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Ab Initio Study of the Regiochemistry of 1,3-Dipolar Cycloadditions. Reactions of Diazomethane and Formonitrile Oxide with Ethene, Propene, Acrylonitrile, and Methyl Vinyl Ether

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Structures and energetics of reactants and transition structures of the cycloadditions of diazomethane (DZM) and formonitrile oxide (FNO) with ethene (ET), propene (PR), acrylonitrile (ACN), and methyl vinyl ether (MVE) have been investigated with the use of ab initio molecular orbital calculations. The reaction of acetonitrile oxide (MNO) with acrylonitrile has been also included for comparisons. Structure optimizations were performed at the RHF/6-31G(d) and density functional B3LYP/6-31G(d) levels of approximation. Single-point electronic energies were computed up to the MP4SDTQ/6-31G(d) level. Kinetic contributions to activation enthalpies and entropies were computed at the RHF/6-31G(d) level. Transition structures of ethene cycloadditions (prototype reactions) were also checked with the MP2/6-31G(d) approximation. Solvent effects were introduced both at a semiempirical level (AMSOL) and at an ab initio level using the Pisa model (interlocking spheres) and the IPCM procedure (isodensity surface polarized continuum model). Electronic activation energies are found to be very sensitive to the treatment of electron correlation and failed to converge to values unaffected by further theoretical improvements: indeed, the inclusion of full fourth-order correlation (MP4) decreases the activation energies by 5−10 kcal/mol with respect to the preceding level of correlation (MP3). Anyway, activation free enthalpies and entropies of the reactions under study appear to be close to the experimental values available for this class of reactions. Still in agreement with experimental observations is the effect of solvent polarity on the reaction rates. Theoretical regioselectivity is less sensitive to the level of calculation, although the inclusion of electron correlation, both with the Moeller−Plesset technique and the use of the density functional theory, is able to reverse the regiochemical predictions obtained with RHF energies for the reactions of nitrile oxides with acrylonitrile. This explains why the frontier orbital theory, which is based on uncorrelated HF-wave functions, cannot arrive at the correct prediction of the regiochemistry in these cases. Calculated solvent effects appear to influence the regiochemistry of 1,3-dipolar cycloaddition, but in general, they reinforce the prediction obtained in vacuo.

1,3-Dipolar cycloaddition reactions[1] are attractive systems for theoretical investigations, given the relatively small size of the most simple "real" reactions and the controversy regarding the origin of product selectivities. As a matter of fact, regiochemical selectivity is a major feature of 1,3-dipolar cycloaddition since it occurs with all the unsymmetrically substituted dipolarophiles; moreover, it can be driven to yield regiospecificity (i.e., the production of a single adduct) and also reversed by suitable modeling of the reactants. Owing to the importance of these reactions for the synthesis of a large variety of functionalized five-membered heterocyclic systems, which in turn often lend themselves as ideal synthons of "non heterocyclic" derivatives,[2] extensive experimental and theoretical studies aimed at understanding the reaction mechanism and the origin of regiochemistry are fully justified.

The pioneering work of Huisgen has provided both a general definition of 1,3-dipolar cycloaddition reactions and very convincing experimental support to the hypothesis that they proceed over a barrier with a concerted mechanism.[3,4] This view, as opposed to that envisaging a diradical mechanism in a nonconcerted pathway,[4,5] has also been corroborated by ab initio calculations of a few prototype reactions.[6,7] A general rationalization of the regiochemistry of 1,3-dipolar cycloadditions, based on the frontier molecular orbital theory (FMO), was proposed by Houk in 1973.[8]

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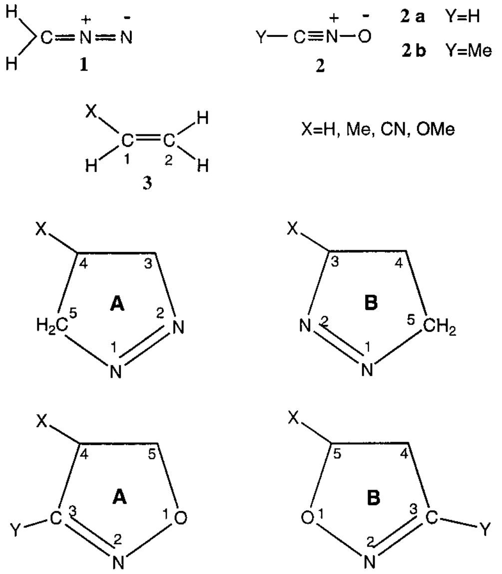
According to this theory, when electron-donating and electron-withdrawing sustituents are attached directly to an alkene, the frontier orbital energies and coefficients undergo opposite variations, which are used to understand changes in reactivity and regiochemistry. The same substituent effect alters electrostatic potentials, and so regioselectivity of cycloadditions can also be explained in such terms.[9] In the last 20 years, the FMO theory of cycloaddition regiochemistry has had a formidable impact on the production and explanation of an enormous mass of new experimental results and has been included in many textbooks as an important tool for the understanding of organic chemistry.[10] However, it has been noted that the success of the theory also rests on the exceptional flexibility of its practical use[11,12] owing to the introduction of several optional effects that are able to reverse the prediction and on the general tendency to avoid a priori predictions in favor of a posteriori explanations. As an example, the *plain* FMO theory failed to predict the correct regiochemistry of the reaction of alkyl vinyl ethers with diazomethane,[5d] yet at least three different explanations are now available, in the context of FMO theory, for the correct regiochemistry: first, it has been stated as a fact[10b] that with electron-rich alkenes the regiochemical control is assumed by the LUMO(1,3-dipole)−HOMO(alkene) interaction (instead of the previously postulated HOMO(1,3-dipole)−LUMO(alkene)), which switches the prediction from one regioisomer to the other; a second explanation[13] postulates that a repulsive secondary orbital interaction is able to steer the reaction centers to the opposite regiochemical approach; a third explanation[14] maintains that distortions of the alkene in the transition state, due to closed-shell repulsions, are responsible for the FMO interactions that favor the experimental regiochemistry. Finally, in a recent study[12] of the reaction of methyl vinyl ether with diazomethane we found that the favored (lowest energy) transition structure (TS) of the four TSs corresponding to the two regioisomeric approaches and to the synperiplanar and antiperiplanar conformations of the OMe substituent has the correct regiochemistry and the unexpected anti conformation, whereas the TSs with syn conformations fall in the wrong sequence.

Selectivity in 1,3-dipolar cycloadditions, in particular regioselectivity, has only recently become the subject of theoretical investigations by means of good level ab initio procedures directed to the calculation of TSs and activation parameters. In regard to regioselectivity, a few examples recently reported[12,15,16] appear to yield the correct regiochemistry, even if there is some indication that the regiochemical problem represents a more demanding challenge[15,16] than other kinds of selectivity, such as diastereoselectivity.[17] This latter observation amply justifies a systematic investigation of the level of theory necessary for reliable predictions and which will serve to explain and illustrate the control factors of regiochemistry.

Chart 1. Diazomethane 1, Formonitrile Oxide 2a, Acetonitrile Oxide 2b, Substituted Ethenes 3, A and B Regioadducts of Diazomethane, and Nitrile Oxide Cycloaddition



In this paper, we report some noteworthy examples of reactions of two 1,3-dipoles with low steric demand and very different electrostatic features, namely, diazomethane (DZM), which has a low dipole moment (1.5 D),[3e] and formonitrile oxide (FNO), which has a significantly larger one (3.1 D).[18] Regarding dipolarophiles, we have selected an electron-rich substituted alkene, methyl vinyl ether (MVE), an electron-deficient one, acrylonitrile (ACN), and propene (PR). The reactions of unsubstituted ethene with DZM and FNO (prototype reactions), as well as that of acetonitrile oxide (MNO) with ACN, have also been investigated for the sake of comparison. The regiochemical alternatives are outlined in Chart 1; in particular, A regiochemistry arises from attack by the carbon atom of the 1,3-dipole on the substituted carbon atom of the alkene dipolarophile.

The reactions studied include some of the most controversial regiochemical experiments present in the literature and form a preliminary set aimed at the systematic investigation of the regiochemistry of 1,3-dipolar cycloadditions.

Computational Methods

Geometries for all the structures were obtained at the HF/6-31G(d) level of theory[19] utilizing gradient geometry optimization and default threshold for convergence.[20] The searches for TSs were limited to concerted transition structures. Critical points of all the HF-TSs were fully characterized as minima

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or first-order saddle points by diagonalizing the Hessian matrixes of the optimized structures. HF-TSs were found to have only one negative eigenvalue, the corresponding eigenvector involving the expected formation of the two new bonds. Electron correlation was included via the Möller–Plesset perturbation theory up to the fourth order (MP4(SDTQ)/6-31G-(d)). Vibrational frequencies, in the harmonic approximation, were calculated for all the optimized structures and used, unscaled,[15] to compute the zero-point energies, their thermal corrections, the vibrational entropies, and their contributions to activation enthalpies, entropies, and free enthalpies.

