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Quantitative Characterization of the Local Electrophilicity of Organic Molecules. Understanding the Regioselectivity on Diels−Alder Reactions

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Regional electrophilicity at the active sites of the reagents involved in polar Diels−Alder processes may be described on a quantitative basis using an extension of the global electrophilicity index recently introduced by Parr et al. (*J. Am. Chem. Soc.* **1999**, *121*, 1922). The local or regional electrophilicity provides useful clues about the expected regioselectivity of the products on Diels−Alder reactions showing significant polar character. The local (regional) electrophilicity index shows significant advantages over other unnormalized definitions of relative electrophilicity proposed in the literature in the sense that it clearly identifies the relevant electrophilic sites in a molecule without restricting the search to those sites having comparable values of regional electrophilic/nucleophilic softness.

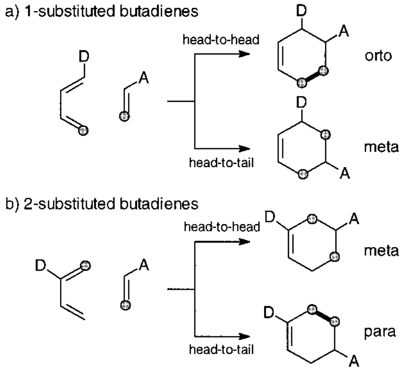
1. Introduction

The Diels−Alder (DA) reaction is one of the most useful synthetic reactions, and its overwhelming importance is well-known and thoroughly documented in organic chemistry. Many synthetic routes to cyclic compounds are made possible through DA reactions, which can involve a large variety of dienes and dienophiles. The usefulness of the DA reaction arises from its versatility and from its remarkable stereochemistry.[1,2] By varying the nature of the diene and dienophile, many different types of carbocyclic structures can be built up.

The interaction between unsymmetrical dienes and dienophiles can give two isomeric adducts, depending upon the relative position of the substituent in the cycloadduct—head-to-head or head-to-tail (see Scheme 1). The selectivity for the formation of one adduct over the other is called regioselectivity, and this kind of isomer is called a regioisomer. In this class of cycloaddition, the degree of regioselectivity is often high,[1−6] yet it is rather well established that the more powerful the electron-releasing and electron-withdrawing substituents on the diene/dienophile pair, the more regioselective is the reaction.[3] Regioselectivity has been described in terms of a local hard and soft acid and base (HSAB) principle, and some empirical rules have been proposed to rationalize the experimental regioselectivity pattern observed in some DA reactions.[7,8] There is not a single criterion, however, to explain most of the experimental evidence that has accumulated in cycloaddition processes involving four-center interactions. An excellent source for the discussion of regioselectivity in concerted pericyclic reactions is given in ref 9.

Recent density functional theory (DFT) studies devoted to the Diels−Alder reaction have shown that the classification of the diene/dienophile pair in a unique electrophilicity scale is an useful tool for predicting the feasibility of a cycloaddition process.[10−14] Diene/dienophile pairs located at the ends of this scale will display polar reactivity that is characterized by a large charge transfer at the transition-state structures involved in the mechanism of this particular cycloaddition reaction.[10] For these polar cycloadditions, the more favorable regiosiomeric pathways can be associated with bond formation at the more electrophilic and nucleophilic sites of unsymmetrical dienophile and diene reagents, respectively. The local electrophilicity/nucleophilicity character of reagents, however, may also be of significant utility in predicting the regioselectivity patterns that can be expected for a given reaction and in quantitatively assessing the effects of electron-releasing and electron-withdrawing substituents in the electrophile/nucleophile interacting pair. In this work, we test an extension of the global electrophilicity index that was recently proposed by Parr et al.[15] to deal with the local or regional counterpart of this property. The model is tested against a series of well-known DA reactions presenting different regioselectivity patterns, for which both experimental kinetic data as well as computational models are well documented in the literature.

