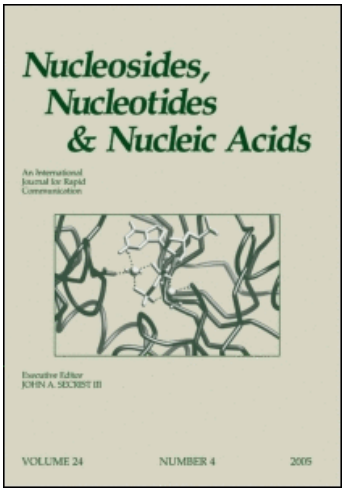

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Substituent Influence on the Reaction Rate of Deoxyribonucleoside Phosphoramidites with Deoxyribonucleosides Catalysed by Tetrazole

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To cite this Article Dahl, Bjarne H. , Nielsen, John and Dahl, Otto(1987) 'Substituent Influence on the Reaction Rate of Deoxyribonucleoside Phosphoramidites with Deoxyribonucleosides Catalysed by Tetrazole', Nucleosides, Nucleotides and Nucleic Acids, 6: 1, 457 — 460
To link to this Article: DOI: 10.1080/07328318708056255
URL: http://dx.doi.org/10.1080/07328318708056255

NUCLEOSIDES & NUCLEOTIDES, 6(1&2), 457-460 (1987)

SUBSTITUENT INFLUENCE ON THE REACTION RATE OF DEOXYRIBONUCLEOSIDE PHOSPHORAMIDITES WITH DEOXYRIBONUCLEOSIDES CATALYSED BY TETRAZOLE

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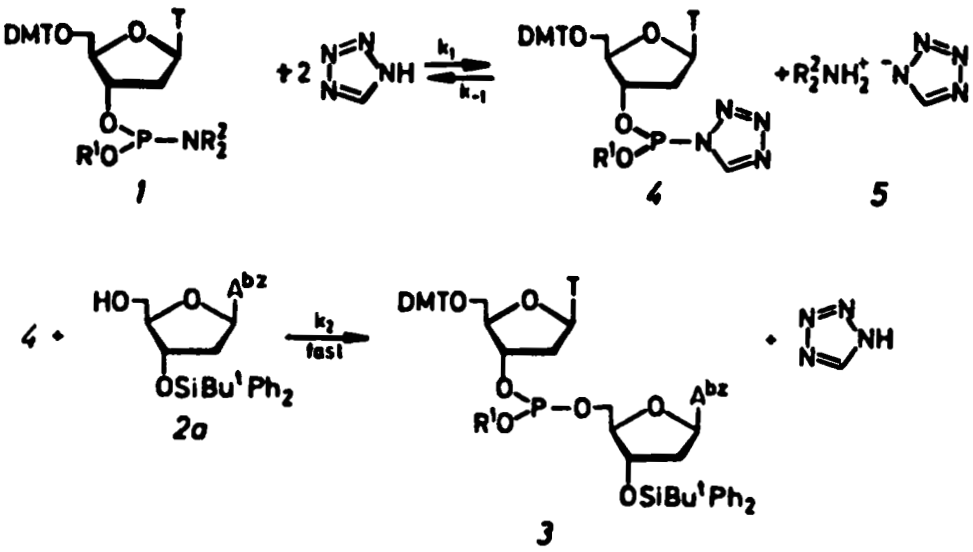
The rates of formation of some dinucleoside phosphites 3 from different deoxyribonucleoside phosphoramidites 1 and a common nucleoside 2a (Scheme) have been compared.



R^1	Me	Me	Me	Me	CH_2CH_2CN	$CHCH_2CN$ (Me)	$C(Me)-CH_2CN$ (Me)	Cl
NR^2_2	NEt_2	NPr^1_2	N O	NMePh	$INPr^1_2$	NPr^1_2	NPr^1_2	NPr^1_2

Scheme

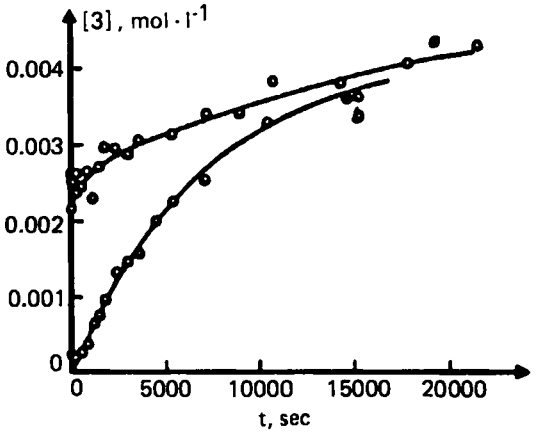


Fig. 1

a, 2a last added

b, tetrazole added last

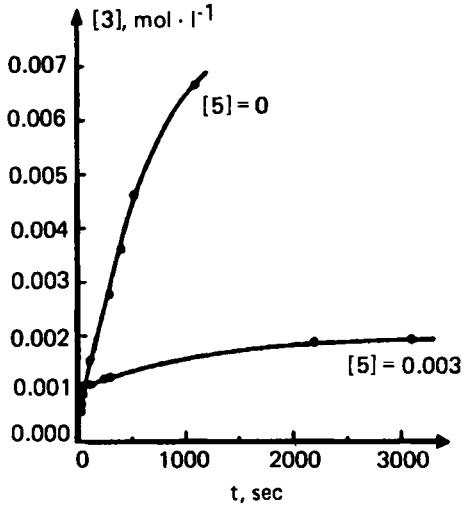


Fig. 2

Effect of added salt 5.