As an alternative to HF and post-HF schemes, a DFT-based approach was also employed for comparison. Becke's three-parameter hybrid exchange functional[21] in combination with the gradient-corrected correlation functional of Lee, Yang, and Parr,[22] generally referred as B3LYP, was used throughout; the basis set for structure optimizations was the standard 6-31G-(d).[19]

The reactions of ethene with DZM and FNO were also studied with MP2/6-31G(d)-optimized geometries and with the use of a DZVP basis set (double-ζ split-valence plus polarization, equivalent to the 6-31G(d,p) basis set) DFT-optimized[23] with the pure Becke's exchange functional[24] and the LYP correlation functional[22] (BLYP).

The effect of the solvent on the electronic activation free enthalpy was evaluated by different self-consistent reaction field (SCRF) procedures: (i) the parametrization AM1-SM4 for cyclohexane and AM1-SM2.1 for water, implemented on the AMSOL-V[25] suite of programs, (ii) the ab initio Pisa model (interlocking spheres)[26] implemented in the Gamess (Rev.97) package, and (iii) the ab initio parametrization IPCM, isosurface perturbation continuum model, implemented in the Gaussian 94 package.[20] In the ab initio procedures the calculation was limited to the evaluation of the electrostatic contribution to the activation free enthalpy; nonelectrostatic contributions (cavitation and dispersion–repulsion terms) were evaluated only for a subset of reactions in water with the Pisa model.

Results and Discussion

The computed electronic energies and the contributions of nuclear motions to the thermodynamic properties (H, S, G) of reactants and TSs are provided as Supporting Information.

Table 1 reports the activation electronic energies, the kinetic contributions to the activation thermodynamic parameters, and the activation free enthalpies (gas phase) for the prototype reactions (DZM and FNO with ET) at different levels of calculation; the corresponding calculated geometries of the TSs are illustrated in Figure 1.

Table 2 reports the calculated solvent effects in cyclohexane (AMSOL)[25] and water (AMSOL[25] and Tomasi[26]) on a sample of diazomethane and formonitrile oxide cycloadditions; Table 3 collects the electrostatic contributions to the total solvent effect for all the reactions under study.

Table 4 lists the computed MP4SDTQ/6-31G(d)//HF/6-31G(d) electronic activation energies and the activation enthalpies, entropies, and free enthalpies at 298 K together with the relative free enthalpies to be compared with the experimental regiochemistries. For a more direct comparison of $\Delta^{\ddagger}H$, $\Delta^{\ddagger}S$, and $\Delta^{\ddagger}G$ with experiment where concentrations are given in mol/L, the standard state of molar concentration has been adopted.[15] The experimental $\Delta^{\ddagger}G_{\mathrm{emp}}$ is compared with the theoretical apparent $\Delta^{\ddagger}G$, thus including the effect of concomitant reactions, i.e., the contemporaneous formation of A/B and syn/anti (for MVE) TSs.[27]

Although the analysis of solvent effects is fully reported in Tables 2 and 3, Table 4 includes the activation free enthalpies in a solvent of moderate dielectric constant (carbon tetrachloride, $\epsilon = 2.22$); the solvent effect, limited to its electrostatic contribution, is calculated according to the Pisa model.[24] Figures 2–5 and Table 5 contain theoretical information about structures, dipole moments, and electronic activation energies at various levels of theory; these results will be useful for the discussion of the origin of regioselectivity and for a general appraisal of the reliability of theoretical predictions.

First, let us compare the results obtained at different levels of calculations for the prototype reactions.

The Prototype Cycloadditions of Ethene with Diazomethane and Formonitrile Oxide. The effects of including electron correlation in the calculation of activation electronic energies for the reactions of diazomethane and formonitrile oxide with ethene (both with the density functional (B3LYP) and Moeller–Plesset (MPn) perturbation technique) are dramatically large and strongly dependent on the approximation adopted. However, as is shown in Table 1 (first section), the changes are only marginally a reflection of the geometrical changes of reactants and TSs; indeed, when reactants and TSs optimized at the HF, B3LYP, and MP2 levels are treated at the same level of single-point calculation (e.g., B3LYP/6-311+G(2d,p) or MPn), the resulting activation energies appear to be quite similar. For example, the electronic activation energy of the reaction ET + DZM varies only from 5.74 to 6.47 kcal·mol^{-1} with the MP2 level of correlation, from 15.44 to 16.13 kcal·mol^{-1} with MP3, from 10.30 to 10.79 kcal·mol^{-1} with MP4, and from 17.06 to 17.21 kcal·mol^{-1} with B3LYP/6-311++G(2d,p). Much less satisfactory is the finding that the results obtained with the most extended calculations (MP4SDTQ/

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(27) The apparent activation parameters of an overall reaction of two reactants yielding to a plurality of transition structures (e.g., A and B TSs) can be readily obtained by the relative values of activation free enthalpies of the TSs: after calculating the fraction p_i of the transition structure i, one obtains $\Delta^{\ddagger}G_{\mathrm{app}} = \Delta^{\ddagger}G_i + RT \ln p_i$, $\Delta^{\ddagger}H_{\mathrm{app}} = \Sigma p_i\Delta^{\ddagger}H_i$ (the weighted average of $\Delta^{\ddagger}H_i$), and $T\Delta^{\ddagger}S_{\mathrm{app}} = -\Delta^{\ddagger}G_{\mathrm{app}} + \Delta^{\ddagger}H_{\mathrm{app}}$. The apparent activation parameters for the reactions of MVE$_{\mathrm{syn}}$ and MVE$_{\mathrm{anti}}$ leading to A_{syn} and A_{anti} are given by $\Delta^{\ddagger}G_{A_{\mathrm{app}}} = \Delta^{\ddagger}G_{A_{\mathrm{syn}}} + RT \ln p_{A_{\mathrm{syn}}} - RT \ln p_{\mathrm{syn}}$ and $\Delta^{\ddagger}H_{A_{\mathrm{app}}} = p_{A_{\mathrm{syn}}}\Delta^{\ddagger}H_{A_{\mathrm{syn}}} + (1 - p_{A_{\mathrm{syn}}})\Delta^{\ddagger}H_{A_{\mathrm{anti}}} - (1 - p_{\mathrm{syn}})(H_{\mathrm{anti}} - H_{\mathrm{syn}})$, where $p_{A_{\mathrm{syn}}}$ is the fraction of A_{syn} in the mixture of A–TSs, p_{syn} is the fraction of the conformer MVE$_{\mathrm{syn}}$, and $(H_{\mathrm{anti}} - H_{\mathrm{syn}}) = 2.327$ kcal·mol^{-1} is the enthalpy difference between the conformers of MVE. For the calculation of p_{syn}, the free enthalpy differences, $G_{\mathrm{anti}} - G_{\mathrm{syn}}$, are 1.785 kcal·mol^{-1} in the gas phase and 1.430, 1.156, and 0.853 kcal·mol^{-1} in solution with dielectric constants of 2.23, 4.9, and 38.2, respectively.

Table 1. Electronic Activation Energies, Kinetic Contributions, and Activation Free Enthalpy of the Cycloaddition of Ethene (ET) to Diazomethane (DZM) and Formonitrile Oxide (FNO)[a]

	ET-DZM			ET-FNO		
X/6-31G(d)	X = HF	X = MP2	X = B3LYP	X = HF	X = MP2	X = B3LYP
HF/6-31G(d)	32.21			32.42		
MP2/6-31G(d)	6.47	5.74	6.16	8.94	7.61	6.56
MP3/6-31G(d)	15.44	16.13	15.58	17.17	14.67	16.41
MP4SDTQ/6-31G(d)	10.79	10.39	10.70	9.11	9.06	7.03
MP2/6-31+G(d,p)	6.67			8.80		
MP3/6-31+G(d,p)	15.72			17.16		
MP4SDTQ/6-31+G(d,p)	10.83			8.55		
B3LYP/6-31G(d)	13.89		14.27	11.27		11.36
B3LYP/6-311+G(2d,p)	17.22		17.08	15.16		14.62
B3LYP/6-311++G(2d,p)	17.21		17.06	15.14		14.61
B3LYP/DZVP[b]			15.88 (13.92)			12.77 (12.78)
BLYP/DZVP[b]			14.22 (14.12)			9.70 (9.58)
MP4SDTQ/6-311G(d,p)[c]				9.53[c]		
$\delta^{\ddagger}$ZPE	2.71	2.74	2.37	1.37	2.85	1.92
$\delta^{\ddagger}H$	1.25	1.16	1.63	0.20	1.36	1.10
$\Delta^{\ddagger}S$	−29.92	−30.96	−29.06	−26.06	−28.12	−27.54
$\delta^{\ddagger}G$	10.77	10.99	10.29	8.57	10.35	9.31
B3LYP/6-31G(d)	24.66		24.56	18.94		20.67
B3LYP/6-311+G(2d,p)	27.99		27.37	23.73		23.93
B3LYP/6-311++G(2d,p)	27.98		27.35	23.71		23.92
MP4SDTQ/6-31G(d)	21.56	21.38	20.99	17.68	19.41	16.34
MP4SDTQ/6-31+G(d,p)	21.61			17.13		