SCHEME 1



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2. Local Electrophilicity

The quantification of the electrophilicity concept is based on a second-order model for the energy changes describing the charge transfer between the electrophile and an unspecified environment. It is described in terms of the electronic chemical potential μ and the chemical hardness η as[15]

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

Because the electrophilicity index ω is a positive, definite quantity, the direction of the charge transfer is completely determined by the electronic chemical potential of the molecule; because an electrophile is a chemical species capable of accepting electrons from the environment, its energy must decrease upon accepting electronic charge; therefore, its electronic chemical potential must be negative.[16] However, the additional charge is not homogeneously distributed in the molecule; some electron-attracting sites may contribute differently to accommodate the extra charge ΔN. The local (regional) fluctuations in electron density $\Delta\rho(\mathbf{r})$ may be conveniently described as proposed by Parr and Ayers[17] as $\Delta\rho(\mathbf{r}) = f(\mathbf{r})\Delta N$, where $f(\mathbf{r})$ is the Fukui function for the system with N electrons in an external potential $v(\mathbf{r})$.[18] An alternative description of the $\Delta\rho(\mathbf{r})$ quantity is $\Delta\rho(\mathbf{r}) = s(\mathbf{r})\Delta\mu$.[19,20] Whereas the first expression shows that the extra charge will be distributed following the Fukui function, the second one suggests that the local electrophilicity will be related to the local charge capacity of the electrophile. Useful expressions for the local electrophilicity index $\omega(\mathbf{r})$ in terms of the electrophilic Fukui function and local (regional) softness have been recently proposed.[16] They were obtained as a generalization of eq 1 as follows: starting from eq 1 and using the inverse relationship between chemical hardness and the global softness $S = {}^1/_\eta$,[21] eq 1 may be rewritten as

$$\omega = \frac{\mu^2}{2\eta} = \frac{\mu^2}{2}S = \frac{\mu^2}{2}\sum_k s_k^+ = \sum_k \omega_k \tag{2}$$

from which we may define a semilocal or regional electrophilicity power condensed to atom k that is given by

$$\omega_k = \frac{\mu^2}{2}s_k^+ \tag{3}$$

In deriving eq 3, we have used the additivity rule for the global softness, namely, $S = \sum_k s_k^+$.[21−24] We have also assumed that the electrophilic sites in the molecule will be those described by the local softness for a nucleophilic attack s_k^+.[21] Note that within the present model the maximum electrophilicity power within a molecule will be located at the softest site of the system. Furthermore, if we use the exact relationship between local softness and the Fukui function, namely, $s_k^+ = f_k^+ S$,[21] then the local electrophilicity power given in eq 3 may also be expressed as

$$\omega_k = \frac{\mu^2}{2}s_k^+ = \frac{\mu^2 S}{2}f_k^+ = \omega f_k^+ \tag{4}$$

thereby showing that the maximum electrophilicity power in a molecule will be developed at the site where the Fukui function for a nucleophilic attack f_k^+ displays its maximum value (i.e., at the active site of the electrophile). Local (regional) descriptors of electrophilicity/nucleophilicity have been previously proposed in the literature.[25,26] The relative electrophilicity (s_k^+/s_k^-) and relative nucleophilicity (s_k^-/s_k^+) indexes introduced by Roy et al.,[25,26] which are defined in terms of the electrophilic and nucleophilic softness, apply only to those sites having comparable and higher values of s_k^+ and s_k^-, and in this sense, these definitions are less universal than the one presented in eqs 3 and 4 for local electrophilicity. Another advantage of eqs 3 and 4 is that they provide a normalized definition of local electrophilicity.

If we further assume that the maximum extra charge $\Delta N_{\max} = -\mu/\eta$[15] that is acquired by the electrophile until it reach a stabilization energy $\Delta E = -\omega$ is distributed on each atomic center k in the molecule, then the maximum electronic charge that the electrophile may accept may be cast into the partitioned form

$$\Delta N_{\max} = \sum_k \Delta N_{\max}(k) = -\mu S = -\mu\sum_k s_k^+ = -\mu S\sum_k f_k^+ = \Delta N_{\max}\sum_k f_k^+ \tag{5}$$

which gives an additional expression for the maximum regional electronic charge that an atom k in the electrophile may accept from the environment, namely,[16]

$$\Delta N_{\max}(k) = \Delta N_{\max} f_k^+ \tag{6}$$

The complete reactivity analysis on DA reactions may be performed within the present approach in terms of the set of reactivity indexes defined in eqs 1−6 as follows: whereas eq 1 quantitatively defines a unique scale of electrophilicity, where the polar character of the electrophile/nucleophile interaction is dictated by the global electrophilicity gap within this scale, $\Delta\omega$,[10] eqs 3 and 4 describe the selectivity at the electrophilic end for the electrophile/nucleophile interaction. The quantity $\Delta N_{\max}(k)$ that is defined in eqs 5 and 6 is useful in describing the amount of charge transfer between the electrophile/nucleophile pair; therefore, it may be used to establish the polar character of the different cycloadduct species present as intermediates or transition-state structures in the potential energy surface for DA reactions.

