of C–C double bond character. In Figure 1b, one can see that the largest electronic charge concentration around a carbon atom is significantly off the Y–C bonding direction. This result shows a significantly bent Y–C bond which results from the C atoms' use of sp^2 hybrids to maximize C–C π bonding.

In summary, the high stability of the M_8C_{12} cluster is due to the weak metal–carbon d_π–p_π interaction. This weak π interaction allows maximum C–C π bonding. The role of the transition metal in this class of clusters is simply linking the six C=C double bonding units through σ bonding. Each metal atom in the M_8C_{12} cluster has local C_{3v} symmetry and contributes three orbitals to form σ bonds with carbon atoms. On each metal, there are six unused orbitals with $2a_1 + 2e$ symmetry. We expect that only one set of $a_1 + e$ orbitals is energetically favorable enough to be occupied by additional d electrons. Therefore, in addition to group 4 and 5 transition metals, other transition-metal atoms with three to nine valence electrons are possible for M_8C_{12} clusters. However, with an increase in the number of valence electrons in the transition-metal atoms, the repulsive interactions between metal d electrons and C–C π-bonding electron pairs increase, and the stabilities of M_8C_{12} clusters decrease. Therefore, M_8C_{12} clusters are expected to be less stable for transition-metal atoms with more than five valence electrons. Our model with weak M–C π bonding predicts that the Ti and V clusters would be paramagnetic, while a model with strong M–C π bonding could lead to diamagnetic clusters.

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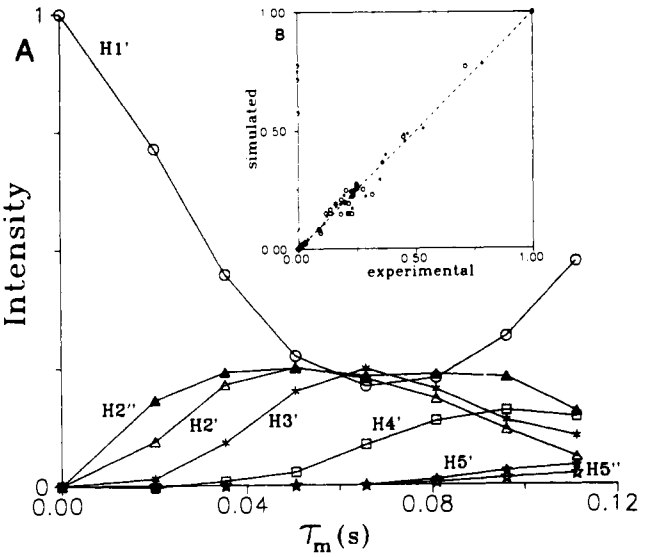

Figure 1. (A) Experimental buildup curves for coherence transfer in TOCSY (MLEV17) from the H1′ resonance of the dG moiety in cd(CpGp), recorded at 400 MHz and 298 K, with the carrier at 4.75 ppm and a radio-frequency field strength of 10 kHz. The TOCSY intensities were scaled in a manner that preserved the total magnetization. The inset (B) shows a plot of the experimental H1′ TOCSY ladder connectivities of the cytidine (*) and guanosine (O) sugar ring spin system in cd(CpGp) versus the values of the simulation which employed experimental J-couplings in hertz [$J_{1'2'}$ = 3.8 (2.9), $J_{1'2''}$ = 7.5 (7.7), $J_{2'2''}$ = −14.3 (−14.2), $J_{2'3'}$ = 7.5 (7.7), $J_{2''3'}$ = 7.5 (8.4), $J_{3'4'}$ = 6.5 (7.5), $J_{4'5'}$ = 3.5 (2.5), $J_{4'5''}$ = 2.5 (1.9), $J_{5'5''}$ = −11.8 (−11.6)] and chemical shift data in ppm [H1′, 6.27 (6.20); H2′, 2.92 (2.57); H2″, 2.72 (2.63); H3′, 5.00 (4.85); H4′, 4.23 (4.16); H5′, 4.12 (4.20); H5″, 4.02 (4.05)]; the data for cytidine are given in parentheses.

Quantitative Evaluation of TOCSY Data. Application to Sugar Ring Conformational Analysis

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For the structure determination of (bio)molecules by NMR, extraction of J-coupling constants from NMR spectra is of vital importance, since from this information torsion angle values can be derived via Karplus equations.[1] J-Coupling constants are usually obtained from the fine structure of the cross peaks in COSY spectra.[1-3] For large molecules this becomes difficult due to cancellation of the components of the cross peaks and/or overlap. An alternative is then to use TOCSY,[4,5] which has become very popular as an assignment tool for crowded spectra, but not as a tool to extract J-couplings or related structural parameters. We show that quantitative structure information can be obtained directly from TOCSY spectra, via the method of iterative back-calculation of the cross peak intensities. We demonstrate this approach through the quantitative analysis of the conformation of the sugar rings in the cyclic dinucleotide cd(CpGp).

