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Toward an Understanding of the Catalytic Role of Hydrogen-Bond Donor Solvents in the Hetero-Diels−Alder Reaction between Acetone and Butadiene Derivative

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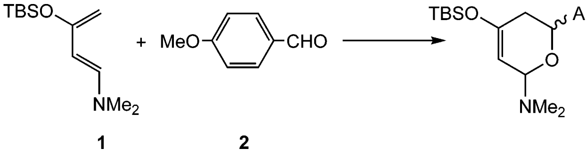
A detailed theoretical investigation of the catalytic role of hydrogen-bond- (HB-) donor molecules (water, methanol, chloroform, dichloromethane, and chloromethane) in the hetero-Diels−Alder reaction between acetone and *N*,*N*-dimethyl-1-amino-3-methoxy-1,3-butadiene is presented. This work extends a previous study (Domingo, L. R.; Andres, J. *J. Org. Chem.* 2003, *68*, 8662) in which the importance of weak HB-donor solvents to catalyze more effectively than solvents with a higher dielectric constant but no HB-donor capability was analyzed. Now, based on density functional theory (DFT) at B3LYP/6-31+G(d) level calculations, different techniques for analyzing the nature of HB interaction, namely, natural bond orbital (NBO) theory, topological analysis of the electron density (atoms in molecules, AIM, theory), and the electron localization function (ELF) and decomposition of the interaction energy between monomers (energy decomposition analysis, EDA), have been applied to understand why only some HB-donor solvents are able to catalyze the reaction. The catalytic effect of the solvent arises from the improved HB-acceptor capability of the oxygen atom at the transition structure (TS) due to the strong polarization of the carbonyl group. The HB acceptor presents three lone pairs (NBO analysis), and the ELF shows an increment of the electronic charge of the lone pairs of 0.50e with respect to the reactant. All solvent molecules form stronger HB interactions at the TS, but only those presenting larger charge-transfer interactions (water, methanol, chloroform) benefit more from the polarization of the carbonyl group than other solvents (dichloromethane, chloromethane) with less “covalent” character.

Introduction

Since Sutor discovered the presence of C−H···X hydrogen bonds (HBs) in some organic crystal structures,[1] the ability of C−H bonds to act as HB donors in determining molecular conformations and crystal packing,[2] supramolecular architecture,[3] and the structure of biological systems such as nucleic acids[4] has become widely recognized. However, the catalytic role of C−H HB donors of solvent molecules in the course of a chemical reaction has been recognized only recently.[5] In particular, HB-promoted hetero-Diels−Alder reactions,[6] 1,3-dipolar cycloadditions,[7] and pericyclic Meisenheimer rearrangements[8] have been described.

The carbonyl C═O group is one of the more important functional group in organic chemistry because of its synthetic and biological implications.[9−11] The presence of a carbonyl group in an organic molecule involves an electrophilic reactive center that allows its conversion to a wide variety of functional groups or the building of a more complex structure, but such reactions usually must be catalyzed by the presence of a Brønsted or Lewis acid catalysts. Coordination of these species to the oxygen atom substantially increases the electrophilicity of the carbonyl compound by a large stabilization of the negative charge that becomes located at the carbonyl oxygen atom during the nucleophilic attack.

SCHEME 1



Although α,*β*-unsaturated carbonyl compounds are widely used as dienophiles in Diels−Alder reactions, the counterpart carbonyl compounds are less frequently used because participation of the carbonyl C═O group as a dienophile in a hetero-Diels−Alder (HDA) reaction requires long reaction times, high temperatures, and sometimes high pressures. Recently, Huang and Rawal reported the HB-promoted HDA reactions of inactivated ketones.[5b] Thus, for the reaction between 1-amino-3-silyloxy-1,3-butadiene (**1**) and *p*-anisaldehyde (**2**) (see Scheme 1), they found that solvent effects produce a significantly higher reaction rate in chloroform than in other aprotic organic solvents. These authors concluded that the increased reaction rate in chloroform could arise from C−H···O═C interactions, which would render the carbonyl group a stronger heterodienophile.

To understand the key role of HB formation associated with chloroform in influencing the chemical reactivity of ketones, the HDA reaction of *N*,*N*-dimethyl-1-amino-3-methoxy-1,3-butadiene (**3**) and acetone HB to a chloroform molecule was recently studied at the B3LYP/6-31G* level by Domingo and Andres[5d] (see Scheme 2). Inclusion of solvent effects by means of combined discrete and polarizable continuum models yielded a change of molecular mechanism from a concerted to a two-

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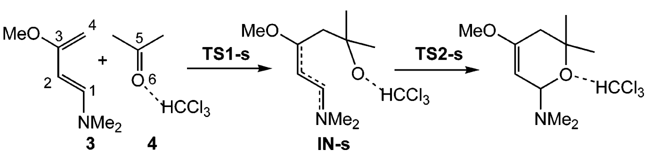
SCHEME 2



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step mechanism. The chloroform HB to the oxygen carbonyl atom decreases the activation barrier by 5.1 kcal/mol. The density functional theory (DFT) study accounted for the experimental observation that chloroform accelerates the reaction more markedly than a polar but aprotic solvent such as acetonitrile.