[a] Energy in kcal/mol, entropy in eu, standard state of the molar concentration at 298 K. First section: single-point electronic activation energies at the levels of calculation showns in the first column for the structures optimized at the HF/6-31G(d), MP2/6-31G(d), and B3LYP/6-31G(d) levels. [b] DFT calculations with the DZVP basis set of ref 23; the barriers obtained with full structure optimizations are given in parentheses. [c] Reference 7; structure optimizations at the HF/6-311(d,p) level. Second section: $\delta^{\ddagger}H$, $\delta^{\ddagger}G$ are the nuclear kinetic contributions to the activation enthalpy and free enthalpy (to be added to the electronic activation energy); $\delta^{\ddagger}$ZPE is the contribution of zero point energy; $\Delta^{\ddagger}S$ is the activation entropy; $\Delta^{\ddagger}S$ and $\delta^{\ddagger}G$ include the reaction statistical factors. Third section: activation free enthalpy.

6-31G(d) and B3LYP/6-311++G(2d,p)) show a difference of about 6 kcal·mol^{-1}. Significantly, the same happens for the reaction of ET + FNO and for the reactions of alkene derivatives, thus giving evidence of a systematic difference in the calculated activation energies for this class of reactions due to intrinsic features of the calculations. It has been suggested that accurate DFT predictions of reaction energies require the use of DFT-optimized Gaussian-type basis sets;[28] so, we have checked the DZVP basis set (contraction pattern (5211/411/1) for C, N, O and (41/1) for H) DFT-optimized by Sim et al.[23] and found that the activation electronic energies amount to 15.88(ET + DZM) and 12.77(ET + FNO) kcal·mol^{-1} when B3LYP/6-31G(d) optimized geometries of reactants and transition structure are used and to 13.92, 12.78 kcal·mol^{-1}, respectively, when optimizations are done with the B3LYP/DZVP model. All these values are still higher than the corresponding predictions obtained with the MP4SDTQ/6-31G(d) calculations; hovewer, since the DZVP basis set had been optimized[23] with the use of the pure Becke's exchange functional[24] instead of the B3 hybrid one, we have repeated the calculations with the BLYP/DZVP model and found lower activation barriers that, for the case of ET + FNO, are very near to the MP4 prediction. This last prediction (9.11 kcal·mol^{-1}) is confirmed by the MP4SDTQ/6-311G(d,p) reported by Sosa et al.[7] for the same reaction (9.53 kcal·mol^{-1}), whereas their BLYP prediction (8.5 kcal·mol^{-1}) is probably due to the introduction of auxiliary basis sets within the LSD approximation, which are not present in our calculations.

The contributions of nuclear motions to activation free enthalpy are almost independent of the approximation used for structure optimization (second section of Table 1), so that the systematic difference found between electronic activation energies is conserved also in activation free enthalpies (third section of Table 1).

Comparing the theoretical predictions with the experimental findings, one finds that activation entropies have the correct values[29] and that the MP4/6-31G(d) results match the experimental order of magnitude of the reaction rates in the gas phase fairly well. Indeed, the activation free enhalpies are 22.0 kcal·mol^{-1} for the reaction ET + DZM (in dimethylformamide at 298 K)[30] and 20.1 kcal·mol^{-1} for the reaction of ET with benzonitrile oxide (ethyl ether at 298 K).[31,32] Inspection of Table 2, which will be discussed in full in a subsequent section, reveals that solvent effects on activation free enthalpy, according to the AMSOL evaluation in cyclohexane and water, are low for the reaction of ET with DZM and large positive for the reactions with FNO; according to the Tomasi evaluation in water, they are slightly negative and negligible, respectively, for the two reactions. It can be concluded that the gas-phase activation free enthalpy should be near 22.0 kcal·mol^{-1} for the reaction of DZM with ET and less than 20.1 kcal·mol^{-1} for the reaction of ET with FNO, in agreement with the MP4 calculations.

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[29] Unfortunately, in a previous paper of ours (ref 15, Table 1) formonitrile oxide was given incorrect values of ZPE, δH, S, δG, and in particular, a definitely lower value for the standard entropy (41.81 instead of 53.26 eu). There we concluded that for formonitrile oxide cycloadditions "the calculated absolute value of the negative activation entropy is probably significantly underestimated (by, at least, 10 eu) with respect to the experimental values ...". Now, we observe that the disagreement between theory and experiment disappears when the correct values are used.

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[31] Bast, K.; Christl, M.; Huisgen, R.; Mack, W. *Chem. Ber.* **1973**, *106*, 3312.

[32] Battaglia, A.; Dondoni, A. *Ric. Sci.* **1968**, *38*, 201.

The computed TSs are illustrated in Figure 1 where also the dipole moments (μ, D) and the reaction mode imaginary frequencies (rm, cm^{-1}) are given. TSs appear to be well concerted at all the levels of optimization with the CC forming bonds shorter than the CX ones.

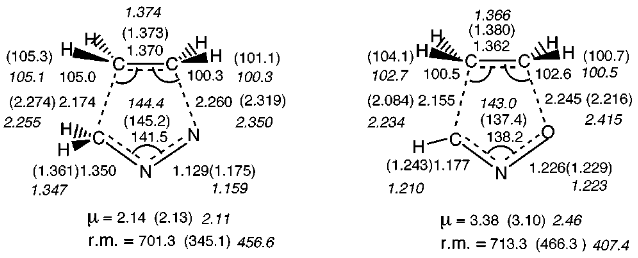

Figure 1. Optimized transition structures of diazomethane/ethene and formonitrile oxide/ethene cycloadditions. Geometry, dipole moments, and imaginary frequency of reaction mode. HF/6-31G(d), MP2/6-31G(d) in parentheses, B3LYP/6-31G(d) in italics. Distances in Å, angles in deg, dipole moments in D, reaction mode imaginary frequencies in cm^{-1}.

The inclusion of MP2 correlation produces opposite effects in the two reactions, longer forming bonds (earlier TS) and a more synchronous TS for the reaction of DZM and shorter forming bonds and a less synchronous TS for the reaction of FNO; coherently, the CNN angle is increased (lower deformation of diazomethane moiety in the earlier TS) and the CNO angle is slightly decreased. B3LYP optimization, on the other hand, produces the most early and the less synchronous TSs in both reactions. These changes of incipient bond lengths and bond angles are fairly large and cannot be considered negligible for these reactions, which share with the other pericyclic reactions the tendency to show remarkable constancy of calculated structures of their TSs.[33]

The above analysis justifies the choices made for the calculation of the electronic activation energies of the reactions with substituted alkenes, i.e., the choice of controlling the geometry optimization both at the HF and at the B3LYP level and the choice of performing the energy calculation at the full MP4 level of correlation. Let us stress that MP2, MP3, and B3LYP electronic activation energies must be considered inadequate.

Solvent Effect. The contributions of solvent effects on the activation free enthalpies of the reactions under study are reported in Tables 2 and 3 where comparisons can also be done with different procedures. These effects are given by the differences between the solvent effects on the TSs and those on the reactants.

In Table 2, the total solvent effect (TOT for reactants and TOT‡ for the activation free enthalpy) consists of two contributions, labeled CDS(CDS‡) for "cavitation + dispersion + structural" and ENP(ENP‡) for "electronic + nuclear + polarization" in the AMSOL procedure, CDR(CDR‡) for "cavitation + dispersion + repulsion", and ELEC(ELEC‡) for "electrostatic" in the Tomasi procedure.

All the calculations were done with unrelaxed gas-phase geometries (reactants and TSs) calculated at the HF/6-31G(d) level. Since this choice could be unfit for the AMSOL procedure, which according to its parametrization, requires AM1 gas-phase and solvent-phase relaxed structures, we checked it with a few examples of full AMSOL evaluation and found that the calculated solvent effects are not largely affected by geometry relaxation. For ethene in water, for example, the unrelaxed HF/6-31G(d) calculation gives ENP = −0.37, CDS = 1.10, and TOT = 0.73, while the complete procedure furnishes −0.42, 1.10, and 0.68 kcal·mol^{-1}, respectively. Let us note that both calculations match well the experimental free enthalpy of solvation of ethene (1.3 kcal·mol^{-1}).[34] For other cases, the differences between the results of unrelaxed and relaxed calculations of ENP are larger than for ethene; however, the unrelaxed results can still be accepted for qualitative considerations.