The correct back-calculation of the TOCSY spectra requires numerical evaluation of the evolution of the density matrix under the influence of the mixing Hamiltonian.[4-6] The computer program written to perform this evaluation allows for a variety of different types of mixing Hamiltonians (e.g., WALTZ,[7] MLEV,[4,8] and DIPSY[9]). In addition, the program is provided with the J-couplings and the determinants of the off-resonance effects, namely, chemical shifts and the strength of the applied radio-frequency field. With this approach the experimental coherence transfer can indeed by correctly reproduced, as shown in Figure 1. Figure 1A presents the experimentally determined evolution of the TOCSY (MLEV17[4]) intensities of the cross peaks between H1′ of dG and the other members of the scalar coupled network, while Figure 1B shows the neat correspondence between the experimental TOCSY and the numerically simulated intensities. Thus, the inclusion of off-resonance effects in the calculation is sufficient to correctly reproduce the experimental TOCSY intensities.

It it well-known that deoxyribose sugars may rapidly interconvert between two puckered states, the N- and S-conformers, which can be characterized by the phase angle of pseudorotation, P, and the puckering amplitude, Φ, with their pseudorotation angles in the ranges $-20° < P_N < 20°$ and $117° < P_S < 189°$,

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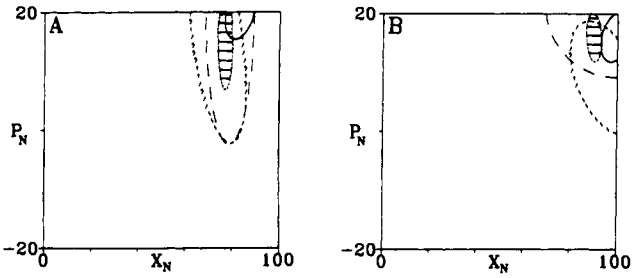

Figure 2. The 90% confidence limits, based on the formal covariance matrices on the assumption of normally distributed errors,[13] of (X_N, P_N) after minimization (see text) for H1′ TOCSY ladder intensities obtained at 35 ms (···), 95 ms (– – –), and seven different mixing times between 20 and 110 ms (—); shaded areas are for sets of experimental J-couplings, given in the caption below Figure 1, for (A) the cytidine and (B) the guanosine sugar ring spin system in cd(CpGp).

respectively, and the pucker amplitudes in the range $30° < \Phi_N, \Phi_S < 40°$.[1,10,11] The average sugar ring conformation can thus be described in terms of P_N, P_S, Φ_N, Φ_S, and X_N, the fraction N conformer. The J-couplings for the pure N and S conformations can be derived by means of the EOS Karplus equations, while the set of effective J-couplings of the average sugar conformation is the weighted average of the J-couplings of the pure N and S conformers.[1,10-12] Thus, instead of describing the TOCSY coherence transfer in terms of the effective J-couplings, we may describe it directly in terms of the sugar ring conformational parameters, which has the advantage of introducing independent and physically interpretable parameters. To determine these parameters from the experimental TOCSY data, the nonlinear least-squares algorithm of Marquardt[13] was used. To avoid excessive use of the time-consuming TOCSY simulation in the iterative fitting process, we constructed, in advance, a database of simulated TOCSY data, which was subsequently used as a model data grid in the Marquardt algorithm. We demonstrate the approach using only H1′ TOCSY connectivities, to give an indication of the results obtained with a limited number of experimental intensities, and because the H1′ resonances are generally less likely to overlap. Even if the direct H1′H2′ cross peak overlaps, preventing COSY cross peak simulation, the approach proposed here still works, as it is unlikely that all of the relay peaks will do so as well. In the fitting procedure we kept $\Phi_{S,N}$ and P_S fixed at 35° and 162°, respectively, leaving P_N and X_N as adjustable parameters. In Figure 2 the results of these minimizations are given and compared with those obtained with the usually applied procedure,[1,3,11,12,14] which is to establish P_N and X_N from J-couplings determined from COSY cross peak fine structure or, herer, 1D spectra. To aid in the comparison for the latter, an (analogous) Marquardt fitting procedure was used. Examination of Figure 2 shows that the accuracy of the values derived for P_N is about the same for the values obtained from the J-coupling and TOCSY data, in the latter case depending somewhat on the mixing times involved. A similar remark can be made with respect to the value of the fraction N conformer, X_N.

The present result shows that it is possible to obtain accurate structure parameters from TOCSY data. This is of particular interest for future quantitative evaluation of structural features in (bio)macromolecular systems for which accurate J-coupling data cannot be obtained directly but where TOCSY still yields good quality spectra.

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Total Synthesis of (+)-Duocarmycin SA

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(+)-Duocarmycin SA (**1**),[2] a naturally occurring and exceptionally potent antitumor antibiotic, represents the newest and most potent member of a growing class of agents[3,4] that derive their biological properties through a sequence-selective minor groove alkylation of duplex DNA.[5] Because of its enhanced solvolytic stability[2] relative to (+)-duocarmycin A[3] and (+)-CC-1065,[6] the examination of (+)-duocarmycin SA[7] promises to be especially interesting. Herein, we report the first total synthesis of (+)-duocarmycin SA based on sequential regioselective nucleophilic substitution reactions[8] of the unsymmetrical *p*-quinone diimide **3** in the preparation of a functionalized dihydropyrroloindole precursor to its alkylation subunit. In addition to constituting a new synthetic strategy for the preparation of natural or synthetic members of this growing class of agents,[9-14] both

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