The electrostatic and "covalent" nature of the HB interaction presents difficulties for a strict definition.[12] In the past decade, investigations have identified new types of HB interactions ranging from typical covalent bonds to van der Waals interactions.[13,14] Recently, the mechanism of HB formation was a matter of debate because of the possibility of X−H bond elongation or shortening upon complexation, manifested by a red or blue shift[15] of the X−H stretching frequency. These investigations of HB interactions indicate the difficult characterization of the HB and the necessity of using more than a single criterion.

Modern techniques for the analysis of chemical bonding have been developed recently based on properties of the topological analysis of the electron density, as in the atoms in molecules (AIM) approach of Bader[16] or the electron localization function (ELF) proposed by Becke and Edgecombe[17] and extensively developed for the study of electron pairing by Silvi and Savin.[18] The AIM theory of Bader uses the gradient dynamical system of the electron density to define basins of attractors and a partitioning of the molecular space into atomic domains. This theory has proven to be valuable for characterizing HBs in theoretical and experimental electron density distributions. On the basis of AIM theory, Popelier[19] proposed a set of criteria to be fulfilled by the hydrogen atom to characterize HB formation. The advantage of using the ELF methodology is that it provides a direct local measure of the Pauli principle, allowing for the direct treatment of electron pairs and electron delocalization. Several applications of the topological analysis for a better understanding of bonding,[20] aromaticity,[21] and chemical reactivity[22] have been addressed recently. The suitability of the ELF for the characterization of HBs has been demonstrated by Silvi et al.[23,24] in several HB complexes. They also established criteria to distinguish between weak, medium, and strong HBs, relying only on local values of the ELF at bond critical points (BCPs) as well as the electron population and its variances for the basins, in a similar manner as deduced from AIM theory with the electron density.

The assessment of the electrostatic or covalent character of HB interactions by means of the decomposition of intermolecular interactions is difficult because of the nonexistence of formal operators for electrostatic, polarization, charge transfer, or any other type of intermolecular interaction. Thus, several strategies are available for the analysis of intermolecular interactions; the most often employed are the Morokuma−Kitaura (MK) decomposition[25] and other more recent implementations such as the extended transition state (ETS) of Ziegler and Rauk[26] or the energy decomposition analysis of Baerends et al.,[27] the perturbation-type decomposition (SAPT),[28] the divide-and-conquer decomposition, [29] or the natural energy decomposition[30] based on natural bond orbital (NBO) analysis.

The structure of this article is as follows: the theoretical methods employed are described first. Geometrical and energetic criteria are analyzed in section 1 of Results and Discussion; followed by NBO analysis reported in section 2; and topological criteria based on AIM theory and the ELF in sections 3 and 4, respectively. The results of the decomposition of the HB interaction energy according to the MK scheme are discussed in 5, and finally, thermochemical considerations are presented in section 6. A brief section of concluding remarks closes the article.

Theoretical Methods

All quantum mechanical calculations were carried out employing methods based on density functional theory, in particular, the B3LYP exchange-correlation potential.[31] The basis set was chosen among several standard Pople basis sets, from 6-31G(d) to 6-311++G(3df,3pd) quality,[32] to find optimal energies and geometries for the system at reasonable cost. The basis set superposition error (BSSE) for the stabilization energy was estimated using the counterpoise method of Boys and Bernardi.[33] For each HB complex, the energy of each monomer was computed with and without the basis functions for the other monomer present by using the "counterpoise" keyword in Gaussian 03.[34] The sum of energy differences from including basis functions provides the counterpoise correction for the BSSE. For the chosen basis set, the BSSE is a small part of the total interaction energy, and we have chosen not to include the BSSE correction in the optimization or energy correction.

All stationary points were confirmed as minima or transition states (TSs) via vibrational frequency calculations. Both geometry optimizations and vibrational frequency calculations were carried out at the B3LYP/6-31+G(d) level. The NBO analysis was performed as it is implemented in the Gaussian 03 code. The orbitals converged from the B3LYP calculation were employed to analyze the electron density using the XAIM program[35] and the ELF using the package of programs TopMod[36] and the graphical representation with the MOLEKEL program.[37]

In addition to the topological analysis of the electron density and the ELF, an energy decomposition analysis following the MK scheme was undertaken on the complex formed by the solvent molecule and acetone and the TS. Although the MK decomposition is available only for the Hartree−Fock (HF) methodology, as implemented in the GAMESS package,[38] it was performed on the B3LYP/6-31+G(d)-optimized geometries. The calculated HF interaction energies are similar to B3LYP ones at the same basis set level.