3. Computational Details

Full geometry optimizations for the whole series of dienes and dienophiles have been performed at the B3LYP/6-31G* level of theory,[27,28] which is implemented in the Gaussian 98 package of programs.[29] The global electrophilicity power was evaluated using eq 1. The electronic chemical potential μ and chemical hardness η values were approximated in terms of the one-electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO, ϵ_H and ϵ_L, respectively using $\mu \approx \epsilon_H + \epsilon_L/2$ and $\eta \approx \epsilon_L - \epsilon_H$,[21] respectively, at the ground state (GS) of the molecules. The global maximum charge transfer toward the electrophile was evaluated using $\Delta N_{\max} = -{}^\mu/_\eta$.[15]

Regional Fukui functions for electrophilic (f_k^-) and nucleophilic (f_k^+) attacks were obtained from a single point calculation at the optimized structures of the GS of molecules by a method described elsewhere.[30,31] Within this approach, the electrophilic and nucleophilic Fukui functions that were condensed to atoms or groups are evaluated in terms of the coefficients of the frontier molecular orbitals involved and the overlap matrix. With the nucleophilic Fukui function at hand, the regional (site) electrophilicity power is readily obtained via eq 4. Values of the global and local maximum charge transfer

TABLE 1: Static Global and Local Properties of Common Dienophiles and Dienes Involved in DA Reactions[a]

	molecule	ω	ΔN_{max}	site (k)	f_k^-	f_k^+	ω_k	$\Delta N_{max(k)}$
	(a) Dienophiles							
1	*N*-methylmethyleneammonium cation	8.97	1.516	C	0.235	0.671	6.022	1.02
				N	0.274	0.299	2.680	0.45
2	acrolein−BH$_3$ complex	3.20	1.245	C1	0.014	0.079	0.253	0.10
				C2	0.056	0.357	1.144	0.45
3	1,1-dicyanoethylene	2.82	1.000	C1	0.198	0.209	0.589	0.21
				C2	0.336	0.499	1.407	0.50
4	nitroethylene	2.61	0.979	C1	0.010	0.077	0.200	0.14
				C2	0.006	0.279	0.726	0.27
5	acrolein	1.84	0.838	C1	0.096	0.137	0.253	0.12
				C2	0.011	0.372	0.685	0.31
6	acrylonitrile	1.74	0.740	C1	0.268	0.265	0.461	0.20
				C2	0.367	0.469	0.816	0.35
7	methyl vinyl ketone	1.65	0.789	C1	0.091	0.152	0.250	0.12
				C2	0.011	0.351	0.579	0.28
8	methyl acrylate	1.51	0.699	C1	0.060	0.199	0.300	0.14
				C2	0.013	0.409	0.617	0.29
9	ethylene	0.73	0.430	C1	0.500	0.500	0.365	0.22
				C2	0.500	0.500	0.365	0.22
10	acetylene	0.54	0.343	C1	0.500	0.500	0.268	0.17
				C2	0.500	0.500	0.268	0.17
11	methyl vinyl ether	0.42	0.350	C1	0.203	0.463	0.194	0.16
				C2	0.470	0.435	0.183	0.15
12	dimethylvinylamine	0.27	0.290	C1	0.093	0.442	0.119	0.13
				C2	0.411	0.399	0.108	0.14
	(b) Dienes							
13	1,3-butadiene	1.05	0.610	C1	0.338	0.332	0.355	0.21
				C4	0.338	0.332	0.355	0.21
14	2-methyl-1,3-butadiene	1.04	0.620	C1	0.380	0.304	0.316	0.19
				C4	0.289	0.341	0.354	0.21
15	(*E*)-1,3-pentadiene	0.93	0.580	C1	0.296	0.302	0.282	0.18
				C4	0.309	0.321	0.300	0.19
16	2-trimethylsilyloxy-1,3-butadiene	0.88	0.568	C1	0.465	0.274	0.240	0.16
				C4	0.212	0.359	0.315	0.20
17	4-methyl-1,3-pentadiene	0.86	0.560	C1	0.277	0.273	0.234	0.15
				C4	0.273	0.322	0.277	0.18
18	1-methoxy-1,3-butadiene	0.77	0.548	C1	0.217	0.312	0.240	0.17
				C4	0.290	0.326	0.251	0.18
19	1-trimethylsilyloxy-1,3-butadiene	0.73	0.523	C1	0.218	0.297	0.217	0.16
				C4	0.264	0.318	0.232	0.17
20	*N*,*N*-dimethyl-1,3-butadien-1-amine	0.57	0.481	C1	0.117	0.293	0.162	0.14
				C4	0.230	0.304	0.173	0.15