c_1° = 0.030 M, c_{tet}° = 0.015 M

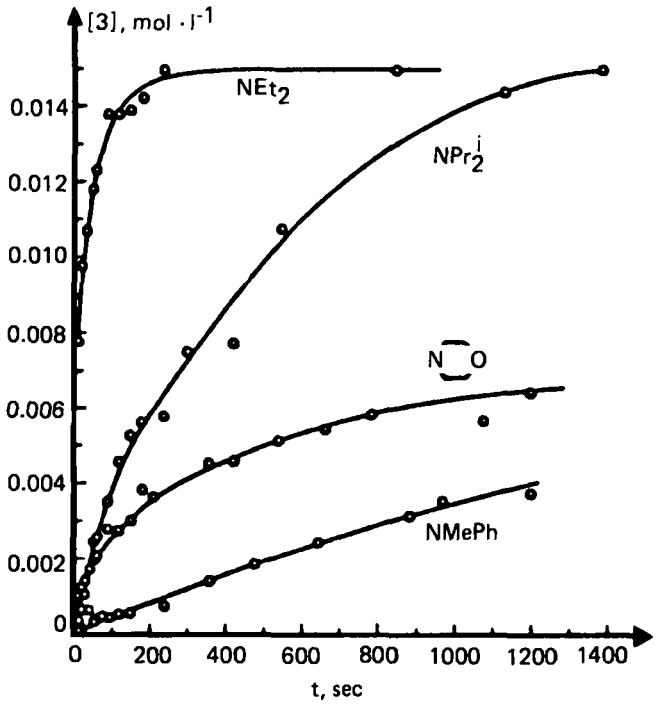


Fig. 3, R^1 = Me

Nucleophilic catalysis via intermediate 4, when substantial amounts of the catalyst tetrazole are used, is inferred from experiments illustrated in Fig. 1 and Fig. 2. The rate variations with the amino substituents are shown in Fig. 3, and those with the alkoxy substituents in Fig. 4. Under the conditions used to obtain the curves (premixing 1 with 2a and adding tetrazole at time zero) the formation of 4 is probably rate-limiting; accordingly it is the rate of formation of this intermediate which is illustrated.

Fig. 3 shows that the more basic the $R^2{}_2NH$, the higher is the rate. The opposite order is found for model systems catalysed by small amounts of $R_2NH_2{}^+Cl^-$,[1], where probably only acid catalysis occur (the stereochemistry was inversion[2]), and where the leaving group ability is important. With large amounts of tetrazole the formation of

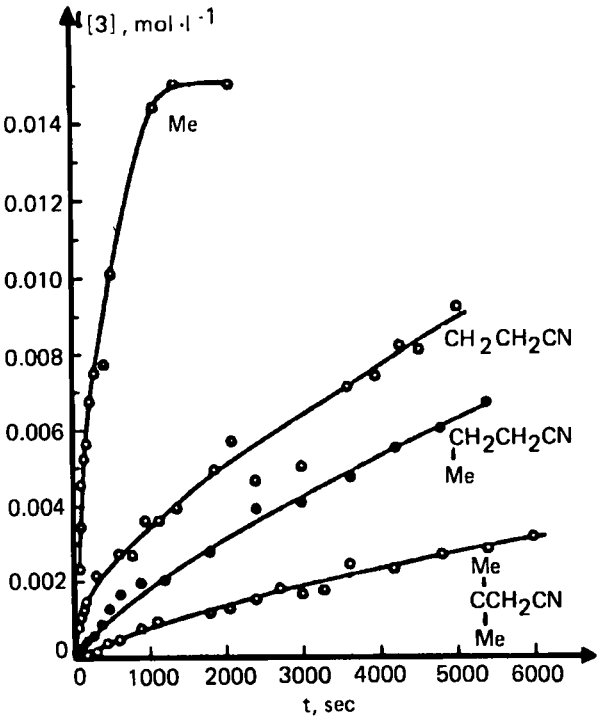


Fig. 4, R^2 = Pr^i

5 apparently drives the reaction. Fig. 4 shows that a 2-cyanoethyl amidite is less reactive than a methyl amidite, and that the reaction is subject to some steric hindrance.

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2. Nielsen, J.; Dahl, O.; J. Chem. Soc. Perkin Trans II, 1984, 553.