Results and Discussion

1. Geometries and Energies. Selected B3LYP/6-31+G(d)-optimized geometrical parameters are listed in Table 1. The X−H and H···O distances (in angstroms) for the free solvent molecule (only for X−H) and complexation with the reactant (acetone) and TS are directly related to the strength of the HB interaction. The intermolecular θ(HOC) and θ(XHO) bond angles account for the directionality of the HB and the linearity of the XHO bond. However, complexes with H_2O and MeOH deviate from linearity because of the HB interaction of the oxygen lone pairs with two hydrogens of the acetone or the butadiene derivative. The last entries report the intermolecular C4−C5 and C1−O6 distances for the bond-forming processes at the TS (see Scheme 2), reflecting the different extensions of bond formation during the cycloaddition process: r(C4−C5) ranges from 1.851 to 1.921 Å, whereas r(C1−O6) ranges from 2.672 to 2.857 Å. In Table 2, complexation energies of the HB donor with the reactant and TS are listed. The BSSE is also

TABLE 1: Selected B3LYP/6-31+G(d)-optimized Geometrical Parameters for the Free Solvent Molecules and Solvent Molecules Forming HB Complexes with Reactant (R) and TS[a]

	r(X−H)			r(H···O)		θ(COH)		θ(XHO)		r(C4−C5)[b]	r(C1−O6)[b]
	free	R	TS	R	TS	R	TS	R	TS	TS	TS
H_2O	0.969	0.979	1.005	1.905	1.671	118.2	122.4	161.5	167.1	1.921	2.857
MeOH	0.969	0.978	1.002	1.912	1.675	118.5	122.9	146.9	168.5	1.902	2.843
Cl_3CH	1.086	1.088	1.100	2.113	1.875	141.5	132.5	175.3	174.7	1.908	2.732
Cl_2CH_2	1.088	1.088	1.096	2.214	1.992	135.0	130.6	172.6	175.3	1.882	2.703
$ClCH_3$	1.090	1.090	1.094	2.390	2.140	131.5	131.7	171.1	171.5	1.851	2.672

[a] Distances are in angstroms, angles in degrees. [b] r(C4−C5) and r(C1−O6) in the gas phase are 1.836 and 2.492 Å, respectively.

TABLE 2: B3LYP/6-31+G(d) Complexation Energies (and BSSEs) for the Solvent Molecules with the Reactant (R) and TS, Activation Barriers (Including ZPE), and Imaginary Frequencies of the TS

	complexation energy (BSSE)		activation barrier[b] (frequency[c])
	R	TS	
H_2O	5.1 (0.57)	12.4 (1.24)	14.3 (291.0i)
MeOH	4.7 (0.63)	12.7 (1.41)	14.3 (289.0i)
Cl_3CH	3.8 (0.35)	9.1 (0.81)	16.7 (291.7i)
Cl_2CH_2	2.9 (0.25)	7.0 (0.63)	17.8 (271.6i)
$ClCH_3$	1.7 (0.15)	4.5 (0.38)	19.3 (249.7i)

[a] Activation barriers in kcal/mol. [b] In the gas phase, the activation barrier is 22.0 kcal/mol (262.8i). [c] Imaginary frequency of the TS in cm^{-1}.

reported, and in all cases, it is a small amount of the total interaction energy. Activation energies are also displayed (including zero-point energy, ZPE, corrections) and the imaginary frequency of the TS.

In all investigated complexes, the formation and strengthening of the HB formed (at the reactant and TS, respectively) is accompanied by an elongation of the X−H distance, resulting in relatively large extensions for H_2O, MeOH, and Cl_3CH and almost negligible extensions for weaker HB donors (Cl_2CH_2 and $ClCH_3$). The lengthening of the X−H bond in the H-donor monomer is a well-known HB effect whose magnitude usually correlates well with the strength of the interaction.[12,39−43] The red shift in frequencies of X−H vibrations associated with the lengthening of this bond upon formation of X−H···O links has traditionally been considered as evidence of HB formation.[12] In some HB systems, however, experiments have revealed that the A−H stretching vibration can be shifted toward higher frequencies, which has led to discussion of blue-shifted or "improper" HBs in such cases. Recently, the theoretical data on investigations of red/blue shifting of XH bonds have been critically summarized by Weinhold and co-workers.[44] Using NBO analysis, they showed that the XH bond length in the XH···O complexes is controlled by a balance between two main factors acting in opposite directions: the hyperconjugative interaction from the lone pair of oxygen to the σ*(X−H) antibonding orbital, leading to an elongation of the X−H bond, and the increase of the s character and polarization of the XH bond, which could lead to a shortening of the X−H distance. Hence, in all complexes studied in this work, the first effect is dominant.