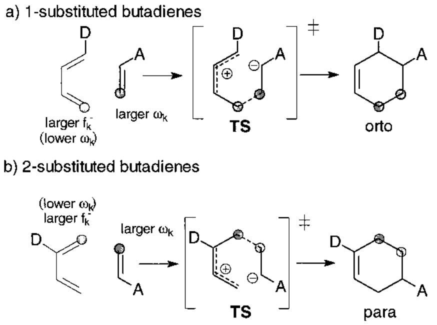
[a] Global and local electrophilicity values are in eV; ΔN_{max} and $\Delta N_{max(k)}$ values are in au. See Figure 1 for atom numbering.

toward the electrophile are evaluated using eqs 5 and 6, respectively.

4. Results and Discussion

A useful simplification for the study of the regioselectivity in DA reactions may be obtained by looking at those processes having markedly polar character, where the transition structure associated with the rate-determining step mostly involves the formation of one single bond between the most electrophilic and other nucleophilic sites in the DA reagent pair (see Scheme 2). This approximation is true when more powerful electron-releasing and electron-withdrawing substituents are present at both diene and dienophile pairs. In the absence of a precise definition of local nucleophilicity, we will assume that the most nucleophilic site at the nucleophile moiety will be the one presenting the highest value of the Fukui function for an electrophilic attack f_k^-. The polar character of the interaction is described, according to our proposed model, by the difference in the absolute electrophilicity power $\Delta\omega$.[10] Local parameters of reactivity, including the condensed-to-atom electrophilic and nucleophilic Fukui functions and the local electrophilicity index defined in eqs 3 and 4, are therefore expected to be useful descriptors of regional electrophilicity/nucleophilicity patterns that may account for the observed regioselectivity in those DA reactions with polar character.

SCHEME 2



Consider, for instance, the interaction between acrolein **5** and 1-methoxy-1,3-butadiene **18**, which according to our classification will show a global electrophilicity difference of $\Delta\omega = 1.07$ eV. This interaction corresponds to a DA reaction of normal electron demand (NED) in which the electron-poor dienophile **5**—the electrophile—reacts with the electron-rich diene **18**—the nucleophile. The electrophilic site in acrolein **5** is the C2 carbon, which has a local electrophilicity value of $\omega_k = 0.685$ eV (see Table 1 and Figure 1 for atom numbering). The highest value

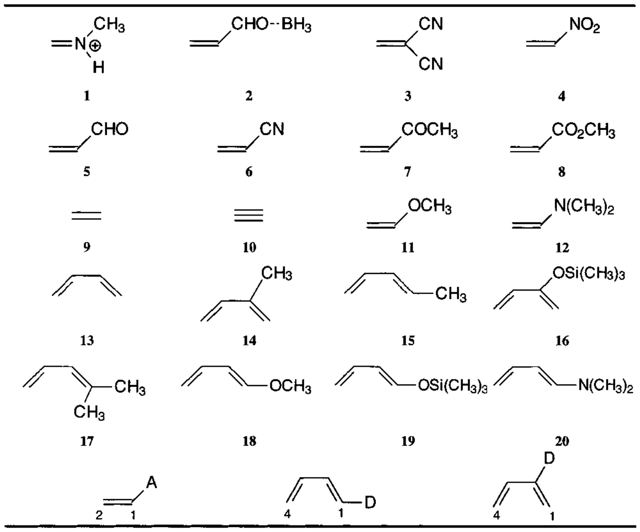


Figure 1. Schematic structures of common dienophiles, **1**−**12**, and dienes, **13**−**20**, involved in DA cycloadditions and atom numbering.