The CDS‡ contribution to the activation free enthalpy appears to slightly decrease (in cyclohexane) or increase (in water) the activation free enthalpy of the cycloaddition without introducing significant differences on the A/B regiochemistry; the ENP‡ term is large and positive for FNO cycloadditions so that these reactions appear to be heavily slowed by solvent effects, whereas for DZM cycloadditions it is rather low, positive for cyclohexane and negative for water, and opposed to the CDS‡ term so that the total effect results to be small. Furthermore, the ENP‡ term tends to favor B-TSs over A-TSs, a feature that is well evident for the cycloadditions of acrylonitrile (ACN) and much more evident in water than in cyclohexane.

The ab initio evaluation of solvent effects (in water) according to the Tomasi model leads to very different figures, but the overall qualitative trends are alike. The CDR‡ term is negative, large, and fairly independent of the cycloaddition considered (−1.85 ± 0.20 kcal·mol^{-1}); we have also found that the cycloadditions of nitrones with substituted alkenes give values in the same range.[35] This finding can be traced back to the view that the CDR term is approximately proportional to the solvent-accessible surface area (the cavity area) of solutes and to the feature of TSs of having very alike structures of the new forming pentatomic ring so that the change of the cavity areas from the reactants to the TSs are similar. The ELEC‡ term, on the contrary, differentiates significantly the cycloadditions of DZM (small positive, in general, and large negative for the reaction of ACN in the B orientation) from those of FNO (large positive, in general, and larger for the A orientation than for the B orientation of the reaction of ACN). The ELEC‡ contributions, calculated for various solvents whose dielectric constants range from 2.02 (cyclohexane) to 78.4 (water) reported in Table 3, show increasing effects (both positive and negative) on increasing the dielectric constant. The trend of ELEC‡ appears to conform to experimental studies on the effect of solvent polarity on reaction rates. Indeed, it has been found that the cycloaddition rate of DZM with methyl acrylate increases by increasing solvent polarity, whereas it remains substantially unaltered with norbornene;[36] moreover, it is common experience, although systematic quantitative studies are not present in the literature, that nitrile oxide cycloadditions are disfavored by highly polar solvents with a change in activation free enthalpy of less than 1.0 kcal·mol^{-1} on passing from benzene solutions to acetonitrile solutions.[3g,32] The whole

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[33] Houk, K. N.; Li, Y.; Evanseck, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *30*, 682.

[34] Cabani, S.; Gianni, P.; Mollica, V.; Lepori, L. *J. Sol. Chem.* **1981**, *10*, 563.

[35] Rastelli, A.; Gandolfi, R.; Sarzi Amadè, M. Manuscript in preparation.

[36] Geittner, J.; Huisgen, R.; Reissig, H.-U. *Heterocycles* **1978**, *11*, 109.

of experimental information and theoretical evaluations leads to the conclusion that the negative CDR‡ contribution to these reactions is probably overestimated by more than 1 kcal·mol^{-1}; scaling this term reduces the total solvent effect of DZM cycloadditions to the experimental qualitative trend (and to the AMSOL evaluation) and preserves a reasonable description of solvent effects in FNO cycloadditions. The view of a possible systematic overestimation of the CDR term is also supported by the value obtained for ET in water, 5.76 kcal·mol^{-1}, which leads to a calculated total effect of 4.64 in front of the experimental 1.3 kcal·mol^{-1}.

Table 3 reports also the ELEC‡ contributions obtained with the IPCM model at the RHF/6-31G(d) level and at the B3LYP/6-31G(d) level; IPCM calculations furnish results that are similar to those of the Tomasi model at the RHF level, whereas the inclusion of electron correlation, both via the B3LYP and the MP2 (not reported) procedure, reduces the effect on nitrile oxide reactions and leaves unaltered the effects on DZM reactions.

Diazomethane Cycloadditions. Cycloadditions of diazomethane to monosubstituted alkenes are known to lead to a large dominance (or exclusive formation) of 3-substituted 1-pyrazolines (adduct B in Chart 1) both with electron-donor[5d,37] and electron-acceptor substituents;[37] even the substitution of an alkyl group causes a significant selectivity (88:12 for propene)[38a] in favor of adduct B.[38b]

The theoretical results of Table 4 show a perfect agreement with the experimental regiochemistry. The neat dominance of the B adduct predicted for the reaction of propene with diazomethane, in vacuo, is scarcely affected by the solvent, not unexpectedly for a low polarized olefin and for two competing TSs exhibiting almost the same value of dipole moment. At variance, the reaction of acrylonitrile gains B specificity by the effect of the solvent consistently with the fact that the regioisomeric TSs show a sizable difference (ca. 3 D) of dipole moments. Likewise, the reaction of methyl vinyl ether, predicted to be highly B regioselective (in the anti conformation), has its regioselectivity reinforced by the solvent.

One can observe that the above regioselectivities are also well explained by the electronic activation energies ($\Delta^‡E_e$ at the MP4 level) and that also B3LYP/6-31G(d) electronic activation energies reproduce the correct regiochemistry (Table 5).

The availability of very reliable experimental results produced by the Huisgen's group permits an interesting appreciation of the calculated activation parameters. First, it has been observed that the activation entropies of diazomethane cycloadditions appear to be remarkably constant in the range of −28 to −33 eu,[3f,36] whereas rate constants cover the impressive range of 10^7, namely, from 1.12 L·mol^{-1}·s^{-1} for the cycloaddition of methyl acrylate to 1 × 10^{-7} L·mol^{-1}·s^{-1} for butylvinyl ether.[30] Unsubstituted ethene shows a rate constant of 4 × 10^{-4} L·mol^{-1}·s^{-1}, which is intermediate between those of electron-donor and electron-acceptor derivatives; the rate constant for 1-hexene is reported to be 4.4 × 10^{-6} L·mol^{-1}·s^{-1}, and the rate constant of the cycloaddition of acrylonitrile was evaluated by us[39] to be 0.84 L·mol^{-1}·s^{-1}, in qualitative agreement with the finding that acrylonitrile, in general, shows a lower reactivity than acrylate with “electron-rich” 1,3-dipoles.[40] From the estimated rate constants, one obtains the following activation free enthalpies (in dimethylformamide at 298 K): 26.9, 24.7, 22.0, 17.5, and 17.3 kcal·mol^{-1} for the reactions of diazomethane with butyl vinyl ether, 1-hexene, ethene, acrylonitrile, and methyl acrylate, respectively.

The calculated activation entropies for the diazomethane cycloadditions (Table 4) fall between the values of −28.8 eu for methyl vinyl ether and −31.1 eu for propene, thus confirming the observed constancy; moreover, the calculated absolute values of activation entropy are surprisingly close to the experimental ones.

If we assume, as usual for the reactions studied, that methyl vinyl ether and propene are good models for butylvinyl ether and 1-hexene, respectively, *the comparison between the calculated activation free enthalpies and their empirical values (Table 4) shows an impressive agreement both in the trend and in the absolute values*.

Nitrile Oxide Cycloadditions. Unfortunately, cycloadditions of formonitrile oxide (FNO) have not been greatly investigated experimentally. However, the observed regiochemistry of FNO cycloadditions[41] has been found to correspond to that of the most investigated benzonitrile oxide,[18,41b,42,43] showing, in addition, a larger tendency to give B adducts; so, cycloadditions of FNO to monosubstituted alkenes yield invariabily the B adduct either as the dominant adduct or as the exclusive one.

The relative reaction rates have been determined by the Huisgen group[31] by measuring the relative product yields in competition reactions of an excess of couples of dipolarophiles with benzonitrile oxide in ethereal solutions (the missing result for ACN has been produced by us[39] using the same procedure; ACN was five times less reactive than methyl acrylate). The absolute reaction rate of benzonitrile oxide with styrene in carbon tetrachloride was found[32] to be 1.1 × 10^{-2} L·mol^{-1}·s^{-1} at 25 °C, so that the absolute reaction rates can be roughly estimated (0.95 × 10^{-2}, 0.30 × 10^{-2}, 1.99 × 10^{-2}, 7.88 × 10^{-2}, and 1.58 × 10^{-2} L·mol^{-1}·s^{-1} for ethene, propene, butyl vinyl ether, methyl acrylate, and acrylonitrile, respectively) and converted into activation free enthalpies (20.1, 20.8, 19.7, 18.9, 19.8 kcal·mol^{-1}, in the same sequence). In the absence of similar studies for FNO, we adopt in Table 4 the values of benzonitrile oxide for the comparison with our theoretical results. A further

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[37] Regitz, M.; Heydt, H. Diazoalkanes. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, p 393.

[38] (a) Firestone, R. A. *Tetrahedron Lett.* **1980**, *21*, 121. (b) Huisgen, R.; Koszinowski, J.; Ohta, A.; Schiffer, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 202.