Complexation energies of the HB donor and reactant range from weak ($ClCH_3$, 1.7 kcal/mol) to moderate (H_2O, 5.1 kcal/mol). These values are considerably increased at the TS to a moderate type of hydrogen bonding (4.5−12.7 kcal/mol). The different stabilizations of the reactant and TS by the solvent-assisted HBs lead to a reduction of the activation barrier from the value of 22.0 kcal/mol in the gas phase to 14.3 kcal/mol for both O−H HB donors or to the range of 16.7−19.3 kcal/mol for C−H HB donors.

2. NBO Analysis. Formation of an HB implies a charge-transfer process from the HB acceptor to the HB donor[45] and a rearrangement of the electron density within each monomer. In Tables 3 and 4, the results of the NBO analysis are summarized for the HB-donor molecule while free and after complexation with the reactant and TS. Table 3 reports the atomic charges of the X−H···O atoms for all species investigated, and Table 4 shows the overall charge transfer occurring from acetone and the TS to the solvent molecule, the occupation of the σ* antibonding orbitals of the X−H (X═C,O) bonds, the variation of the percentage of s character of selected bonds upon complexation, and the energies of the hyperconjugative interactions n(O) → σ*(X−H).

TABLE 3: NBO Atomic Charges (e) of the X−H···O Atoms Involved in the Free Molecule and Complexation with Reactant and TS

	H			X═C,O			O[a]	
	free	R	TS	free	R	TS	R	TS
H_2O	0.4920	0.5069	0.5196	−0.9839	−1.0203	−1.0627	−0.5869	−0.7814
MeOH	0.4904	0.5107	0.5240	−0.7765	−0.8108	−0.8435	−0.5846	−0.7784
Cl_3CH	0.2932	0.3204	0.3440	−0.3836	−0.3805	−0.3802	−0.5827	−0.7943
Cl_2CH_2	0.2730	0.2983	0.3220	−0.4995	−0.4956	−0.4903	−0.5781	−0.7899
$ClCH_3$	0.2518	0.2751	0.2980	−0.6695	−0.6666	−0.6610	−0.5721	−0.7916

[a] Charge (O) in acetone, −0.5618e; in TS, −0.7653e.

TABLE 4: NBO Analysis of the Percentage of s Character in the X−H Bond (X═C,O), Occupation of Antibonding σ*(A−H) Orbital, Hyperconjugative Energies (kcal/mol), and Charge Transfer (CT) (e)

	% X−H s character			σ*(X−H) occupation		E(2)		CT	
	free	R	TS	R	TS	R	TS	R	TS
H_2O	23.5	27.4	30.4	0.0273	0.0695	3.62	7.19	−0.0242	−0.0523
MeOH	21.1	25.0	27.6	0.0338	0.0757	4.09	7.89	−0.0245	−0.0517
Cl_3CH	31.6	33.8	35.8	0.0417	0.0589	5.12	9.05	−0.0150	−0.0344
Cl_2CH_2	29.3	31.1	32.8	0.0299	0.0426	3.38	6.27	−0.0105	−0.0212
$ClCH_3$	27.2	28.5	29.8	0.0169	0.0250	1.64	4.01	−0.0037	−0.0102

TABLE 5: Properties[a] of the Bond Critical Point of the B3LYP/6-31+G(d) Electron Density on the HB Path[b]

	Xc		ρ(r)		L(r)		G(r)		V(r)		H(r)	
	R	TS	R	TS	R	TS	R	TS	R	TS	R	TS
H_2O	0.359	0.335	0.0287	0.0498	0.0905	0.1516	0.0234	0.0403	−0.0226	−0.0379	0.0008	0.0024
MeOH	0.360	0.336	0.0285	0.0496	0.0891	0.1515	0.0231	0.0402	−0.0223	−0.0379	0.0008	0.0023
Cl_3CH	0.386	0.368	0.0183	0.0316	0.0603	0.0999	0.0148	0.0255	−0.0151	−0.0250	−0.0003	0.0005
Cl_2CH_2	0.390	0.375	0.0153	0.0251	0.0496	0.0769	0.0120	0.0198	−0.0124	−0.0192	−0.0003	0.0006
$ClCH_3$	0.396	0.386	0.0108	0.0183	0.0361	0.0576	0.0084	0.0144	−0.0090	−0.0144	−0.0007	0.0000

[a] Xc, H···O distance; ρ(r), electron density; $L(\mathbf{r})$, Laplacian of the electron density; $G(\mathbf{r})$, kinetic energy density; $V(\mathbf{r})$, potential energy density; and $H(\mathbf{r})$, total energy density. All values are in au. [b] Location given as a fraction of the H···O distance, Xc.

