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THE REAGENT DESIGN AND STUDY OF THIOPHENE DERIVATIVES ON THE BASIS OF THE CONCEPT OF THE CYCLIC CONJUGATION

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Abstract - The concept of continuity and discontinuity of the cyclic conjugation provides us a reliable way of predicting the cycloadditivity of five-membered heterocyclic compounds as 4π-source in the cycloaddition.

The ever-increasing interest in the chemistry of cycloaddition has led to a continuing search for new and reactive diene components that can be applied to carbon skeleton constructions. Use of cyclopentadienones as potential 4π source achieved great success in the field of strained cage molecules which are used for a model of solar energy storing systems.[1] In this sence, many attempts have been made to use conveniently available five-membered heterocyclic compounds as the four carbon (4C) source. However, many workers have recorded a lack of success in the attempted reactions of the compound with dienophiles. In general, these reactions are expected to be difficult. Few examples are known of reactions with this class of compounds. Exceptions perhaps are the cycloaddition of electron-deficient dienophiles and furans.[2]

Taking thought for this situation, it seems to be necessary to make a comprehensive compilation of the scattered reports to establish a principle for prediction of reactivity of the five membered heterocyclic compounds. We wish to present here a report on employment of the concept of the cyclic conjugation[3] in designing powerfull 4C-synthon using thiophene derivatives in comparison with the previous works.[4]

For the prediction of cycloadditivity of diene and dienophile, frontier molecular orbital (FMO) theory[5] is very useful and provides us a simple but a reliable way of predicting the reactivity of reactants in the cycloaddition by inspection of their FMO levels and coefficients. If only frontier orbital separation was considered,[6] unsubstituted thiophene (Ia) (HOMO -11.9 eV), which has HOMO level ca. 1 eV higher than butadiene (HOMO -13.0 eV), would be expected to behave like a conjugated alkene with LUMO-controlled dienophiles. However, in general, these reactions could not be observed (Figure 1).

In expectation of enhancement of the reactivity toward electron-rich species such as seven-membered ring unsaturated compounds, we have undertaken the synthesis of thiophene derivatives with a low LUMO energy level by introducing the electron-attracting substituents. On the contrary to the expectation, 2,3,4,5-tetrakis(methoxycarbonyl)thiophene (Ib) also did not show any reactivity toward good donor dienophiles such as alkyl vinyl ether or N-vinylcarbazole. On the other hand, elec-

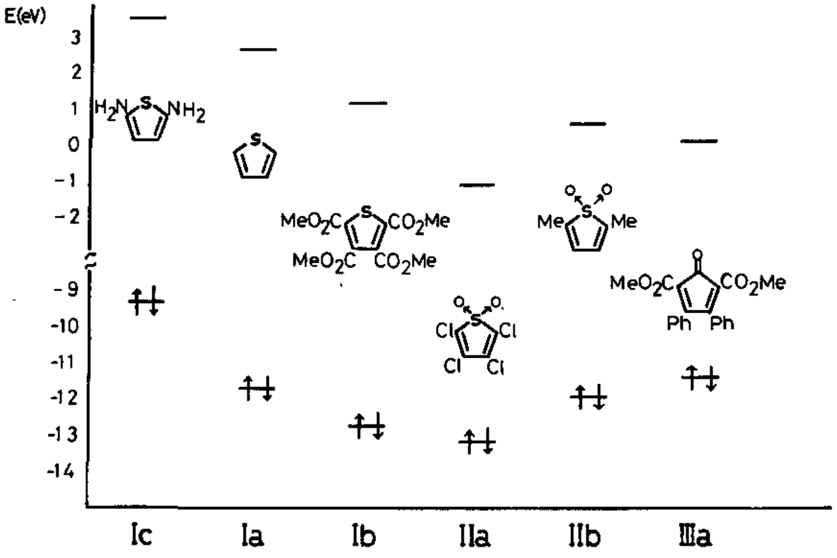
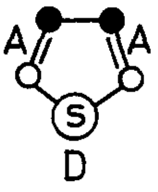


Figure 1. Frontier orbital energy levels calculated by the CNDO/2 MO method.

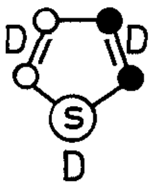
tron-rich disubstituted thiophenes with amino group were reported to act as diene toward electron-deficient dienophiles under severe conditions to give the desulfurized adducts.[7] Thus, the cycloaddition behavior of thiophene derivatives has been outstandingly puzzling for synthetic chemists.

Recently, Inagaki and Hirabayashi[3] reported that the degree of cyclic electron delocalization depends on mode of donor-acceptor arrangements of component systems as well as orbital phase continuity requirements and a novel notion of continuity-discontinuity of cyclic conjugation is able to be employed in predicting electron properties of unknown molecules without nuisance theoretical calculations.

