) with trifluoroacetic acid (TFA) were examined at room temperature.[6] It has been found that the pathways were markedly different from each other due to the presence and absence of methoxy substituents at 3- and 4-position of an aromatic ring. Unsubstituted methyl cinnamate (7a) and 3-methoxy derivative (7d) were recovered unchanged even after a prolonged treatment. The 4-methoxy derivative (7b) underwent a cationic polymerization on the vinyl bond to give a oligomer (9) in essentially quantitative yield, which was of ca. 2100 molecular weight as determined by GPC measurement, whereas the 3,4-dimethoxy derivative (7c) underwent a relatively rapid dimerization to afford, virtually quantitatively, a dimer (10) in which one of the aromatic ring participated in the reaction.[7] The structure of these products follow from their spectral properties.[8] These results are summarized in Chart 1.

One can expect that the selectivity between an intermolecualr polymerization and an intramolecular cyclization, as in the case of 7b and 7c, would be controlled by the HOMO properties of alkylated phenol derivatives as shown Chart 1. Thus, we have also carried out similar calculations on several cresol derivatives and found that their HOMO nodal properties and relative energy levels have the same trend as those of the corresponding cinnamate derivatives, except for 3,5-dihydroxy derivative. This indicates that the hydroxy groups, in general, exert greater influence on the HOMO properties than acrylic group. The intramolecular cyclization, therefore, was preferred in the case of 7c due to the presence of the 3-methoxy substituent.

With a view to further examining the criteria of the calculated indices, we also performed the similar treatment of 7c with 7d in TFA and obtained the dimer (11)[8] in 41% yield along with 10 in accordance with the expectation, as shown in Chart 1.

Thus, our results provide a novel example of the ways in which substituents can alter the reaction course and the site selectivity can be rationalized in terms of frontier electron densities (f_r). Further theoretical and experimental work aimed at observing such cooperative substituent effects on the excited state of cinnamate derivatives and on those incorporated into polymer backbone chain are in progress.

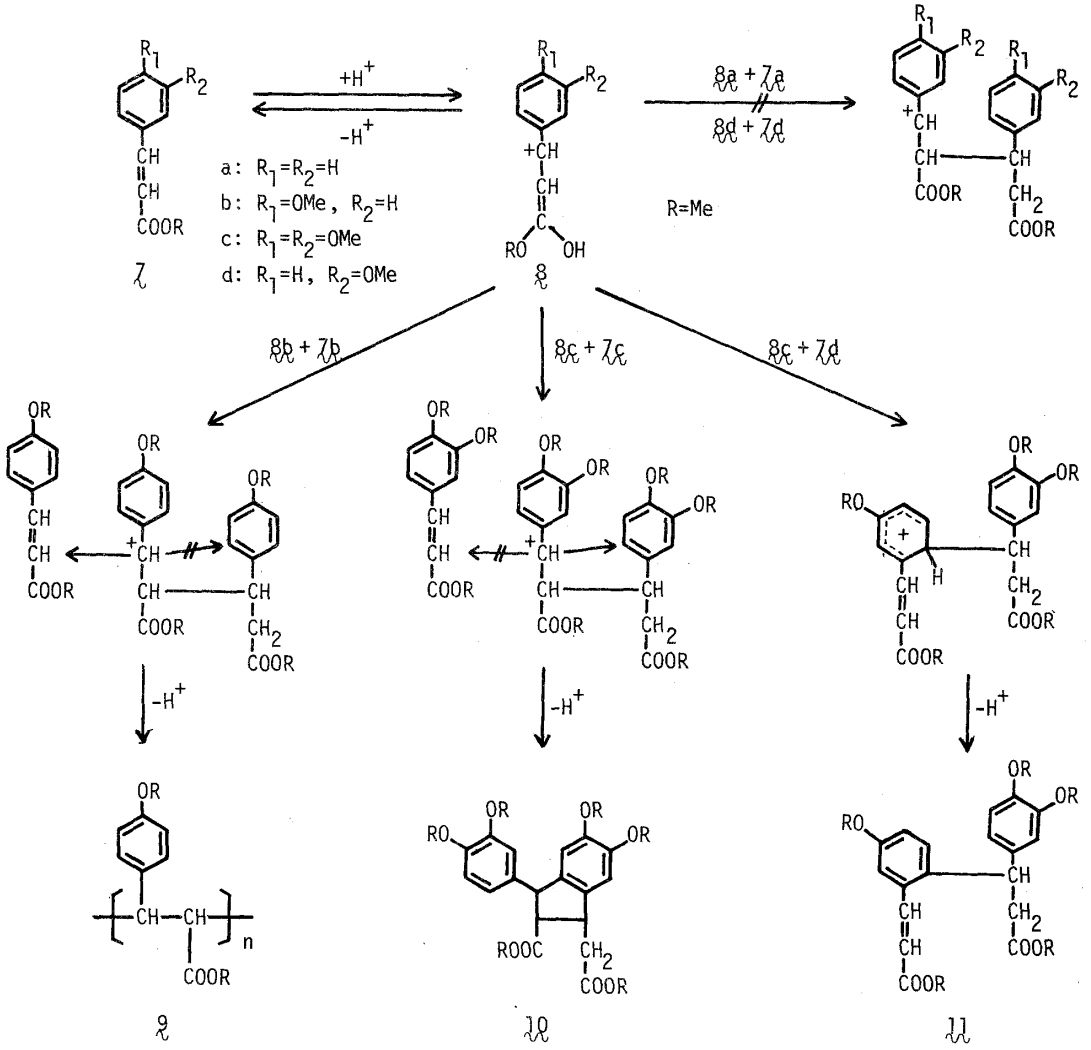

Chart 1

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5) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGrow-Hill, New York (1970). The geometries of the cinnamates with C_s symmetry were taken, and the values of the parameters adopted are the same as those in the original paper.
6) Preliminary treatment of various hydroxy cinnamic acids with TFA was found to give the same type of product as the methoxy derivatives of methyl cinnamates. Thus, detailed examinations were carried out on methoxy derivatives for ease of the product purification.
7) K. Freudenberg and G. Schuhmacher, Chem. Ber., 87 1882 (1954).
8) Full details of the spectral data will be presented in a full paper.

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