Inspection of the atomic charges reported in Table 3 shows a decrement of electronic charge on the H atom upon complexation or an increment of X−H$^+$ polarization, with the absolute polarization being stronger for O$^-$H$^+$ than C$^-$H$^+$ bonds. Interestingly, the total positive charge on the H atom correlates well with the complexation energy but not with the decrement of charge after complexation; thus, C−H HB donors lose more charge on H than do O−H HB donors. Within the methyl chloride derivatives, the charge on C increases with the number of C−H bonds. Considering the charge on the HB acceptor, a slight increment is observed on the density charge after complexation and a further gain upon reaching the TS. In Table 4, the percentage of s character in the X−H bond is listed for the free molecules and for the molecules upon complexation with the reactant and TS. It is noteworthy that, in agreement with Bent's rule,[46] the decrease of electronic charge on H implies an increase in the percentage of s character of X bonded to H.

An important result of the NBO analysis is that the occupation of the σ*(X−H) orbital increases after complex formation with the reactant and TS. The strength of the HB interaction also correlates well with the occupation of the σ*(X−H) orbital. The NBO analysis yields two n(O) orbitals for acetone and three n(O) orbitals at the TS, reflecting the change in the electronic structure as the reaction progress. Hyperconjugative energies, $n(O) \rightarrow \sigma^*(X-H)$, calculated by second-order perturbation theory[47] are moderate (from 1.64 to 5.12 kcal/mol) for the reactive complexation but relatively large (from 4.01 to 9.05 kcal/mol) for the HB formed at the TS. Interestingly, chloroform gives hyperconjugative energies larger (less than 2 kcal/mol) than O−H HB donors because of larger elements in the Fock matrix between the NBO orbitals n(O) and σ*(X−H). All complexes present a charge transfer from the reactant or TS to the HB-donor molecule. The amount of charge transferred varies from very small (−0.0037 and −0.0102) for $ClCH_3$ to moderate (−0.0245 and −0.0520) for water and methanol, in HBs formed with the reactant and TS, respectively.

3. Topological Descriptors of HBs Based on the Electron Density. One fundamental feature of X−H···O HBs is the existence of a saddle point or (3,−1) BCP of the electron density on the H···O path. The topological properties of this BCP are the subject of AIM criteria proposed to characterize the interaction.[16,19,48] Much theoretical effort has been devoted in recent years to relating these topological descriptors to the strength of HBs.[19] The local measure of the density at the BCP has been often treated as a measure of the HB strength because it correlates with HB energies. [13,43,49]

In Table 5, the properties of the BCPs on the HO bond paths for the reactant and the TS are listed. In all cases, the BCP is located near the H, approaching hydrogen at the TS. The electron density and its Laplacian in the C−H···O plane are represented in Figure 1a,b. As noted by Popelier et al. in prescribing AIM criteria for HBs,[19,48] the order of magnitude of the density at the BCP is about 10^{-2} au, becoming larger as H···O lengths become shorter. As a general trend, the weaker the HB, the lower the density in the BCP. However, the relationship between ρ(r) and HB strength should be used with caution. More information can be obtained from the Laplacian of the electron density at the BCP. Positive values of the Laplacian indicate a local depletion of charge, characteristic of noncovalent interactions such as HBs.[19] In Table 5, all values are positive and increase in magnitude with decreasing H···O distances. A similar behavior was found in a recent comparative study of experimental and theoretical electron densities for crystals of six complexes of amino acids with water.[50]