[39] The competition reaction of DZM (ethereal solution) with a high excess (= 100 molar equiv) of acrylonitrile/methyl acrilate mixture was carried out in ethyl ether at room temperature to give a quantitative yield of adducts. The 3-substituted 1-pyrazolines, formed as primary adducts, isomerized under the reaction conditions to 3-substituted 2-pyrazolines. Adduct ratios, obtained by ^{1}H NMR (300 MHz), allowed evaluation of $k_{ACN}/k_{methyl\ acrylate}$ (0.75 ± 0.02). The competition reaction of benzonitrile oxide (generated in situ with solid sodium carbonate in benzene from benzohydroximic acid chloride) demonstrated that methyl acrylate is more reactive than acrylonitrile ($k_{ACN}/k_{methyl\ acrylate}$ = 0.20 ± 0.01).

[40] Huisgen, R.; Xingya, L. A. *Tetrahedron Lett.* **1983**, *24*, 4185.

[41] (a) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291. (b) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345.

[42] (a) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258. (b) Christl, M.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3275.

[43] Caramella, P.; Grunanger, P. Nitrile Oxides and Imines. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, p 291.

Table 2. Solvent Effects[a]

	AMSOL/SM4 cyclohexane ($\epsilon = 2.02$)			AMSOL/SM2.1 water ($\epsilon = 78.4$)			TOMASI/GAMESS97 water ($\epsilon = 78.4$)		
reactants	CDS	ENP	TOT	CDS	ENP	TOT	CDR	ELEC	TOT
ET	−0.79	−0.19	−0.98	1.10	−0.37	0.73	5.76	−1.12	4.64
ET[b]	−0.80	−0.21	−1.01	1.10	−0.42	0.68			
PR	−1.56	−0.22	−1.78	1.30	−0.44	0.86	7.81	−1.12	6.69
ACN	−0.93	−1.96	−2.89	−2.03	−1.94	−3.97	6.26	−6.41	−0.15
DZM	0.59	−0.95	−0.36	−3.18	0.41	−2.78	4.32	−2.26	2.06
DZM[b]	0.62	−0.94	−0.32	−3.30	−0.02	−3.21			
FNO	−0.07	−7.90	−7.96	−2.70	−9.45	−12.15	3.34	−8.19	−4.85
FNO[b]	−0.04	−7.81	−7.86	−2.70	−10.06	−12.77			
MNO	−0.39	−5.57	−5.95	−2.52	−6.91	−9.43			
MNO[b]	−0.36	−4.83	−5.19	−2.54	−5.74	−8.27			

		AMSOL/SM4 cyclohexane ($\epsilon = 2.02$)			AMSOL/SM2.1 water ($\epsilon = 78.4$)			TOMASI/GAMESS97 water ($\epsilon = 78.4$)		
TSs	regio	CDS‡	ENP‡	TOT‡	CDS‡	ENP‡	TOT‡	CDR‡	ELEC‡	TOT‡
ET-DZM		−0.85	0.83	−0.02	0.21	−0.62	−0.41	−1.86	0.45	−1.41
ET-DZM[b]		−0.82	0.70	−0.13	0.11	−0.61	−0.51			
PR-DZM	A	−0.72	0.92	0.20	0.23	−0.47	−0.24	−1.67	0.60	−1.07
	B	−0.91	0.88	−0.04	0.49	−0.53	−0.05	−1.65	0.61	−1.04
ACN-DZM	A	−0.64	0.90	0.26	0.54	−0.47	0.07	−1.96	0.24	−1.72
	B	−0.72	0.20	−0.52	0.86	−1.84	−0.98	−1.87	−2.44	−4.31
ET-FNO		−0.36	5.32	4.95	−0.01	4.88	4.87	−2.12	2.05	−0.07
ET-FNO[b]		−0.39	5.84	5.45	−0.06	6.45	6.39			
ET-MNO[b]		−0.77	3.03	2.25	0.13	2.39	2.52			
PR-FNO	A	−0.23	5.56	5.33	−0.01	5.45	5.44	−1.91	1.97	0.06
	B	−0.36	5.44	5.09	0.19	5.15	5.34	−1.73	1.95	0.22
ACN-FNO	A	−0.15	5.75	5.60	0.34	6.06	6.40	−1.84	3.34	1.50
	B	−0.15	5.41	5.26	0.60	4.76	5.36	−1.87	2.90	1.03

[a] Energies in kcal/mol; unrelaxed HF/6-31G(d) geometries; the total contribution (TOT‡) to the activation free enthalpy is due to the cavitation, solute−solvent dispersion, and solvent structural rearrangement term (CDS‡) and to the electronic−nuclear−polarization term (ENP‡) in the AMSOL model; in the Tomasi model, CDR‡ is the cavitation−dispersion−repulsion term and ELEC‡ is the electrostatic contribution; the basis set of ab initio calculations is the standard 6-31G(d). [b] Full AMSOL calculations with relaxed geometries in solvents.

piece of information concerns the activation entropy of the cycloaddition of *p*-chlorobenzonitrile oxide with styrene, which amounts to −27.0 eu.[32]

Inspection of Table 4 reveals that *B regiochemistry is always correctly predicted and that the calculated values of activation parameters fall in the correct range and, in particular, reproduce the interesting feature of these reactions, in contrast with diazomethane cycloadditions, of spanning a very restrict interval of reaction rates.*

Huisgen et al.[31,41,42] put stress on the finding that both electron-withdrawing and electron-donating substituents increase the reactivity of the dipolarophile toward benzonitrile oxide and argued, in the framework of FMO theory, that these cycloadditions receive contributions from both HO−LU interactions to a comparable extent, at variance with those of diazomethane, which, being favored only by electron-withdrawing substituents, are predominantly controlled by the HO(1,3-dipole)−LU(alkene) interaction. Quantitatively, the experimental argument is supported by the increment of the reaction rate of the electron-deficient acrylonitrile (over ethene with benzonitrile oxide) corresponding to $\Delta\Delta^‡G = -0.3$ kcal·mol^{-1} and by the increment of the reaction rate of the electron-rich butyl vinyl ether (over ethene with benzonitrile oxide) corresponding to $\Delta\Delta^‡G = -0.4$ kcal·mol^{-1}. The theoretical results provide the following increments: for the comparison acrylonitrile/ethene (with formonitrile oxide) −1.28 kcal·mol^{-1} (in vacuo), −0.88 (solution $\epsilon = 2.2$), −0.69 (solution $\epsilon = 4.9$), −0.48 (solution $\epsilon = 38.2$); for the comparison methyl vinyl ether/ethene (with formonitrile oxide) +0.14 kcal·mol^{-1} (in vacuo), +0.04 (solution $\epsilon = 2.2$), −0.12 (solution $\epsilon = 4.9$), −0.39 (solution $\epsilon = 38.2$). In conclusion, the theoretical results confirm the experimental finding and reveal that the relative reaction rate is significantly dependent on the polarity of the solvent, which has the effect of reducing the reaction rate of ACN and of increasing the reaction rate of MVE.

Energies and Geometries of the Transition Structures of Substituted Ethenes. The HF and DFT TSs of the reactions of substituted ethenes are illustrated in Figures 2−5. One can observe that the structures derived by the two optimizations tend to conserve the same differences noted for the prototype TSs. Moreover, the most evident feature is that the average lengths of the forming bonds are scarcely affected by the presence of substituents on the ethene moiety as a result of the fact that the two forming bonds undergo, in general, small opposite changes. This trend conforms to what is already well established for Diels−Alder reactions[33] and can be attributed to the tendency of the reacting system to maintain bonding as strong as possible while leaving room for the asynchronicity (difference in incipient bond lengths) called for by the asymmetry of the reactants.