of f_k^- in 1-methoxy-1,3-butadiene (**18**) is located at the carbon atom C4, with $f_k^- = 0.290$. Therefore, the most favorable interaction will take place between the C2 center of **5** and the C4 center of **18**, leading to the formation of the ortho adduct (see Scheme 2). The addition of 1-methoxy-1,3-butadiene to acrolein is experimentally known to afford the ortho regioisomer preferentially (80% yield at 100 °C after 2 h).[3] Other interactions between electrophile/nucleophile pairs showing higher differences in absolute electrophilicity are therefore predicted to present large regioselectivity. Note that the local electrophilicity descriptor contains, according to eq 4, a global contribution ω as a factor of the genuine local electrophilic index f_k^+ (i.e., the Fukui function for a nucleophilic attack at site k). From Table 1, it may be seen that on the basis of this local descriptor of electrophilicity the C2 site is still three times more favorable than the C1 site in acrolein **5**, ($\omega_k = 0.685$ and 0.253 eV, respectively).

Table 1 summarizes the values of electrophilic and nucleophilic Fukui functions, together with the global and local electrophilicity index for common dienophiles involved in a series of DA reactions. *N*-methylmethyleneammonium cation **1**, the most powerful electrophile considered in the present study, shows the C carbon atom as the preferential site for nucleophilic attack[32] on the basis of both the Fukui function, $f_k^+ = 0.671$, and the local electrophilicity, $\omega_k = 6.022$ eV. Note that the electrophilicity power that is condensed in atoms C and N represents almost the 95% of the global electrophilicity power for this species, thereby showing the high resolution that this local quantity displays.

Because most of the dienophiles considered are substituted ethylenes, we can take ethylene as a reference in discussing the variations in local reactivity induced by chemical substitution. Ethylene **9** presents a local electrophilicity value of $\omega_k = 0.365$ eV at the equivalent carbon atoms C1 and C2. Note that acetylene **10**, having equivalent Fukui functions for both electrophilic and nucleophilic attacks, presents a lower electrophilicity pattern as compared to that of ethylene ($\omega_k = 0.268$ eV at the equivalent carbon centers of structure **10**). This result mainly comes from their difference in global electrophilicity because of the fact that ethylene **9** is predicted to be softer than acetylene **10**. Increasing substitution of hydrogen atoms by one or two electron-withdrawing CN groups in ethylene (structures **6** and **3** in Figure 1, respectively) increases the local electrophilicity power of the C2 atom from 0.365 eV in ethylene **9** to 1.407 eV in 1,1-dicyanoethylene (**3**). Note that the local electrophilicity pattern in this subseries is mainly driven by changes in global electrophilicity because the variations in electrophilic Fukui functions (i.e., Fukui function for nucleophilic attacks f_k^+) show marginal values upon substitution. This result is important in the sense that on the basis of the Fukui function values alone the 1,1-dicyano derivative **3** is predicted to have a nonsubstituted carbon atom that is less electrophilic than that in ethylene **9** ($f_k^+ = 0.499$ and 0.500, respectively), which is inconsistent with the experimental result.