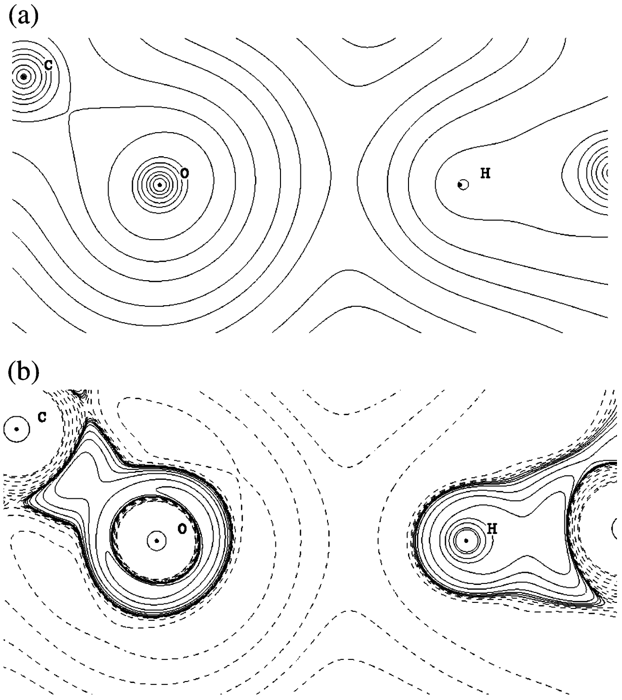

Figure 1. Maps of (a) the electron density and (b) its Laplacian on the C−H···O plane for Cl_3CH−acetone complex. In b, solid contour lines correspond to regions of charge concentration ($\nabla^2\rho < 0$).

Another criterion for the characterization of the interaction is obtained from the local energy densities listed in Table 5. The sum of kinetic, G(r), and potential, $V(\mathbf{r})$, energy densities defines the total energy density, $H(\mathbf{r})$. The sign of $H(\mathbf{r})$ at any point thus depends on which of the two contributions dominates locally there. Thus, positive values of $H(\mathbf{r})$ at a BCP characterize ionic HBs,[16] whereas negative values are typical of covalent bonds. However, negative $H(\mathbf{r})$ values have been found in short HBs, which has led to discussion of partially covalent HBs.[43,51] For the HBs studied here, some of the weaker bonds present negative values of $H(\mathbf{r})$, although the values are too small to be significant.

4. Analysis of the Electronic Structure Using the Electron Localization Function. The ELF provides a local measure of the excess of kinetic energy density due to Pauli repulsion. The

TABLE 6: Integrated Electron Density Basin Populations for Selected ELF Basins

	V(H,X)			$V(\mathrm{O})^a$			$V(\mathrm{C,O})^b$		
	free	R	TS	free	R	TS	free	R	TS
H_2O	1.58	1.63	1.67	5.26	5.28	5.81	2.36	2.31	1.73
MeOH	1.61	1.67	1.69	5.26	5.30	5.81	2.36	2.32	1.72
Cl_3CH	2.16	2.18	2.21	5.26	5.26	5.86	2.36	2.35	1.70
Cl_2CH_2	2.11	2.13	2.15	5.26	5.27	5.85	2.36	2.35	1.70
$ClCH_3$	2.04	2.05	2.07	5.26	5.25	5.86	2.36	2.36	1.69

[a] Sum of $V_{1,2}$(O) basins of the HB-acceptor lone pairs. [b] Disynaptic basin representing the carbonic bond of acetone.

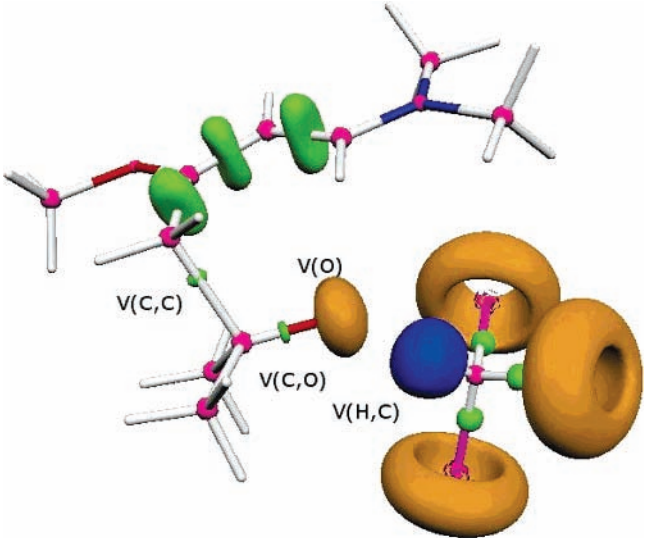

Figure 2. ELF plot ($\eta = 0.85$) of the $Cl_3CH\cdots$TS complex. Only the basins directly involved in the hetero-Diels−Alder reaction and those of chloroform are displayed. Core basins are in purple, monosynaptic basins in orange, disynaptic basins in green, and hydrogenated basins in blue.

topological analysis of the gradient field of the ELF enables partitioning of the molecular space into basins of attractors. The ELF values at the critical points connecting two basins define the electron localization domains of the system. There are mainly two types of ELF basins: core basins around the nuclei and valence basins accounting for the valence electrons. The valence basins are characterized by their synaptic order, defined as the number of cores to which they share a common boundary. A complete description of the ELF concepts can be found elsewhere.[18]