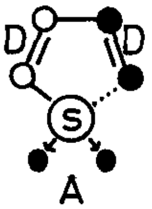
In thiophene (Ia), electron-donating sulfur lone pair electrons and electron-accepting C=C bonds are donor (D) and acceptors (A's), respectively. The cyclic conjugation is continuous and



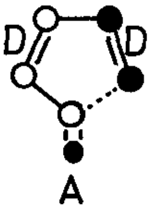
Ia,b



Ic



IIa,b



III

the orbital phase continuity requirements[8] are satisfied responsible for aromatic electron system.

In 2,3,4,5-tetrakis(methoxycarbonyl)thiophene (Ib), electron delocalization is expected to be more extensive, in which replacement of hydrogens by powerful acceptors makes effective donor-acceptor interaction[9] possible. By contrast, in 2,5-diaminothiophene (Ic), donor-acceptor interaction does not occur effectively to result in the destabilization of the cyclic three-system interaction. The localization of the electron destroys the aromatic character of thiophene to allow it to act as donor-diene. According to the CNDO/2 MO calculation on 2,5-diaminothiophene (Ic), considerable energy raising is observed; the calculations indicate 2.6 and 0.94 eV raising of the HOMO and LUMO for Ic respectively as compared to unsubstituted thiophene (Ia). This fact suggests that 2,5-diaminothiophene (Ic) is expected to react merely with electron-deficient dienophiles but to show little reactivity toward electron-rich dienophiles.

Thus, a clear-cut difference between 2,3,4,5-tetrakis(methoxycarbonyl)thiophene (Ib) and 2,5-diaminothiophene (Ic) in the cycloaddition behaviors most elegantly can be accounted for by the concept of the cyclic conjugation. Thus, we can draw the conclusion that thiophene-1,1-dioxides (II) serve our purpose. Indeed, thiophene-1,1-dioxides (II) are predicted to be localized π-electron system: the cyclic conjugation is continuous as in cyclopentadienones (III), but the orbital phase continuity requirements are not satisfied suggesting that thiophene-1,1-dioxides (II) no longer show aromatic character. As shown in Figure 1, in the light of the very low LUMO, thiophene-1,1-dioxides (II) should be more readily trapped by electron-rich dienophiles than other 4π-components, e.g., tetracyclone and 2,5-dimethyl-3,4-diphenylcyclopentadienone.[4c]

There are several efforts to attempt to use thiophene-1,1-dioxides (II) as 4π-component in the cycloaddition reaction, in which subsequent inter- or intramolecular cycloaddition may be expected between another dienophile or the remaining π-electron system and the diene from the primary adduct by extrusion of sulfur dioxide. However, such efforts have ended in failure except a few example because of difficulty of obtaining the corresponding sulfone.[10] During the course of these studies, a synthetic method of several halogenated thiophene-1,1-dioxides by direct oxidation of the corresponding thiophenes with m-chloroperbenzoic acid has appeared.[11]

The CNDO/2 MO calculation (Figure 1) indicates a 1.7 eV lowering of the LUMO for 2,3,4,5-tetrachlorothiophene-1,1-dioxide (IIa) as compared to that for 2,5-dimethylthiophene-1,1-dioxide (IIb) which have previously been used as a diene source in the cycloaddition reaction.[12] Interestingly, the calculated energy of the HOMO orbital of IIb (-11.9 eV) is nearly identical to that of 2,5-dimethylthiophene (-11.8 eV). Substitution at the 2,5-position by alkyl groups may cancel a large lowering effect of sulfone group on the FMO energy resulting in low reactivity toward electron-rich alkenes. In fact, IIb reacts with electron-deficient dienophiles, e.g., maleic anhydride, to give double Diels-Alder adduct and shows reactivity only toward potential electron-rich dienophile, e.g., 6-dimethylaminofulvene to give azulene derivative.[12]

For the quantitative assessment of the additivity of IIa, the kinetic study was carried out. The substituent effects of styrene on the cycloaddition reaction rates were examined by plotting log k/k_H against σ_p^+.[13] As can be seen in Figure 2, linear correlation was obtained. The electron-rich styrenes react much faster with IIa than the electron-deficient ones. This fact may be attributed to the change of the frontier energy level on introduction of the substituent on styrene,