In the reaction of DZM and FNO with propene, the CC-forming bond remains shorter than the CX bond in both regioisomeric TSs and asynchronicity is similar to that of the reaction of ethene. Inversion in incipient bond lengths is observed on going from adduct B to adduct A (with the CX bond shorter than the CC bond in the latter adduct) in the reaction of ACN with both DZM and FNO. Asynchronicity is particularly relevant in the B-TS of DZM reaction (CC bond shorter than CN bond) and in the A-TS of FNO reaction (CC longer than CO). The

Table 3. Electrostatic Solvent Effect on Activation Free Enthalpy[a]

		IPCM/GAUSSIAN 94		TOMASI/GAMESS97				
reaction	regio	RHF ($\epsilon = 5.0$)	DFT ($\epsilon = 5.0$)	RHF ($\epsilon = 2.02$)	($\epsilon = 2.22$)	($\epsilon = 4.9$)	($\epsilon = 38.2$)	($\epsilon = 78.4$)
ET-DZM		0.46	0.65	0.21	0.23	0.35	0.45	0.45
PR-DZM	A	0.26	0.34	0.28	0.31	0.48	0.60	0.60
	B	0.59	0.79	0.27	0.30	0.47	0.60	0.61
ACN-DZM	A	0.21	0.13	0.08	0.09	0.16	0.24	0.24
	B	−1.75	−1.22	−0.93	−1.03	−1.71	−2.38	−2.44
MVE-DZM	A_{syn}	0.20		0.35	0.38	0.61	0.79	0.78
	A_{anti}	0.13		0.19	0.20	0.25	0.19	0.15
	B_{syn}	−0.97		−0.18	−0.22	−0.50	−0.76	−1.04
	B_{anti}	0.22		0.12	0.13	0.16	0.20	0.19
ET-FNO		1.81	1.03	0.91	1.00	1.57	2.02	2.05
PR-FNO	A	1.40	0.75	0.91	1.01	1.57	1.98	1.97
	B	1.44	1.11	0.94	1.03	1.58	1.95	1.95
ACN-FNO	A	3.07	1.61	1.38	1.53	2.48	3.28	3.34
	B	3.24	1.16	1.26	1.40	2.16	2.82	2.90
MVE-FNO	A_{syn}	1.76		1.12	1.25	1.99	2.84	2.85
	A_{anti}	1.66		1.04	1.15	1.77	2.20	2.23
	B_{syn}	−0.96		0.19	0.19	0.12	−0.18	−0.27
	B_{anti}	1.37		0.84	0.92	1.39	1.72	1.70
ACN-MNO	A	4.41		2.15	2.38	3.81	5.02	5.05
	B	3.01		1.71	1.88	2.92	3.70	3.68

[a] Energies in kcal/mol; unrelaxed HF/6-31G(d) or B3LYP/6-31G(d) geometries are used; the basis set of ab initio calculations is the standard 6-31G(d).

geometrical features of these two TSs nicely conform to a nucleophilic attack by the C end of DZM and the O end of FNO, respectively, to the "electrophilic" β-position of ACN as a result of the dominant $HO_{dipole}-LU_{ACN}$ interaction (see paragraph on FMO interactions). The presence of the methyl group in acetonitrile oxide appears to be responsible of a longer CC- and a shorter CO-forming bond, as compared to FNO, both in the A and in the B adduct.

The reactions of MVE give rise to four TSs (both with DZM and FNO, Figures 3 and 5, respectively) where each regioadduct (A, B) bears the methyl group both in a synperiplanar relation and in an antiperiplanar relation to the CC bond of the alkene fragment. MVE itself shows two minima, the former corresponding to a syn (CCOMe = 0°) conformer while the latter, higher in energy by 1.98 kcal·mol^{-1} (HF/6-31G(d)), to an anti (CCOMe = 159.5°) conformer and a very flat potential double-well showing a saddle point at the anti conformation with CCOMe = 180°. Conformation angles of syn and anti TSs are significantly different from those of MVE, and the calculated values are reported in the figures. It is worth noting (Table 5) that the Banti TSs, corresponding to the higher energy MVE conformation, exhibit the lowest activation energies and that it is only with the Banti structure that the experimental B regiochemistry of the cycloaddition of diazomethane is theoretically confirmed. As for geometrical data, it is noteworthy that all TSs of the reaction of MVE with DZM show a low asynchronicity (CC slightly shorter than CX), which is also similar to that of the reactions of ethene and propene with the same 1,3-dipole.

TSs of the reaction of DZM with MVE are certainly different from those of DZM with ACN; however, it is remarkable that the very large difference in activation free enthalpies of these two reactions (experimental: 9 kcal·mol^{-1}, calculated $\geq$ 7 kcal·mol^{-1}) are compatible with the small difference in the average bond length (ca. 0.02 Å for both A and B TSs). This feature, as stated above, seems to be characteristic for pericyclic reactions, i.e. very large differences in reaction rates are compatible with small changes in forming and breaking bond lengths.[33]

Inspection of Table 5 reveals that the inclusion of MPn correlation has large effects on electronic activation energies that show qualitative trends quite similar to those discussed above for the reactions of the unsubstituted ethene. Moreover, electron correlation does have significant effects on the predicted regiochemistry (activation energy of the B-TS relative to the A-TS), and it is able to reverse the prediction of the regiochemistry of the reaction of acrylonitrile with formonitrile oxide. This last feature is also common to the reaction, not reported in Table 5, of acrylonitrile with acetonitrile oxide where the relative electronic activation energy of the B-TS amounts to +4.56, −3.96, −0.35, −2.74, and −0.37 kcal·mol^{-1} in the calculations HF/6-31G(d), MP2, MP3, MP4, and B3LYP, respectively. It is worth stressing that *the cycloadditions of acrylonitrile with nitrile oxides show experimental B regiospecificity, so that the inclusion of electron correlation is essential for reproducing theoretically the experimental results.*

Anyway, the observation that HF/6-31G(d) calculations may give a wrong answer to regiochemical problems is certainly very disappointing; examples of wrong regioselectivity predictions by HF calculations, which are reversed by the inclusion of electron correlation, are known also for Diels−Alder reactions.[44]

Frontier Orbital Considerations. The theoretical results reported in the preceding sections lend themselves to considerations that can shed light on the debated problem of the reliability of PMO (pertubation molecular orbital) predictions and, in particular, of FO predictions of the regiochemistry of cycloadditions. We start our argument by reporting (Table 6) the energies of the highest occupied (HO) and lowest unoccupied (LU) molecular orbitals of the 1,3-dipoles and of the dipolarophiles together with the MO coefficients of the reacting centers (the terminal atoms of 1,3-dipoles and the α and β carbon atoms of monosubstituted alkenes). Then, according to the FO rules, the orbital energy separations of the

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(44) Gonzales, J.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3033. Cioslowski, J.; Sauer, J.; Hetzenegger, J.; Karcher, T.; Hierstetter, T. *J. Am. Chem. Soc.* **1993**, *115*, 1353.

Table 4. Calculated Activation Parameters and Product Selectivity[a]

structure	regio	$\Delta^{\ddagger}E_e$	$\Delta^{\ddagger}H$	$\Delta^{\ddagger}S$	$\Delta^{\ddagger}G$	$\Delta^{\ddagger}G_{emp}$	$\Delta^{\ddagger}G$ CCl_4	selectivity[b] gas phase	selectivity[b] CCl_4
ET-DZM		10.79	12.64	−29.93	21.56	22.0	21.79		
PR-DZM	A	12.64	14.33	−32.23	23.94		24.25		
	B	11.48	13.23	−31.78	22.70		23.00	−1.23	−1.25
	Tot		13.35	−31.12	22.63	24.7[c]	22.93		
ACN-DZM	A	8.12	9.95	−32.47	19.63		19.72		
	B	7.20	9.03	−31.35	18.38		17.35	−1.25	−2.37
	Tot		9.13	−30.79	18.31	17.5[d]	17.34		
MVE-DZM	A_{syn}	16.24	17.56	−31.23	26.87		27.25		
	A_{anti}	16.31	17.43	−29.28	26.16		26.36		
	A_{app}		17.35	−29.11	26.03		26.29		
	B_{syn}	15.89	17.44	−31.01	26.69		26.47		
	B_{anti}	14.21	15.59	−28.78	24.17		24.30		
	B_{app}		15.51	−29.11	24.19		24.33	−1.84	−1.96
	Tot		15.59	−28.76	24.16	26.9[e]	24.31		
ET-FNO		9.11	9.90	−26.06	17.67	20.1[f]	18.67		
PR-FNO	A	10.23	10.91	−28.03	19.26		20.27		
	B	8.84	9.46	−27.51	17.66		18.69	−1.60	−1.58
	Tot		9.55	−27.06	17.62	20.8[f]	18.65		
ACN-FNO	A	10.44	11.21	−28.56	19.72		21.25		
	B	7.14	7.86	−28.60	16.39		17.79	−3.33	−3.46
	Tot		7.87	−28.56	16.39	19.8[f,d]	17.79		
MVE-FNO	A_{syn}	12.50	12.91	−27.72	21.17		22.42		
	A_{anti}	15.49	15.66	−25.24	23.19		24.34		
	A_{app}		12.89	−27.81	21.18		22.45		
	B_{syn}	11.67	12.07	−26.03	19.83		20.02		
	B_{anti}	10.22	10.50	−24.49	17.80		18.72		
	B_{app}		10.44	−24.72	17.81		18.71	−3.37	−3.74
	Tot		10.45	−24.68	17.81	19.7[f,e]	18.71		
ACN-MNO	A	8.59	9.50	−32.56	19.21		21.59		
	B	5.85	6.65	−32.18	16.24		18.12	−2.97	−3.47
	Tot		6.67	−32.09	16.24		18.12		

[a] Tot labels the total reaction; A_{app} (B_{app}) labels the couple of reactions leading to the A (B) adduct; $\Delta^{\ddagger}E_e$, electronic activation energies, from MP4/6-31G(d)//HF/6-31G(d) calculations; kinetic contributions from HF/6-31G(d). For the reactions of MVE thermodynamic parameters are given with respect to MVE_{syn}. $\Delta^{\ddagger}G_{emp}$ are the empirical activation free enthalpies (see text); $\Delta^{\ddagger}G$(solution) includes the electrostatic solvent effect ($ELEC^{\ddagger}$ of CCl_4) according to the Tomasi model at the HF/6-31G(d) level (see text); energies in kcal/mol, entropy in eu; standard state (298 K) of the molar concentration scale. [b] Free enthalpy relative to the A orientation. [c] Reaction of 1-hexene. [d] Reference 39. [e] Reaction of butyl vinyl ether. [f] Reactions of benzonitrile oxide in carbon tetrachloride.