Populations and variances of basins involved in the HBs, V(H,X) and V(O), are reported in Table 6. First, it is interesting to observe the position and orientation of the hydrogenated basin V(H,X) along the HB facing the monosynaptic lone-pair basin V(O) of the acceptor oxygen (see Figure 2 for a plot of selected ELF basins of the $Cl_3CH\cdots$TS complex). The ELF analysis provides new arguments to measure the covalent character by means of the transfer of charge density from the V(O) basin toward the V(H,X) basin upon formation or strengthening of the HB. This charge-transfer interaction is equivalent to, using the language of molecular orbitals, hyperconjugative charge transfer from n(O) toward the σ^*(H−X) orbital. Thus, the initial formation of the solvent−acetone complex implies charge transfers of 0.05e, 0.06e, 0.02e, 0.02e, and 0.01e, and at the TS, there are further transfers of 0.04e, 0.02e, 0.03e, 0.02e, and 0.02e, for H_2O, MeOH, Cl_3CH, Cl_2CH_2, and $ClCH_3$ respectively, reflecting the increment of the covalent character of the HBs.[52] These values, although slightly larger, are in reasonable agreement of the NBO results discussed in section 2.

At the reactant, the acceptor O exhibits two well-defined lone pairs integrating to 5.25−5.30e and one disynaptic V(C,O) basin representing a double bond (for a detailed discussion on the Lewis structures of the C−O group, see ref 53). Although the population of the oxygen lone pairs and the C═O double bond (2.31−2.36e) deviates strongly from the expected four electrons, the oxygen polarizes the C−O bond, transferring part of its electronic charge toward the lone pairs. Analyzing the ELF at the TS, the electronic structure has been modified by the formation of a new bond [or V(C,C) basin] between the adducts, and consequently, a large amount of charge density has migrated from the C−O bond to the lone pairs of oxygen atom. Surprisingly, the lone pairs of the HB-acceptor oxygen, V(O), do not show a decrease of charge density but rather show a slight increase at the complexation stage and a stronger increase at the TS (5.20−5.30e minimum, 5.81−5.86e TS). This unexpected behavior is explained by taking into account the adjacent ELF basin, corresponding to the C−O bond (see Table 6). Hence, the ELF analysis indicates that, in the studied cases, HB formation involves also a charge transfer from the electron pairs forming the C−O bond, $V(\mathrm{H,X}) \leftarrow V(\mathrm{O}) \leftarrow V(\mathrm{C,O})$, rather than just a local transfer, $V(\mathrm{H,X}) \leftarrow V(\mathrm{O})$. An external factor, such as the progress along the reaction path in which the reaction mechanism presents an asynchronous formation of C−C and C−O bonds, produces a high polarization of the carbonyl group at the TS and an enhancement of the $V(\mathrm{O}) \leftarrow V(\mathrm{C,O})$ transfer, thus improving the HB-acceptor character. Therefore, even weak HB-donor solvents such as chloroform can catalyze the reaction.

The ELF analysis provides a consistent picture of changes in the electronic structure going from the reactant to the TS rather than a quantitative characterization of the HB by topological descriptors. For a better assessment of the HB interaction, energy decomposition analysis is also employed.

5. Energy Decomposition Analysis (EDA). The Morokuma−Kitaura decomposition[25] partitions the interaction energy (E_{int}) into five components

$$E_{\mathrm{int}} = E_{\mathrm{es}} + E_{\mathrm{xr}} + E_{\mathrm{pl}} + E_{\mathrm{ct}} + E_{\mathrm{mix}}$$

This decomposition can be described by considering the molecular orbitals of two interacting monomers, HB donor (D) and HB acceptor (A). The electrostatic energy (E_{es}) is a Coulombic-type interaction energy, corresponding to the interaction of the occupied orbitals of D with the occupied orbitals of A. The polarization energy (E_{pl}) is the result of one monomer D (A) responding to the field created by the other monomer A (D) by mixing the occupied/virtual orbitals within D (A). The polarization energy is often called the induction energy. The exchange repulsion energy (E_{xr}) is dependent on the antisymmetrization of the occupied orbitals on monomers D and A. The charge-transfer energy (E_{ct}) measures the interaction of the occupied orbitals of monomer D (A) with the virtual orbitals of monomer A (D), including the HOMO−LUMO interactions. Finally, E_{mix}, the mixing energy, is just the higher-order correction, which yields the net HF result.