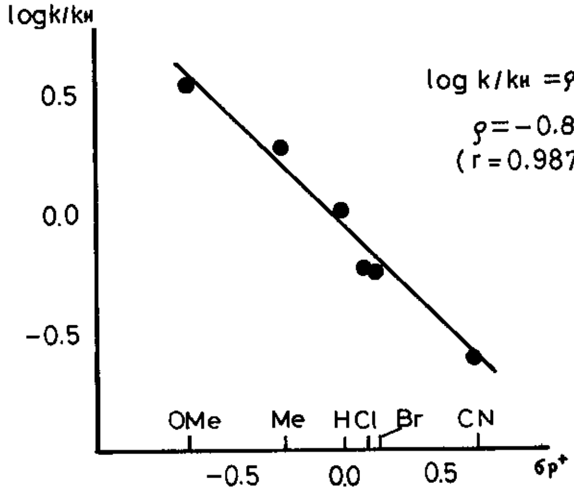
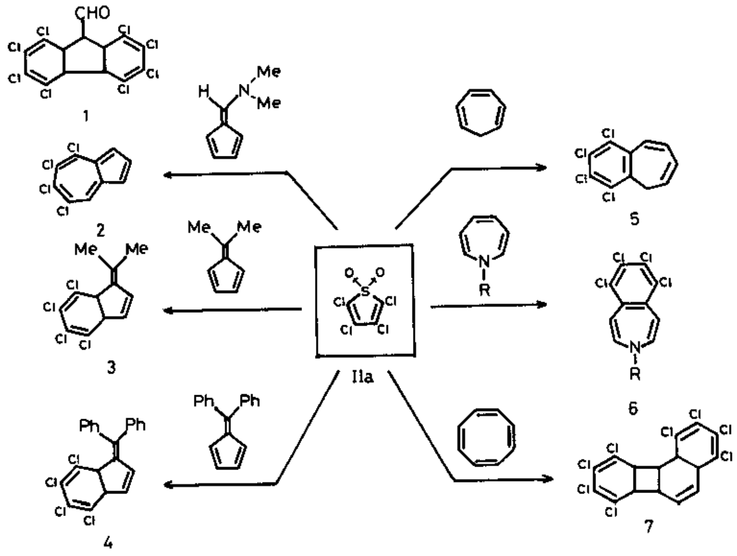


Figure 2. Plot of log k/k_H against σ_p^+ for cycloaddition of IIa with p-substituted styrenes.

wherein the interaction of the diene LUMO with the dienophile HOMO is greatest. The behavior of IIa with various styrenes is explained in terms of an "inverse" type reaction in Sustman's classification of Diels-Alder reaction which is devided into three types, depending on the relative disposi-



Scheme I. Pericyclic Reactions of IIa

tion of diene and dienophile frontier orbitals. The activation parameters (Ea = 12.4 kcal/mol and $\Delta S^{\ddagger}$ = -34 eu) for the reaction of IIa with styrene are almost same as those of usual Diels-Alder reactions.[14] Based on these theoretical expectation and experimental data, we have undertaken to investigate the cycloadditivity and periselectivity of IIa toward a series of medium-membered ring unsaturated compounds, which has not been ever studied systematically. The results are summarized in Scheme I.[15]

In conclusion, 2,3,4,5-tetrachlorothiophene-1,1-dioxide (IIa) shows high reactivity and selectivity toward seven-membered ring unsaturated compounds such as cycloheptatriene, fulvene, azepine, and cyclooctatetraene in their pericyclic reactions. The source of the high reactivity and specificity of IIa in the cycloadditions will be not only due to the narrow frontier orbital separation but also due to the effectiveness of secondary orbital interaction assisted by a coplanarity effect.[4a]

Thus, thiophene-1,1-dioxides are promising reagents for the pericyclic reaction as well as cyclopentadienones, e.g., 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (IIIa)[4b]. The more reactive derivatives are expected to be synthesized.

Besides this work, we successfully accounted for a hitherto unexplained experimental observation of cycloaddition behavior of 6-dimethylaminofulvene with several dienes,[16] which will be described in a forthcoming paper.

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References and Notes

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(6) For the simple discussion, the steric interaction was ignored because of the effects of the addends treated in this paper being not serious. See ref. 4a (*J. Org. Chem.* 1980, *45*, 659) for the steric effect in cycloadditions. The calculations reported here were carried out by CNDO/2 MO method (*Q.C.P.E.* 1969, *11*, 141) on the model near the actual geometry. All calculations were performed on the FACOM M-200 computer in the computer center of Kyushu University.

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(8) The orbital phase continuity requirements[3] are as follows; a) the HOMO's of the neighboring systems should be out of phase; b) the LUMO's of the neighboring systems should be in phase; c) the HOMO and the LUMO of the neighboring systems should be in phase.

(9) Similar trend was observed in furan derivatives, 2,3,4,5-tetrakis(methoxycarbonyl)furan do not show any reactivity toward electron-deficient dienophiles.

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(13) The pseudo-first-order rate constants of the reaction of IIa with para-substituted styrenes in chlorobenzene at 34.1 °C were measured by following the disappearance of the absorption band by ultraviolet spectrometry. See ref. 5b and 4a (*J. Org. Chem.* 1980, *45*, 659) for usefulness of σ_p^+.

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(15) The data for the cycloadditions in benzene solution are as follows: with dimethylaminofulvene, room temp., 20 min, 1 (49 %, mp 184-186 °C), 2 (11 %, mp 147-149 °C); with dimethylfulvene, room temp., 3 h, 3 (82 %, mp 47-49 °C); with diphenylfulvene, 50 °C, 2 h, 4 (91 %, mp 177-178 °C); with cycloheptatriene, reflux, 12 h, 5 (57 %, oil); with N-ethoxycarbonylazepine, reflux, 20 h, 6 (43 %, mp 133-135 °C); with cyclooctatetraene, reflux, 8 h, 7 (72 %, mp 181-183 °C). The observed periselectivity of IIa is essentially same as that of cyclopentadienones studied previously,[4] which can be rationalized by FMO theory.[5] In the light of the reaction conditions, 5 and 6 are considered to be directly derived from the corresponding primary adducts.

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