Table 5. Electronic Activation Energies of the Cycloaddition of Ethene (ET), Propene (PR), Acrylonitrile (ACN), and Methyl Vinyl Ether (MVE) to Diazomethane (DZM) and Formonitrile Oxide (FNO)[a]

	ET-DZM		PR-DZM		ACN-DZM		MVE-DZM			
	b		A	B	A	B	A_{syn}	A_{anti}	B_{syn}	B_{anti}
HF/6-31G(d) opt		32.21	35.98	−1.23	30.96	−3.80	39.85	−0.38	+0.00	−2.28
MP2/6-31G(d)	5.74	6.47	8.23	−1.04	3.99	−1.48	12.20	+0.06	+0.40	−1.38
MP3/6-31G(d)	16.13	15.44	17.95	−1.09	13.79	−1.66	21.35	−0.13	+0.05	−2.05
MP4SDTQ/6-31G(d)	10.39	10.79	12.64	−1.16	8.12	−0.92	16.24	+0.07	−0.35	−2.03
B3LYP/6-31G(d) opt		14.27	17.86	−1.24	13.44	−2.93	21.51	−0.44	−0.64	−2.56

	ET-FNO		PR-FNO		ACN-FNO		MVE-FNO			
	b		A	B	A	B	A_{syn}	A_{anti}	B_{syn}	B_{anti}
HF/6-31G(d) opt		32.42	36.03	−3.61	32.46	+2.51	40.57	+0.03	−8.49	−11.39
MP2/6-31G(d)	7.61	8.94	10.25	−0.63	9.78	−4.78	12.84	+2.39	+0.99	−0.49
MP3/6-31G(d)	14.67	17.17	19.39	−1.86	17.90	−1.85	22.12	+1.29	−2.30	−4.56
MP4SDTQ/6-31G(d)	9.06	9.11	10.23	−1.39	10.44	−3.30	12.50	+2.99	−0.83	−2.28
B3LYP/6-31G(d) opt		11.36	14.46	−2.40	13.11	−1.98	17.49	+0.99	−4.89	−6.63

[a] Energy in kcal/mol; absolute values for A (A_{syn} for MVE) and relative values for the other TSs. HF/6-31G(d)-optimized geometries are used for MPn calculations. [b] MP2/6-31G(d) optimized geometries are used.

interaction HO(1,3-dipole)−LU(dipolarophile), where the 1,3-dipole acts as electron donor, and of the interaction LU(1,3-dipole)−HO(dipolarophile), where the 1,3-dipole acts as electron acceptor, are calculated and compared; when the energy separations show definitely different values, the FO interaction corresponding to the lower value has the dominant effect. The regiochemical orientation is then established by the rule that the reacting centers choose the alternative of facing large−large and small−small coefficients. Obviously, all these rules descend from the conditions of the most stabilizing frontier interactions.

Actually, the procedure is usually applied with a few improvements (e.g., introduction of resonance integrals, distorted reactant geometries to mimic the transition structure, inclusion of nonfrontier orbitals, etc.) which will be discussed later on.

Table 7 collects the HO−LU and LU−HO energy separations and the relative regiochimical predictions for all the reactions under study and allows a comparison

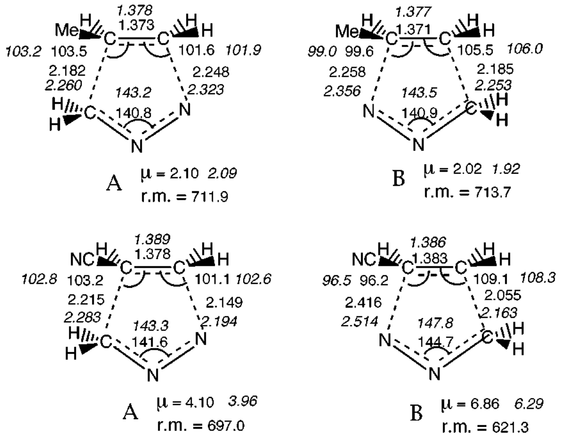

Figure 2. Optimized transition structures of the cycloaddition of diazomethane with propene and acrylonitrile. HF/6-31G(d), B3LYP/6-31G(d) in italics.

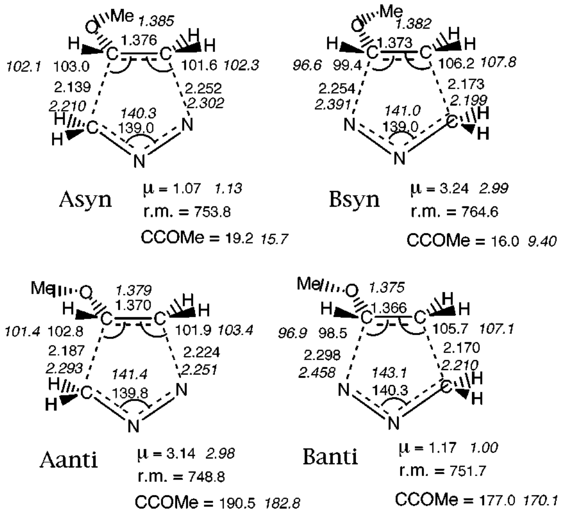

Figure 3. Optimized transition structures of the cycloaddition of diazomethane with methyl vinyl ether. The CCOMe dihedral angles show the syn and anti conformations. HF/6-31G(d), B3LYP/6-31G(d) in italics.

Table 6. Frontier MO Energies (ϵ_{HO}, ϵ_{LU}) and MO Coefficients[a]

1,3-dipole	ϵ_{HO}	ϵ_{LU}	$(C)_{HO}$	$(X)_{HO}$	$(C)_{LU}$	$(X)_{LU}$
DZM	−8.80	5.36	0.771	−0.620	0.549	0.528
FNO	−11.00	5.31	0.568	−0.783	0.678	0.332
MNO	−10.37	5.51	0.548	−0.762	0.647	0.319
dipolaroph	ϵ_{HO}	ϵ_{LU}	$(\alpha)_{HO}$	$(\beta)_{HO}$	$(\alpha)_{LU}$	$(\beta)_{LU}$
PR	−9.72	5.25	0.627	0.687	0.687	−0.696
ACN	−10.82	2.80	0.634	0.650	0.573	−0.687
MVE_{syn}	−9.25	5.75	0.463	0.696	0.716	−0.656
MVE_{anti}	−9.07	5.49	0.476	0.676	0.706	−0.670

[a] Orbital energy (HF/6-31G(d)) in eV; MO coefficients from AM1(orthogonal atomic basis). C and X are the frontier coefficients of the terminal atoms of 1,3-dipole, X being nitrogen for diazomethane and oxygen for nitrile oxides; α and β are the frontier coefficients of the alkene carbon atoms where (α) refers to the substituted carbon.

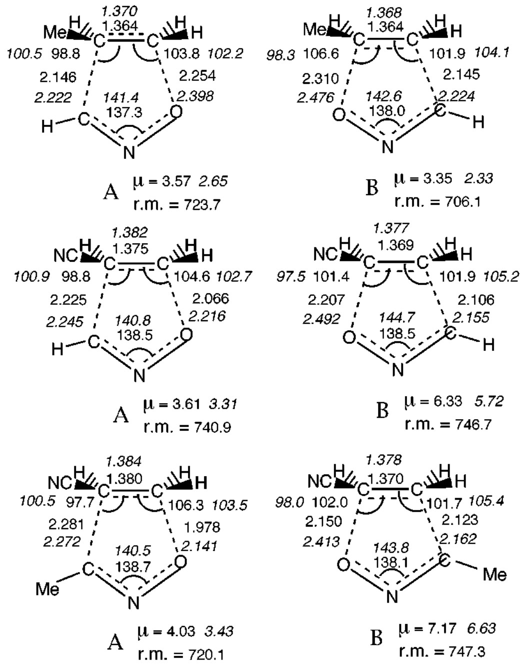

Figure 4. Optimized transition structures of the cycloaddition of formonitrile oxide with propene and acrylonitrile and of acetonitrile oxide with acrylonitrile. HF/6-31G(d), B3LYP/6-31G(d) in italics.