Another interesting result follows from the comparison of the site reactivity of acrolein and the acrolein−BH_3 complex, representing the Lewis acid-catalyzed processes (structures **5** and **2** in Figure 1, respectively). On the basis of the Fukui function alone, the C2 carbon in acrolein is predicted to be slightly more electrophilic than that in the Lewis acid coordinated species, in contrast with the significant enhancement in the rate constant experimentally observed for the Lewis acid-catalyzed process ($f_k^+ = 0.372$ and 0.357 for **5** and **2**, respectively). However, on the basis of the local electrophilicity index ω_k, the C2 carbon in acrolein−BH_3 complex **2**, with $\omega_k = 1.144$ eV, is approximately twice as electrophilic as the corresponding site in acrolein **5**, with $\omega_k = 0.685$ eV. Moreover, the maximum charge transfer described by the $\Delta N_{\max}(k)$ quantity that is defined in eq 6 correctly assesses the active site of the electrophile that presents the maximum propensity of the system to acquire additional electronic charge from the environment ($\Delta N_{\max}(k) = 0.31e$ and $0.45e$ at C2 for **5** and **2**, respectively). In general, $\Delta N_{\max}(k)$ sums up most of the global $\Delta N_{\max}$ values (see Table 1). For instance, in the case of *N*-methylmethyleneammonium cation **1**, whereas the maximum electronic charge that this system may accept from the environment is $\Delta N_{\max} = 1.52e$, the active site C alone concentrates almost 67% of this potential ($\Delta N_{\max}(k) = 1.02e$).

It is also interesting to examine the effect that the electron-releasing groups may have on the local electrophilicity pattern in ethylene **9**. These systems have some importance in the inverse electron demand (IED) processes. Consider, for instance, compounds **11** and **12** in Figure 1. On the basis of the Fukui function alone, methyl vinyl ether (**11**) shows nucleophilic activation at the C2 carbon, $f_k^- = 0.470$. Dimethylvinylamine (**12**), however, displays a similar local reactivity pattern, with $f_k^- = 0.411$. Note that on the basis of the ω index both compounds are predicted to be marginally electrophilic because of the low value of the global electrophilicity. Therefore, both compounds **11** and **12** are predicted to react with electron-poor dienes such as nitroethylene (**4**) to afford the ortho regioisomer in an IED DA reaction.[33] The interaction of **4** with electron-rich, 2-substituted 1,3-butadienes such as **14** and **16**, however, would lead to the formation of the para regioisomer.[3] It is interesting that although nitroethylene can act as a dienophile or a diene in DA reactions it normally behaves as a strong electrophile, the C2 site being the most electrophilic position.

Table 1 also summarizes the values of local electrophilicity parameters for a series of well-known dienes involved in NED DA reactions. According to the absolute electrophilicity scale, these species have been classified as moderate electrophiles (structures **13**−**17** in Figure 1) and marginal electrophiles or nucleophiles (structures **18**−**20** in Figure 1).[10] The first subgroup usually consists of methyl-substituted butadienes, whereas the second subgroup consists of butadienes substituted with stronger electron-releasing groups.

The dienes of the second subgroup shown in Table 1, **18**−**20**, usually participate as nucleophiles in polar DA reactions.[34] In general, it may be seen that substitution at position C1 in 1,3-butadiene activates the position C4 for an electrophilic attack (see Scheme 2). Compare, for instance, the f_k^- values at C1 and C4 in structures **18**−**20** (for **20**, $f_k^- = 0.117$ and 0.230 at C1 and C4, respectively). This is true even for the weak electron-releasing methyl group, such as the one participating in structure **15**. Substitution at position C2 in butadiene, however, strongly activates position C1 over position C4, thus raising the probability of forming a second regioisomer (see, for instance, the f_k^- values at C1 and C4 for **14** and **16**). Although 1-substituted butadienes react with strong electrophiles activated at the C2 position to afford mostly the ortho adduct, the 2-substituted derivatives are consistently predicted to yield the para regioisomer preferentially (see Scheme 2).[3] This result is consistent with the experimental observation establishing the fact that 2-methyl-1,3-butadiene (**14**) and 2-trimethylsilyloxy-1,3-butadiene (**16**) react with acrolein (**5**) to afford the para-substituted regioisomer with a similar yield (80%).[3,35]

5. Concluding Remarks

In summary, whereas the global electrophilicity index introduced by Parr et al.[15] is useful in classifying the electrophilicity power of a series of dienes and dienophiles within a unique relative scale,[10] the local (regional) counterpart introduced in the present work helps to identify the relevant electrophilic sites within a static reactivity picture. Useful information about the polarity of transition-state structures expected for a given reaction may be obtained from the difference in the global electrophilicity power of the diene/dienophile interacting pair. Changes in local electrophilicity/nucleophilicity patterns with reference to the transition-state structures would provide, in turn, useful clues about site activation that seems to account well for the regioselectivity observed in DA reactions displaying character that is more polar than pericyclic.

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