As expected, the general rule that the stronger HBs exhibit greater covalent character is fulfilled. From the calculated values of the contributions described above and reported in Table 7, the E_{es} and E_{xr} contributions are of the same order but with opposite sign and almost cancel each other, and it is E_{pl} and E_{ct} contributions that play the dominant role. Although the E_{pl} and E_{ct} components of the HB interaction between the solvent molecule and the reactant are comparable, for the TS, the E_{ct} term becomes dominant. Going from reactant to TS, the E_{pl} term almost doubles, whereas the E_{ct} term becomes nearly 4

TABLE 7: Morokuma−Kitaura Energy Decomposition Analysis between HB Donor (Solvent Molecule) and HB Acceptor (Reactant and TS) Monomers[a]

	E_{es}		E_{xr}		E_{pl}		E_{ct}		E_{mix}		E_{int}	
	R	TS	R	TS	R	TS	R	TS	R	TS	R	TS
H_2O	−11.7	−28.0	9.2	25.8	−2.2	−3.9	−2.4	−9.3	1.1	−2.0	−6.0	−17.5
MeOH	−11.2	−28.0	9.0	26.2	−2.1	−4.1	−2.4	−9.5	1.0	−2.1	−5.8	−17.6
Cl_3CH	−7.2	−16.0	5.0	13.2	−1.4	−2.8	−1.4	−4.9	0.6	−0.9	−4.4	−11.5
Cl_2CH_2	−5.9	−12.9	4.0	10.3	−1.0	−2.2	−1.1	−3.9	0.5	−0.8	−3.5	−9.6
$ClCH_3$	−4.1	−8.9	2.8	7.0	−0.6	−1.8	−0.7	−2.8	0.3	−0.5	−2.3	−7.0

[a] B3LYP/6-31+G(d)-optimized geometries. See the text for an explanation of the terms. All values are in kcal/mol.

TABLE 8: B3LYP/6-31+G(d) Complexation[a] **Free Energies, Enthalpies (kcal/mol), and Entropies (cal/mol) Calculated at 298 K and 1 atm**

	ΔG		ΔH		ΔS	
	R	TS	R	TS	R	TS
H_2O	2.7	−3.8	−5.0	−12.9	−25.8	−30.7
MeOH	3.1	−2.9	−4.7	−12.6	−26.3	−32.4
Cl_3CH	2.4	−1.0	−2.9	−8.1	−17.7	−23.8
Cl_2CH_2	4.5	2.6	−2.1	−6.3	−22.1	−29.8
$ClCH_3$	5.5	4.4	−1.1	−3.9	−21.8	−27.6

[a] $\Delta G = G(\mathrm{R,TS}\cdots\mathrm{H{-}X}) - G(\mathrm{R,TS}) - G(\mathrm{H{-}X})$. Equivalent equations apply for H and S.

times larger. Therefore, those HB-donor molecules forming HB interactions with larger charge-transfer character will increase the HB interaction at the TS more strongly than those with more electrostatic character.

6. Thermochemistry. Considering entropic contributions at 298.15 K and 1 atm, there is no stabilizing HB interaction between the studied solvent molecules and acetone (see Table 8). However, there is a reduction of the Gibbs free energy of the TS by the formation HB interactions for H_2O, MeOH, and Cl_3Ch. Relative Gibbs free energies, enthalpies, and entropies upon complexation of the reactant and TS are reported in Table 8. Although all investigated molecules can stabilize the reactant and TS by HB formation, taking into account thermal and entropic contributions, only H_2O, MeOH, and Cl_3CH play a catalytic role for the studied hetero-Diels−Alder reaction.

Concluding Remarks

This study completes a previous one[5d] and presents a detailed analysis of the catalytic effect of O−H (methanol, water) and C−H (chloroform and derivatives) HB-donor solvent molecules in hetero-Diels−Alder rearrangements. Because of the lack of a strict definition of an HB, several properties and techniques have been considered: geometrical changes, NBO investigation, topological analysis of the electron density, AIM theory and the ELF, decomposition of the interaction energy between monomers following the Morokuma−Kitaura scheme, and thermochemical considerations.

Each of these methodologies provides complementary pieces of information to the understanding of the nature of an HB between a solvent molecule and a reactant and transition structure, where the electronic structure of the HB acceptor has been altered. All criteria successfully describe the increment of the strength of the HB at the TS. The increase of the charge-transfer interaction upon complexation at the reactant and, to a greater extent, at the TS is well characterized both electronically by the NBO and ELF and energetically by energy decomposition analysis (EDA).

The essential role of the polarization of the C═O bond at the TS is highlighted by means of the NBO and ELF analyses, showing three lone pairs for the oxygen atom (NBO) and a considerable increment of 0.50e (ELF) in the electronic charge of the lone pairs of the HB-acceptor oxygen as a consequence of the asynchronicity of the cycloaddition reaction. The energy decomposition analysis shows than both the electrostatic and covalent parts of HB interactions increase at the TS; however, the increase of the charge-transfer type is almost twice that of the electrostatic type. Hence, solvents forming HBs with a considerable charge-transfer character will benefit more the improved HB-acceptor feature of the oxygen at the TS.

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