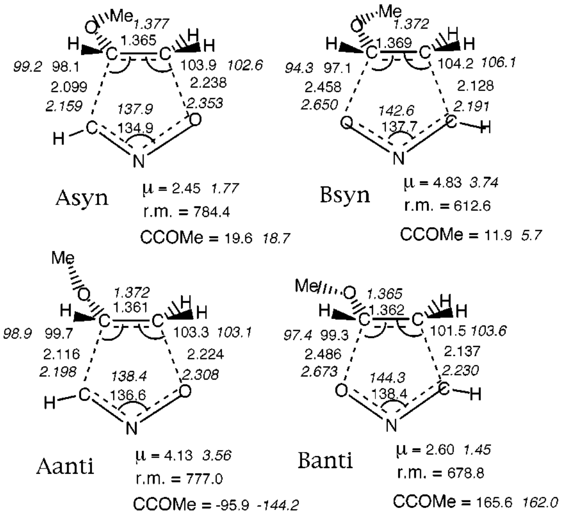

Figure 5. Optimized transition structures of the cycloaddition of formonitrile oxide with methyl vinyl ether. The CCOMe dihedral angles show the syn and anti conformations. HF/6-31G(d), B3LYP/6-31G(d) in italics.

with the predictions obtained with uncorrelated (HF) and correlated (MP4) calculations and with the experiment. As an example, the reaction of diazomethane (DZM) with acrylonitrile (ACN) is controlled by the HO(DZM)−LU(ACN) interaction ($\Delta\epsilon = 11.06$ eV), which dictates B regiochemistry (Chart 1); the LU(DZM)−HO(ACN) interaction is much less effective ($\Delta\epsilon = 16.18$ eV) and also much less selective because it involves MO coefficients scarcely differentiated (the regiochemistry predicted by this interaction is reported in parentheses). The uncorrelated electronic activation energies predict that the B transition structure is favored (over the A transition structure) by −3.80 kcal·mol^{-1} (B regiospecificity) and the correlated calculation (MP4) reduces the preference to −0.92 kcal·mol^{-1} (mixture with prevalence of B adduct), whereas the kinetic contributions reinforce B selectivity (−1.25 kcal·mol^{-1}, Table 4) and the solvent effects recover complete B regiospecificity (−2.37 kcal·mol^{-1}, Table 4). The experiment confirms B regiospecificity (B 100%). It

Table 7. Frontier Energy Separations and Regiochemical Predictions[a]

	PR	ACN	MVE_{syn}	MVE_{anti}
DZM				
HO−LU	14.05 (B)	11.06 B	14.55 A	14.29 A
LU−HO	15.08 (B)	16.18 (B)	14.61 (B)	14.43 (B)
$\Delta G_B^\ddagger - \Delta G_A^\ddagger$	−1.23, −1.16	−3.80, −0.92	0.00, −0.35	−1.90, −2.10
expt	B, 88%	B, 100%	B, 100%	
FNO				
HO−LU	16.25 (A)	13.80 A	16.75 B	16.49 B
LU−HO	15.03 B	16.13 B	14.56 B	14.38 B
$\Delta G_B^\ddagger - \Delta G_A^\ddagger$	−3.61, −1.39	+ 2.51, −3.30	−8.49, −0.83	−11.42, −5.27
expt	B, 100%	B, 100%	B, 100%	
MNO				
HO−LU	15.62 (A)	13.17 A	16.12 B	15.86 B
LU−HO	15.23 B	16.33 B	14.76 B	14.58 B
$\Delta G_B^\ddagger - \Delta G_A^\ddagger$		+4.56, −2.74		
expt	B, 100%	B, 100%	B, 100%	

[a] Orbital energy separations are given in eV; the regiochemical prediction follows from the relative magnitude of the coefficients of the interacting frontier orbitals; predictions in parentheses indicate low selectivity of the orbitals involved. The frontier prediction is compared with the relative ($\Delta G_B^\ddagger - \Delta G_A^\ddagger$) electronic activation energy (in kcal mol^{-1}), the two figures corresponding to uncorrelated HF/6-31G(d) and electron correlated MP4/6-31G(d) evaluations of Table 5. The experimental regiochemistry is given as percent of the B adduct.

is clear from this analysis that the FO prediction agrees with the experiment only because the HF result, correctly mimicked by the FO approximation, largely overestimates the relative electronic stability of the B-TS and puts out of sight that complete B regiospecificity is predicted only when solvent effects are included. This argument is well supported by the following results: the reactions of FNO and MNO with ACN are predicted to be A regiospecific both by the uncorrelated calculation and by the frontier approximation, whereas the experimental B regiospecificity is reached only by the correlated calculation; once again, the FO approximation *correctly* predicts the *wrong* regiochemistry because it is bound, at the best of its performance, to reproduce the uncorrelated result. Obviously, any improvement introduced in the FO treatment, including the calculation of the complete PMO terms, cannot reverse the regiochemical prediction of the uncorrelated calculation; if a reversed prediction is obtained, the "improvement", whatever justified, is an improper adjustment to the requested result.

The regiochemistry of the reactions of propene with DZM (mixture of regioisomers with prevalence of the B adduct) and FNO (B regiospecificity) are correctly foreseen by the FO approximation because the uncorrelated calculation is qualitatively confirmed by the correlated one and not altered by solvent effects.

The reactions of methyl vinyl ether introduce a further feature due to the intervention of low energy B transition structures in their synperiplanar/antiperiplanar conformations. The frontier orbitals of synperiplanar MVE (the lower energy conformer) and of antiperiplanar MVE are quite similar and so are the FO predictions of the regiochemistry, i.e., B-regiochemistry (in agreement with the experiment) for the reaction with nitrile oxides, A regiochemistry (in contrast to experiment) for the reaction with DZM.[45] The HF electronic activation energies of the reaction of MVE with FNO strongly favor B-TSs, in agreement with the FO prediction; however, the inclusion of MP4 electron correlation maintains B regiospecificity only for the anti-TS (one can also note that MP2 correlation indicates a mixture of B_{anti}, A_{syn}, and B_{syn}), and it is only with the complete $\Delta^\ddagger G$ calculation (solvent effects included) that both B-TSs gain full regiospecificity. Both the uncorrelated and correlated electronic activation energies of the reaction of MVEsyn with DZM point to mixtures of adducts, whereas a neat dominance of the B-TS is obtained for the anti forms. In this case, the FO prediction does not conform to HF calculation, even if the inclusion of charge-transfer interactions due to nonfrontier orbitals does predict a mixture of adducts.[45] B regiospecificity, in this case, is due to the unexpectedly low energy of the B_{anti} transition structure; the origin of this result has been traced back to the stabilization brought about by the very strong interactions between the incipient bonds and the oxygen lone pairs, interactions that appear to be more effective in B-TSs than in A-TSs, and to the finding that electrostatic interactions are more favorable to B_{anti} than to B_{syn} orientation.[12]

Conclusions

Both the regiochemistry and the trend of reaction rates of 1,3-dipolar cycloadditions of diazomethane and nitrile oxides are well reproduced by calculations provided that electron correlation be introduced either via the Moeller−Plesset perturbation technique or via the density functional theory in the parametrization B3LYP. In particular, the interesting features of DZM cycloadditions of spanning a wide range of reaction rates (high for electron-withdrawing substituents, low for electron-donating substituents) and of FNO cycloadditions of spanning a very restrict range with a slight increase (over the unsubstituted ethene) with both kinds of substituents are perfectly reproduced, mainly when solvent effects are included.

The absolute values of reaction rates are strongly dependent on the level of electron correlation allowed; indeed, only the full MP4 (fourth-order Moeller−Plesset perturbation) level reproduces the experimental orders of magnitude. B3LYP- and HF-optimized transition structures show systematic differences that give only minor energy differences when single-point calculations are conducted at the same level; moreover, the kinetic contributions to the activation parameters of the prototype reactions are rather independent of the model of structure optimization (HF, MP2, B3LYP), and activation entropies appear to match well the experimental values.

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(45) We showed in ref 11 that the complete charge-transfer term between MVEsyn and DZM, at variance with the simple frontier interaction, points to a mixture of adducts.

Theoretical solvent effects appear to account for the experimental trend of reaction rates in solvents of increasing dielectric constants; moreover, they have a moderate influence on the regiochemistry prediction and usually reinforce the prediction obtained in vacuo.

Uncorrelated HF energy calculations provide wrong regiochemistries for the reactions of FNO with ACN and of DZM with MVEsyn; in the former case the correct regiochemistry is recovered when electron correlation is allowed, in the latter when also the anti-TSs are considered. The frontier orbital approximation does reproduce correctly the regiochemistry of the uncorrelated calculations and, as a consequence, leads to wrong predictions in all the cases where the electron correlation is responsible of the regiochemical inversion.

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Supporting Information Available: Absolute energies and kinetic contributions to thermodynamic properties at the levels of calculations cited in the present paper (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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